GAETANO LANZA
ANDREA KAHLBERG

TECHNOLOGICAL LEAPS IN VASCULAR SURGERY

A 2024 overview of what is expected to revolutionize historical paradigms

Edited by the
Italian Society of Vascular and Endovascular Surgery

SICVE
SOCIETÁ ITALIANA DI CHIRURGIA VASCOLARE ED ENDOVASCOLARE

EDIZIONI MINERVA MEDICA

GAETANO LANZA
ANDREA KAHLBERG

TECHNOLOGICAL LEAPS IN VASCULAR SURGERY

A 2024 overview of what is expected to revolutionize historical paradigms

EDIZIONI MINERVA MEDICA

ISBN: 978-88-5532-289-8

www.minervamedica.it / e-mail: minervamedica@minervamedica.it

Printed in October 2024 by Digital Team srl, Via dei Platani, 4 - Fano (PU) on behalf of Edizioni Minerva Medica

In loving memory of Massimiliano M. Marrocco Trischitta,
Paolo Spada, and all the colleagues who passed away prematurely,
although still in the prime of their lives.
Thank you, dear friends, for the important contribution
you have made to the development of new technologies
in the field of vascular surgery.

CONTENTS

AUTHORS

ALBLAS DIEUWERTJE Department of Applied Mathematics, Technical Medical Centre, University of Twente, Enschede, the Netherlands

ALLIEVI SARA Department of Vascular and Endovascular Surgery, Santa Chiara Hospital, Trento, Italy

ANTONELLO MICHELE Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

AYYALASOMAYAJULA VENKAT Amsterdam University Medical Centers, Department of Vascular Surgery, Amsterdam, the Netherlands

BALDAZZI GIULIA School of Vascular Surgery, University of Ferrara, Ferrara, Italy; Department of Translational Medicine, University of Ferrara, Ferrara, Italy

BALDINO GIUSEPPE Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

BARATI SARA Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

BARTOLI STEFANO Unit of Vascular, Endovascular and Emergency Vascular Surgery, "S. Eugenio" Hospital, Rome, Italy

BASTIANON MARTINA Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

BERTAGNON ALESSANDRO Department of Environmental and Prevention Sciences, University of Ferrara, Italy

BIANCHINI MASSONI CLAUDIO Vascular Surgery, Cardio-Thoracic and Vascular Department, University-Hospital of Parma Parma, Italy

BONFÈ MARCELLO Department of Engineering, University of Ferrara, Italy

BONVINI STEFANO Department of Vascular and Endovascular Surgery, Santa Chiara Hospital, Trento, Italy

BORGHESE OTTAVIA Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

BOSISIO ENRICA Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

BRUNO ANTONINO Laboratory of Cardiovascular Pathophysiology and Regenerative Medicine, IRCCS MultiMedica, Milan, Italy; Laboratory of Immunology and General Pathology, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

BUGNA CARLOTTA Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

CAMPANA FEDERICA Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

CANAUD LUDOVIC Department of Thoracic and Cardio Vascular Surgery, Arnaud de Villeneuve Hospital, Montpellier, France

CAPUTO STEFANIA Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

CARADONNA EUGENIO Department of Pathology and Laboratory Medicine, Centro Diagnostico Italiano, Milan, Italy; Director Board Regenerative Medicine CNOS (CeRICT), Benevento, Italy

CASADEI ALDER School of Ultrasound and Vascular Ultrasound SIUMB, Bolzano, Italy

CATASTA ALEXANDRA Vascular Surgery, Cardio-Thoracic and Vascular Department, University-Hospital of Parma Parma, Italy

CHAKFE NABIL GEPROMED, Strasbourg, France; Department of Vascular Surgery, Kidney Transplantation and Innovation, University Hospital of Strasbourg, Strasbourg, France

CHIESA ROBERTO Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

CHISCI EMILIANO Vascular and Endovascular Surgery Unit San Giovanni Di Dio Hospital, Florence, Italy

COLACCHIO ELDA CHIARA Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

CZERNY MARTIN University Heart Center Freiburg, Freiburg, Germany

D'ORIA MARIO Division of Vascular and Endovascular Surgery, Cardiovascular Department, University Hospital of Trieste, Trieste, Italy

DE CAMPO GIULIA Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

DE KOORT JASPER Unit of Vascular Surgery, Fondazione IRCCS Ca'Granda Policlinico Milano, Milan, Italy

DE NIGRIS FRANCESCA Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

DI LEO ANTONINO Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

DOMANIN MAURIZIO Clinical and Community Sciences Department, Universita` degli Studi di Milano; Unit of Vascular Surgery, Fondazione IRCCS Ca'Granda Policlinico Milano, Milan, Italy

DONATI TOMMASO Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

DOPPIO NICOLA Hub Innovation Trentino, Trento, Italy

DORIGO WALTER Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

ESPOSITO DAVIDE Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

FAGGIOLI GIANLUCA Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

FARGION AARON THOMAS Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

FARSONI SAVERIO Department of Engineering, University of Ferrara, Italy

FAVIA NICOLA Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

FERRARA FULVIO Department of Pathology and Laboratory Medicine, Centro Diagnostico Italiano, Milan, Italy

FORESTI RUBEN Italian National Research Council, Institute of Materials for Electronics and Magnetism (CNR-IMEM); Center of Excellence for Toxicological Research (CERT), University of Parma, Parma, Italy

FREYRIE ANTONIO Vascular Surgery, Cardio-Thoracic and Vascular Department, University-Hospital of Parma Parma, Italy

FULGHERI IRENE Unit of Vascular Surgery, Fondazione IRCCS Ca'Granda Policlinico Milano, Milan, Italy

GALLITTO ENRICO Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

GANDET THOMAS Department of Thoracic and Cardio Vascular Surgery, Arnaud de Villeneuve Hospital, Montpellier, France

GARGIULO MAURO Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

GENTILE ENZO Anughea Network, AI and Interactive Systems Group, Italy

GIACOMELLI ELENA Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

GREGO FRANCO Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

GRIMALDI FABIO Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

GUETARNI FARID Department of Clinical Research, University Hospital of Poitiers, and CNAM, Paris, France

HAZENBERG CONSTANTIJN E.V.B. Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

HEIJMEN ROBIN Department of Cardiothoracic Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands

HEIM FREDERIC GEPROMED, Strasbourg, France; Laboratoire de Physique et Mécanique Textile, Université de Haute-Alsace, Mulhouse, France

HOSTALRICH AURÉLIEN Department of Vascular Surgery, University of Toulouse, France

KAHLBERG ANDREA Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

KAPPE KAJ O. Amsterdam University Medical Centers, Department of Vascular Surgery, Amsterdam, the Netherlands

KLAASSEN JURRE Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

KUNTZ SALOMÉ GEPROMED, Strasbourg, France; Department of Vascular Surgery, Kidney Transplantation and Innovation, University Hospital of Strasbourg, Strasbourg, France

LANZA JESSICA Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

LEJAY ANNE GEPROMED, Strasbourg, France; Department of Vascular Surgery, Kidney Transplantation and Innovation, University Hospital of Strasbourg, Strasbourg, France

LEPIDI SANDRO Division of Vascular and Endovascular Surgery, Cardiovascular Department, University Hospital of Trieste, Trieste, Italy

LESCAN MARIO University Heart Center Freiburg, Freiburg, Germany

LODATO MARCELLO Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

LUPARELLI ANTONIO Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

LURAGHI GIULIA Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

MANDIGERS TIM Unit of Vascular Surgery, Fondazione IRCCS Ca'Granda Policlinico Milano, Milan, Italy

MANGILI BENEDETTA Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

MARTELLI MASSIMILIANO Division of Vascular Surgery, IRCCS MultiMedica, Milan, Italy

MARTINI CHIARA Diagnostic Department, University-Hospital of Parma, Parma, Italy

MASCOLI CHIARA Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

MELANI CATERINA Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

MELISSANO GERMANO Department of Vascular Surgery, Vita-Salute San Raffaele University School of Medicine, IRCCS San Raffaele Hospital, Milan, Italy

MENARA SABRINA Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

MERSANNE ARIANNA Vascular Surgery, Cardio-Thoracic and Vascular Department, University-Hospital of Parma Parma, Italy

MICHELAGNOLI STEFANO Vascular and Endovascular Surgery Unit San Giovanni Di Dio Hospital, Florence, Italy

MIGLIAVACCA FRANCESCO Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

MOZZETTA GADDIEL Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

MUTOLI MARTINA Laboratory of Cardiovascular Pathophysiology and Regenerative Medicine, IRCCS MultiMedica, Milan, Italy

NANO GIOVANNI Unit of Vascular Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Italy; Department of Biomedical Sciences for Health University of Milan, Milan, Italy

PACCIANI CLAUDIA Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

PAGANI ANSELMO Department of Translational Medicine, University of Ferrara, Italy

PEINETTI FLAVIO Department of Vascular Surgery, AUSL VdA, Aosta, Italy

PERINI PAOLO Vascular Surgery, Cardio-Thoracic and Vascular Department, University-Hospital of Parma Parma, Italy

PIAZZA MICHELE Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

PINI RODOLFO Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

PRATESI GIOVANNI Department of Surgical and Integrated Diagnostic Sciences, Clinic of Vascular and Endovascular Surgery, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

PULLI RAFFAELE Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

RAMELLA ANNA Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

RAMPIN ANDREA Laboratory of Cardiovascular Pathophysiology and Regenerative Medicine, IRCCS MultiMedica, Milan, Italy

REINA NICOLA Vascular and Endovascular Surgery, S. Elia Hospital, Caltanisetta, Italy

RICCO JEAN-BAPTISTE French Academy of Medicine and University of Poitiers, Medical School, Poitiers, France

RIJKEN LOTTE Amsterdam University Medical Centers, Department of Vascular Surgery, Amsterdam, the Netherlands

RODRIGUEZ MATAS JOSE F. Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Milan, Italy

RYGIEL PATRYK Department of Applied Mathematics, Technical Medical Centre, University of Twente, Enschede, the Netherlands

SERVI PAOLO Anughea Network, AI and Interactive Systems Group, Italy

SETACCI CARLO Founder of Vascular and Endovascular Surgery Department and Residency Program in Vascular Surgery at the University of Siena, Siena, Italy

SETACCI FRANCESCO Kore University of Enna, Gaspare Rodolico University Hospital Catania, Catania, Italy

SETTEMBRINI ALBERTO M. Division of Vascular Surgery, IRCCS MultiMedica, Milan, Italy

SHYTI BETTI Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

SICA SIMONA Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

SIRIGNANO PASQUALINO Vascular and Endovascular Surgery Unit, Sant'Andrea Hospital of Rome, Department of General and Specialistic Surgery, "Sapienza" University of Rome, Rome, Italy

SMORENBURG STEFAN P.M. Amsterdam University Medical Centers, Department of Vascular Surgery, Amsterdam, the Netherlands

SÖDERLUND TIMO Aortic Dissection Collaborative Advisory Group, Seattle, WA, USA

SPATH PAOLO Vascular Surgery Unit, Hospital "Infermi", AUSL Romagna, Rimini, Italy; Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

SPEZIALI SARA Section of Vascular Surgery, Department of Excellence of Experimental and Clinical Medicine, University of Florence, Florence, Italy

SPINETTI GAIA Laboratory of Cardiovascular Pathophysiology and Regenerative Medicine, IRCCS MultiMedica, Milan, Italy

SQUIZZATO FRANCESCO Division of Vascular and Endovascular Surgery, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

STANA JAN Department of Vascular Surgery, Ludwig-Maximillian University Hospital, Munich, Germany

SUFALI GEMMI Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

TAURINO MAURIZIO Vascular and Endovascular Surgery Unit, Sant'Andrea Hospital of Rome, Department of Molecular and Clinical Medicine, "Sapienza" University of Rome, Rome, Italy

TINELLI GIOVANNI Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

TRIMARCHI SANTI Clinical and Community Sciences Department, Università degli Studi di Milano; Unit of Vascular Surgery, Fondazione IRCCS Ca'Granda Policlinico Milano, Milan, Italy

TSHOMBA YAMUME Università Cattolica del Sacro Cuore, Rome, Italy; Unit of Vascular Surgery, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

TSILIMPARIS NIKOLAOS Department of Vascular Surgery, Ludwig-Maximillian University Hospital, Munich, Germany

VACIRCA ANDREA Vascular Surgery, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

VAN HERWAARDEN JOOST A. Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

VENTO VINCENZO GEPROMED, Strasbourg, France; Vascular Surgery Department, Lancisi Cardiovascular Center, Ancona, Italy

WOLTERINK JELMER Department of Applied Mathematics, Technical Medical Centre, University of Twente, Enschede, the Netherlands

YEUNG KAK KHEE Amsterdam University Medical Centers, Department of Vascular Surgery, Amsterdam, the Netherlands

ZAMBONI PAOLO School of Vascular Surgery, University of Ferrara, Ferrara, Italy; Department of Translational Medicine, University of Ferrara, Ferrara, Italy; Vascular Diseases Center, University of Ferrara, Ferrara, Italy

PREFACE

The challenge to understand, wisely evaluate, and recognize the possible value and risks of rapidly evolving technological offers

GAETANO LANZA
2023-2024 President of the Italian Society of Vascular and Endovascular Surgery

This volume represents a further demonstration of the particular interest of SICVE – Italian Society of Vascular and Endovascular Surgery – in most main recent technological innovations that, as the title suggests, will potentially allow vascular surgery, and more generally medical-surgical science, to make significant 'leaps forward'.

This is an opportunity to outline some general remarks.

Over the millennia, the human species, thanks to an extraordinary and singular development of its cerebral grey matter, has gradually established itself as the dominant species on our planet, characterized precisely by its uniquely human ability to discover and invent ever more innovative techniques that have enabled it to achieve this success. Science and technology have so far proven to be effective, efficient and successful, when applied in the service of humanity, which has benefited so far and will benefit more and more for its survival and existence. Concurrently, they have transformed and will continue to influence the anthropological essence and anthropomorphic connotation on the one hand and the environmental ingredients on the other, as Charles Darwin[1] postulated, in a kind of magical equilibrium and a positive and productive self-sustaining vicious circle.

In his work, The Structure of Scientific Revolutions, the philosopher Thomas Kuhn[2] posits that scientific progress occurs in two distinct phases: periods of normality, during which scientific inquiry operates within an established 'paradigm', and periods of 'crisis', during which new theories, ideas, and technologies emerge that challenge the previous paradigm, leading to the birth of a new, commonly accepted paradigm.

Since the turn of the last millennium, we have been experiencing the *Digital Revolution*. For the past few years, some have suggested that this gave rise to the Fourth Industrial Revolution, which is the result of the increasing interpenetration of the physical, digital and biological worlds. This is the summation and collective force of advances in Artificial Intelligence (AI), robotics, the Internet of Things (IoT), 3D printing, genetic engineering, nanotechnology, quantum computers and other acquired knowledges. A new concept of humanity is emerging, and the advent and pervasiveness of these new cutting-edge technologies and acquisitions is making man a new creature, a 'hybrid' with the Intelligent Machine. This hybrid is in continuous redefinition and accelerated transformation, and a new *post-human* species figure is emerging.

The advent of modern medicine has brought about a profound transformation in the way we approach healthcare. Vascular Surgery is not exempt.

It is crucial to be aware of these developments and this volume aims to contribute to this understanding.

New epistemological and *system governance* scenarios are also opening. It is imperative to govern the significant challenges and contribute to this paradigm shift in contemporary medicine, particularly in light of the 'collective intelligence and consciousness' of humanity, including the medical profession.

In 2000, digital information comprised 25% of all information produced globally. However, by 2013, this figure had reached 98%. 2013 was also the year in which humanity became aware that 90% of global digital information had been generated in the previous two years alone.

The health sector has experienced a remarkable expansion in the digitalization of data, which has occurred to a greater extent than in other sectors. This is due to the increasing prevalence of digital technology, as evidenced by the computerization of medical records, the management of diagnostic imaging, bioinformatics, the study of the genetics of individuals, and the development of medical apps, telemedicine, and innovative systems for transmitting and interpreting data on individual subjects and patients, on whom digital sensors are applied that may soon become electronic microchips. As a result of the exponential growth in the volume of data, *databases* are becoming increasingly

big databases, and the risk of *data leaks* is becoming a significant concern. This is particularly relevant in the context of digital technology, where the sheer volume of data is increasing exponentially.

The advent of the new millennium will be indelibly marked in the annals of medical history as the catalyst for a profound transformation in the delivery of healthcare. The historical Hippocratic physician, who takes notes in his notebook and learns at school and then in his profession, will continue to do so. However, he will already have at his side, like a perennial tutor, the Universal Intelligent Machine, which can perform billions of calculating operations to the thousandth of a second, processing data and experiences from every corner of the planet and continuously kept on file at his disposal. Furthermore, this Intelligent Machine enhances the human senses to an extraordinary degree, enabling it to see what the human eye is unable to see. It can therefore reconstruct and plan what the human genius is unable to do. This is accompanied by the emergence of new developments such as virtual reality systems, augmented reality, the metaverse, cognitive computing, analytics, and machine learning. We have entered and are currently experiencing an era in which algorithms are capable of influencing, transforming, and governing our decisions and our actual existence.

Indeed, in this scenario of analysis of extensive case histories and experiences collected and processed with scientific and mathematical methods from the end of the last century onwards (Evidence Based Medicine), which still constitute the background and basis on which it is still the doctor who outlines and chooses the paths considered most suitable for *their* patients, the interpretative algorithms of supercomputers are gaining ground. These algorithms are capable of processing *big data* and *long data*, allowing them to make decisions that could potentially replace the role of the doctor in certain decision-making processes. The increasing prevalence of computers in healthcare is accompanied by the collection and processing of large amounts of data, both spatially and temporally. This data is used to inform decision-making processes, with computers currently acting as a complement to, and in some cases an alternative to, the doctor. However, it is likely that computers will soon be able to make decisions independently, potentially replacing doctors in certain roles. It is evident that the convergence of biological and silicon intelligence, which is characterized by the integration of human and machine, represents the defining feature of the contemporary medical paradigm. This integration is not only a reflection of the future of medicine but also the new profile of the physician-surgeon of the third millennium.

Nevertheless, numerous criticisms and warnings regarding the limitations and biases of current *machine learning* and *computer-assisted medicine* systems have been made, as recently highlighted by Giampaolo Collecchia[3] who argues the necessity of "methodologically robust, prospective studies comparing teams of doctors using systems based on algorithms and teams that do not use them, instead avoiding direct, less significant comparisons between doctors and AI. It is only in this case that the realization of technologies that are applicable in real clinical contexts rather than experimental ones will occur in the near future".

We should carefully consider several recent reports (Jameson,[4] He,[5] Parikh[6]) highlighting that digital algorithms still present various limitations in medicine. This is due to the need for training data. It is evident that further learning is required of the Machine before it can be deemed reliable. Furthermore, the inherent *bias* associated with the mechanical and automatic use of processed data, without the ability to provide accurate values and interpretative weights, could potentially remain. These considerations, judgements and conclusions for decision-making purposes are currently and will be in the future the exclusive domain of the human mind.

The implementation and validation of AI in medicine is necessary to ensure its reliability in a wider range of applications. Currently, AI is considered reliable only in a few limited areas, mostly research and still experimental.

Given the potential impact on human lives and the future of humanity, it is essential to have clear and irrefutable evidence before embracing AI. This is particularly important to avoid the so-called *pro-innovation bias*, which can result from high expectations and a naive inclination to accept technological innovation uncritically.

The fundamental pact is that it is still and always the case that it is The Human who has the last word and determines or influences his own destiny. Similarly, it is always the Healthcare Professional who determines or influences the patient's fate and not the Machine. Whatever AI will have to deal with in the future, the implications and considerations of good clinical, ethical, legal, socio-political, psycho-social, philosophical, holistic practice will necessarily always have to remain in the human domain.

In the meantime, a new ecology of models and innovative systems is required. One concern is that technology is evolving at a faster pace than humans can comprehend and master. It is possible that, in the future, humans may be at risk of being overtaken by Machines, which could result in a symbiotic relationship between the two species. This could lead to humans evolving at a faster rate than previously thought. This will be a pivotal moment for our species, which will find itself at a crossroads. If the crossroads has already been crossed by the Machine without our awareness, it will be a crucial moment for us to recognize the implications of this event.

The third millennium has already witnessed a paradigm shift in medicine, with the advent of the Universal Intelligent Machine. This has led to a shift towards a more systematic and systemic approach. At the same time, the Machine can be customized to the parameters of the individual or single patient, thus becoming Precision or Personalized Medicine. This is in addition to the emergence of Participatory Medicine, Predictive and Initiative Medicine, and

Preventive and Curative Medicine. This is Hood's 4P Medicine.[7] Similarly, biomedical research has also undergone a paradigm shift, in that it is no longer conducted only *in vitro* or in the laboratory or study; rather, it is generated and applied to reality (real or virtual), thus in a sense *in vivo on a large scale*. Until recently, research and analysis of data generated by ad hoc protocols and projects was considered an additional and reserved activity for particular, sometimes elitist fields. However, the advent of machine-mediated, self-determined and supported network algorithms has transformed this approach, enabling the growth of spontaneous, universal and even more democratic processes.

The profound and surprising question is whether this new form of medicine may in the future also become automated as it is completely entrusted to the Machine. In such a scenario, one would have to consider the role and space that the figure of the 'traditional' physician that has emerged over the last two millennia might still play. Hood's argument suggests that there is a need to shift the focus from diseases to people. Moreover, the focus must extend beyond the sick to encompass those who are not yet ill. In the future, the emphasis will be on maintaining optimal health in individuals, with the goal of enhancing the well-being of the population as a whole. This shift in focus represents a significant departure from the traditional approach, which has been largely disease centric. The advent of genetic bioengineering, when combined with information technology, has the potential to profoundly transform humanity.

In his text entitled "The Singularity Is Near", Ray Kurzweil[8] posits that the pace of change and the evolution of science are exponential and explosive, such that they will soon provoke a qualitative leap and a formidable enhancement of the human species. This enhancement will enable the human species to overcome its biological being and reach the so-called Singularity. Three areas are mainly preparing for this leap: genetic engineering, nanotechnology and AI. The rapid rise of each of these promotes and accelerates that of the others. Kurzweil postulates that soon the human species might even achieve a certain 'immortality'. Roberto Marchesini[9] predicts a *post-human* future characterized by the phenomenon of what he terms a 'biorganism'. This is defined as "the connection at all levels and the interchange of information flows for the sharing of cognitive processes capable of achieving a performance that exceeds the capacities of individual brains". This is made possible by "more and the advent of more sophisticated technologies will facilitate the transfer of cognitive processes from the neurocranium, the traditional repository of human thought, to external interfaces. This will enable a more expedient response to the long-standing desire for immortality".

Returning to Thomas Kuhn,[2] it should be noted that the actions thus far do not represent an error of method, but rather a limitation of previous paradigms. The new paradigm does not necessarily have to eliminate the previous paradigm; however, it must *encompass it in order to overcome it*. Throughout the history of science, new theories or new scientific paradigms have subsumed the results and successes of the theories that preceded them, extending the scope and range of situations that the previous theories were no longer able to understand and justify. However, new theories or paradigms do not entirely remove the previous ones. For instance, in the last century, quantum theory extended the range of understanding of classical mechanics, while Einstein's relativity theory extended the scope of Newton's universal gravitation. Similarly, the new medicine does not entirely replace the traditional classical medicine that has emerged over the last two millennia, the experimental medicine that has emerged over the last two centuries, and the methodological-statistical medicine that has emerged over the last two decades, based on evidence or proof. Rather, it must subsume them.

The individual patient and the physician-surgeon are already participating and contributing, perhaps even unbeknownst to them, to the transition towards a New Medicine, to the increasingly accelerated constitution and growth of a collective health consciousness, and to the evolution of the human species dictated by the new technologies and paradigms of medical sciences.

REFERENCES

1. Darwin C. The origin of species. London: 1859.
2. Kunh T. The Structure of Scientific Revolutions. Chicago: Chicago University Press; 1962.
3. Collecchia G. Artificial intelligence systems and precision medicine: Hopes and realities. Recent Prog Med 2020;111.
4. Jameson JL, Long DL. Precision medicine. Personalized, problematic, and promising. N Engl J Med 2015;372:2229–34.
5. He J, Baxter SL, Xu J, *et al.* The practical implementation of artificial intelligence technologies in medicine. Nat Med 2019;25:30–6.
6. Parikh RB, Teple S, Navathe AS. Addressing bias in artificial intelligence in health care. JAMA 2019;322:2377–8.
7. Hood L. Systems Biology and P4 Medicine: Past, Present, and Future. Rambam Maimonides Med J 2013;62:203.
8. Kurzweil R. La Singolarità è vicina. Milano: Apogeo; 2008.
9. Marchesini R. Post-human. Verso nuovi modelli di esistenza. Torino: Bollati Boringhieri; 2002.

1

OVERVIEW ON STRUCTURAL EVOLVING AREAS IN VASCULAR SURGERY

1.1 REORGANIZATION AND DIGITAL RENOVATION OF THE HEALTH SYSTEM: CONCRETE PERSPECTIVES IN VASCULAR SURGERY

Maurizio Taurino, Pasqualino Sirignano, Stefano Bartoli

ln the last years, technology has irreversibly become entwined with all aspect of our everyday lives. From entertainments to education and to work activities, contemporary peoples spent a huge amount of their time interacting with electronic devices and benefiting from technologies development and advantages deriving form internet connection availability.

As all areas of our society, also healthcare providers and healthcare industries are facing the challenges driven by this digital renovation.

While, historically, the field of medicine, and more in general the entire healthcare section, were the sole impenetrable kingdom of few highly qualified experts, nowadays advances in technologies have promoted a digital renovation in healthcare, as both healthcare providers and patients seem to enjoy better results adopting digital solutions in addressing their needs.

Currently, these solutions are supposed to become the key element to improve patients' healthcare experience and outcomes, as demonstrated by the impressive amount of money and efforts invested in their development according to a report by the Global Market Insights Inc., estimating a digital healthcare market of 504 billion dollars worldwide by the 2025.[1]

Consequently, for every healthcare professional, including Vascular Surgeons, it is vital to be part of this ongoing digital renovation or, at least, knowing what is going on.

To be simple and direct, what is going on, this digital renovation in healthcare, is the establishing practice to use technologies and advantages related to internet connections to actively add value to patients' quality of life and healthcare system, in a manner that maximize benefits for both.

This is a crucial point: digital renovation is precisely intended to maximize benefits *via* a structured application of available technologies (or even via the development of new ones) to real-life healthcare problems. In other words, healthcare digital renovation is far from suggesting that patients surf the web to misdiagnose his/her symptoms before consulting a physician as well as from all other "*solutions*", turning people into qualified doctors.

Instead, wearable devices, internet of things (IoT), artificial intelligence (AI) applications to web based patients' portal and big-data analysis, Robotics, and dimensional (3D) printing are all promising tolls potentially providing useful information and solutions for both the patients and his/her doctor.

Furthermore, the lesson learned by the recent COVID-19 pandemic underlined the urgent need to develop infrastructures, hardware, and software, to support and to promote telemedicine and all other remote and virtual healthcare solutions.

Of course, this digital renovation has become possible only because necessary technologies were developed and spready adopted. The following are the key elements allowing the current digital renovation in healthcare.[2, 3]

ARTIFICIAL INTELLIGENCE

AI is increasingly being integrated into various aspects of medicine in general and also vascular surgery, offering opportunities to enhance patient care, improve outcomes, and streamline clinical workflows. Here are several key applications of AI in vascular surgery.[2, 3]

1. Image analysis and interpretation

AI algorithms may analyze medical imaging data such as angiograms, CT scans (Figure 1.1.1), MRI scans, and ultrasound images to assist in the detection and characterization of vascular lesions, stenosis, aneurysms, and other abnormalities, potentially facilitating diagnosis, treatment planning and intraoperative guidance. For example, AI algorithms could become able to automatically detect and quantify vascular lesions, identify anatomical landmarks and assess blood flow characteristics, helping surgeons make more informed decisions. Soon, by automating tasks like segmentation, feature extraction, and pattern recognition, AI could help vascular surgeons in evaluating complex images more efficiently and accurately.

2. Predictive modelling and risk stratification

AI techniques such as machine learning could analyze large datasets of patient characteristics, clinical outcomes, and treatment interventions to develop predictive models for various vascular conditions. These models could help stratify patients based on their risk profiles, predict treatment responses, and optimize patient selection for different interventions.

3. Surgical planning and simulation

AI-powered software tools will be able to facilitate preoperative planning by generating 3D reconstructions of vascular anatomy from imaging data, allowing surgeons to visualize patient-specific anatomy and plan optimal surgical approaches, and simulating different surgical scenarios. Surgeons could be proficient to use these virtual simulations to visualize optimal approaches, anticipate potential challenges and refine their surgical plans, before entering the operating room.

4. Intraoperative assistance and decision support

AI technologies could provide real-time guidance and assistance to surgeons during procedures by analyzing

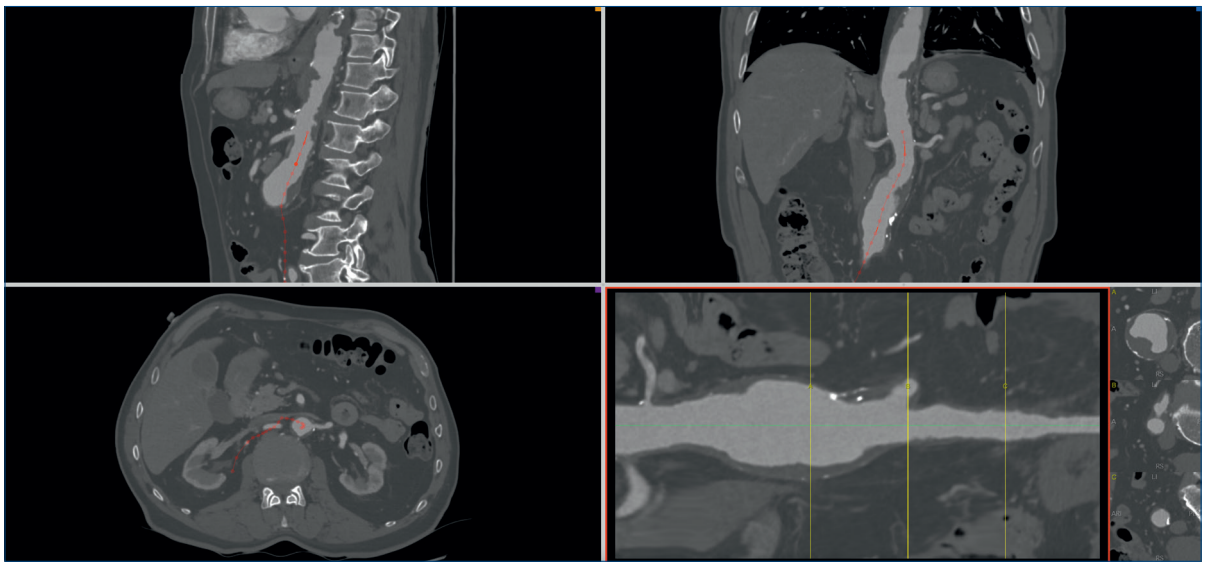


FIGURA 1.1.1 ● Multiplanar and center-lumen-line virtual reconstruction of a preoperative CTA planning an abdominal aortic aneurism intervention.

intraoperative data streams, such as physiological signals and imaging feedback, and offering decision support recommendations.

For example, AI algorithms could effectively overlay virtual images onto the surgical field, helping surgeons precisely localize vascular structures, identify critical landmarks, and navigate complex anatomical regions with greater confidence and accuracy.

5. Postoperative monitoring and follow-up

AI-enabled monitoring systems could analyze postoperative data such as vital signs, laboratory values, and patient-reported outcomes to track recovery progress, detect early signs of complications, and personalize postoperative care plans. This continuous monitoring will potentially improve patient safety and reduce the risk of adverse events and reduce hospital readmissions.

6. Clinical documentation and workflow optimization

AI-powered tools could automate routine tasks such as medical documentation, coding, and administrative tasks, allowing vascular surgeons to focus more on patient care and clinical decision-making. Natural language processing (NLP) algorithms will extract relevant information from clinical notes, streamline documentation processes, and improve the accuracy of electronic health records.

7. Clinical decision support

AI algorithms could provide decision support to surgeons by analyzing patient data, clinical guidelines, and relevant literature to offer evidence-based recommendations for diagnosis, treatment selection, and perioperative management. This will improve clinical decision-making, reducing variability in practice, and enhancing patient safety.

8. Research and innovation

AI-driven analytics could analyze large-scale clinical and genomic data to identify new insights into vascular diseases, risk factors and treatment responses. This could accelerate research efforts, facilitate the discovery of novel therapeutic targets, and drive innovation in vascular surgery. While AI holds great promise for advancing the field of vascular surgery by augmenting surgeons' capabilities, improving diagnostic accuracy, optimizing treatment strategies, and ultimately enhancing patient outcomes, it's important to address challenges such as data privacy, algorithm bias, regulatory considerations, and the need for validation and integration into clinical practice. Collaboration between clinicians, researchers, engineers and regulatory agencies is essential to ensure the safe, ethical and effective implementation of AI technologies in vascular surgery, continued research, validation and integration of AI technologies into clinical practice are essential to ensure their safety, efficacy, and widespread adoption in vascular surgery.[2, 3]

INTERNET OF THINGS

IoT devices has several possible applications in medicine and healthcare. Firstly, and more intuitively, internet connected wearable devices could collect patient's specific biometrical data in his/her daily life activities, providing the basis for a real-time highly accurate patients evaluation. Those gadgets will allow, for example, to exactly evaluate the free walking distance in patients with intermittent claudication patients, consequently driving every further therapeutic action.

ROBOTICS

For thousands of years, robots have inspired the imagination of humans, but it was only about 40 years ago that a robot was used for the first time in medicine. Since then, robot-assisted procedures have become increasingly popular in urology, general surgical specialties, and gynecology (Figure 1.1.2). Consistently, robot-assisted surgery in vascular field was introduced in 2002 to overcome the limitations of laparoscopy. However, robot-assisted vascular surgery did not yet gain widespread popularity. On the other hand, robot-assisted endovascular surgery, although still in its infancy, has become a promising alternative to existing techniques, both promoting better surgical performance and reducing occupational hazards for vascular and endovascular surgeons.

Moreover, it could be speculated that robot-assisted vascular and endovascular interventions and AI will converge to enable robot-assisted vascular surgery, where robotic systems equipped with AI capabilities assist surgeons during any kind of minimally invasive procedures: AI-powered robots will be able to manipulate surgical instruments adapting to patient-specific anatomy and offering potential benefits in terms of reduced tissue trauma, faster recovery and improved outcomes.[4]

3D PRINTING

3D printing, also known as rapid prototyping or additive manufacturing, is a novel adjunct in the medical field. This concept was first described by Hull in 1983, where accurate prototypes were created based on digital data through compound layering of thin photopolymer sheets. This technique was initially limited to automotive and aerospace engineering adaptations only due to high equipment cost. However, with the availability of cheaper commercial printers and free processing software, 3D printing has subsequently been applicable to medical science of various subspecialties, including vascular and endovascular surgery.

3D printing is now well recognized and fully incorporated as a useful adjunct in the field of vascular and endovascular surgery. The production of an accurate anatomic patient-specific replica is showing to bring significant impact in patient management in terms of anatomic understanding, procedural planning and intraoperative navigation, education, and academic research as well as patient communication.[5, 6]

Once spready available, all those technologies will benefit physicians, healthcare professionals, Hospital (and all Medical Institutions) and patients in several way.

FIGURA 1.1.2 ● An operative theater equipped with the Da Vinci Robotic Surgical Systems (Intuitive Surgical, Inc., Sunnyvale, CA – USA).

For doctors and healthcare providers digital renovation will be benefit by:

- allowing for more effective communication, and remote communication, between physicians and patients and his/her family, caregivers and patients' associations;
- allowing an easier peer to peer case revision and planning between different specialists, really useful considering how often a vascular surgeon is consulted form spoke hospitals or is involved in high complexity intervention performed from oncologic or orthopedic surgeons or, lastly, in trauma management;
- optimizing workflows by eliminating paperwork and making data more accessible;
- creating an effective and secure database for electronic medical records.
- For patient digital renovation will benefit by:
- accessing to personalized healthcare services;
- tracking his/her healthcare metrics in real-time;
- getting easier access to his/her medical data and scheduling medical appointment in a more convenient and participate way.

Of course, despite all the theoretical advantages, digital renovation must face challenges and barriers: data privacy and security concerns, natural healthcare organizations and workers' resistance to change, interoperability issue (because legacy systems and newer digital application are not always compatible) and staff shortages (physician and healthcare providers will need to update their skills to include proficiency with new digital healthcare solutions).[2,3]

The way is long, but the future is bright.

REFERENCES

1. C Appleby, J Hendricks, J Wurz, C Shudes, C Chang, M Shukla. Digital transformation – From a buzzword to an imperative for health systems. https://www2.deloitte.com/us/en/insights/industry/health-care/digital-transformation-in-healthcare.html
2. Stoumpos AI, Kitsios F, Talias MA. Digital Transformation in Healthcare: Technology Acceptance and Its Applications. Int J Environ Res Public Health 2023;20:3407.
3. Natakusumah K, Maulina E, Muftiadi A, *et al.* Digital transformation of health quality services in the healthcare industry during disruption and society 5.0 era. Front Public Health 2022;10:971486.
4. Püschel A, Schafmayer C, Groß J. Robot-assisted techniques in vascular and endovascular surgery. Langenbecks Arch Surg 2022;407:1789–95.
5. Hull C. Apparatus for Production of Three-dimensional Objects by Stereolithography. US Patent 4,575,330 1986.
6. Tam CHA, Chan YC, Law Y, *et al.* The Role of Three-Dimensional Printing in Contemporary Vascular and Endovascular Surgery: A Systematic Review. Ann Vasc Surg 2018;53:243-4.

1.2 THE REVOLUTION OF THE HYBRID ROOM: SHARED AND INTEGRATED USE OF NEW SPACES AND TECHNOLOGIES

Giovanni Tinelli, Simona Sica, Ottavia Borghese, Tommaso Donati, Antonio Luparelli, Francesca De Nigris, Yamume Tshomba

The hybrid room (HR) is an advanced procedural space dedicated to a few medical and surgical specialties, that combines features of traditional operating surgical theatres with those of image-guided interventional suites. This combination allows for highly complex surgical procedures, adding innovative radiological tasks to traditional surgical skills. The introduction of HRs in medical daily practice also has entailed a monumental shift in understanding and rationalization of workspaces, particularly within the realm of healthcare, where it is progressively gaining a pivotal role in several surgical fields, mainly including cardiac and vascular surgery, neurosurgery, urology, orthopaedics.

As regards vascular surgery, the HR is able to provide a perfect synergy between precision and innovation. By harnessing state-of-the-art imaging modalities such as fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI), surgeons gain unparalleled insights into the complex anatomy and pathology of the vascular system. This real-time visualization enables them to navigate intricate vascular networks with confidence, ensuring precise placement of therapeutic devices and optimal patient outcomes.

The multifunctional nature of the HR extends beyond its imaging capabilities. It provides a collaborative space where interdisciplinary teams of vascular surgeons, interventional radiologists, cardiologists, and support staff can come together to strategize, execute, and monitor complex procedures. This collaborative approach fosters synergy, creativity, and innovation, driving continuous improvement in patient care and surgical outcomes.

At the heart of vascular surgery lies the quest for precision and innovation, both of which are exemplified in the HR. This dynamic environment seamlessly integrates advanced imaging technologies with surgical instrumentation, creating a synergy that enhances procedural accuracy and patient outcomes (Figure 1.2.1).

PLANNING, EQUIPMENT AND LAYOUT

The HR is used by an interdisciplinary team of surgeons, interventional cardiologists, anaesthesiologists, and others and it is good practise to involve all stakeholders deeply into planning and keeping such a facility. Planning of the HR is truly an interdisciplinary task. Clinicians and technicians of all involved disciplines should define their requirements and form a responsible planning team. The concrete planning is refined in several steps by specialized architects, vendors of operating room equipment, and imaging systems in a close feedback loop with the planning team. Virtual visualization of the room, visits of established HRs, and information exchange with experienced users help tremendously during the planning process.

Ideally, the HR is located next to interventional suites and operating rooms to keep logistics simple. However, if the operating rooms are separated from the interventional cath labs it is recommend establishing the HR next to the other operating rooms, because all equipment and personnel (e.g. heart-lung machine and perfusionists) are immediately ready and anaesthesia and intensive care is available.

A HR should be larger than a standard operating room and the basic principle for planning is the larger the better, because not only the imaging equipment ne-

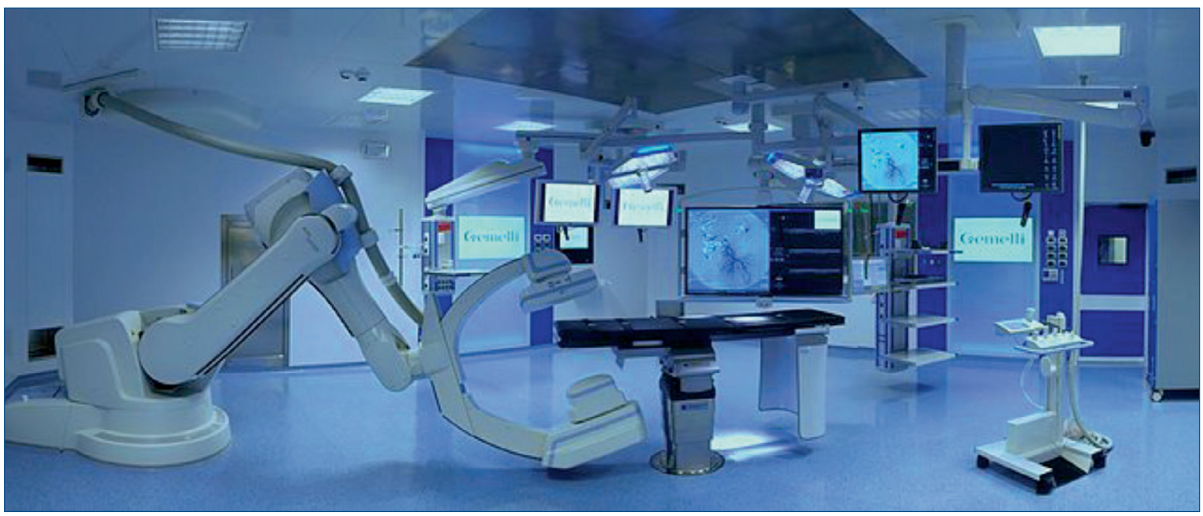


FIGURE 1.2.1 ● Hybrid Room of the Hospital Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy.

eds sufficient space. During hybrid procedures 8 to 20 people are needed in the team including anaesthesiologists, surgeons, nurses, technicians, perfusionists, experts form device companies and so forth. Expert opinions recommend for newly built operating room at least 70 m2. Additional space for a control room and a technical room is mandatory adding up with washing and prep rooms to a total of approximately 150 m2 for the whole area. Rebuilding in terms of lead shielding (2-3 mm) will be needed. Depending on the system it may be necessary to enforce the ceiling or the floor to hold the weight of the stand (approximately 650-1800 kg).[1, 2]

In addition to components of a surgical suite, the following features should be available:[3]

1. high-quality fluoroscopy (generally with flat-panel imaging) in a lead-lined room;
2. integration of other modalities, such as a biplane system, C-arm CT, integrated ultrasound, and electromagnetic navigation systems (optional);
3. a control area for radiologic technicians either inside or outside of the HR with a direct view to the surgical field;
4. a radiolucent, thin, non-metallic carbon fiber operating table that can accommodate both angiography and open operations. It must also be integrated to the imaging system to avoid collisions. Because of a lack of metal parts, some operating table functions are lost, such as isolated movement of upper or lower parts of the patient's body. Nevertheless, a floating tabletop with multidirectional tilt function is needed for accurate catheter manoeuvring;
5. adequate room size (800 square feet [74.3 m^2] to 1000 square feet or more) to accommodate the equipment required by cardiac or vascular surgeons and interventional cardiologists, as well as the anaesthesia team, nursing team, perfusionist, and radiologic technicians. Careful equipment positioning is required to allow fast conversion to conventional surgery if needed;
6. ceiling-mounted monitors placed in positions that allow all team members (surgeons, anaesthesiologists, and interventionists) to visualize the images simultaneously. Images from angiography, echocardiography, and hemodynamic monitoring need to be displayed;
7. circulating heating, ventilation, and laminar air flow to provide a smooth undisturbed air flow suitable for conventional surgical operations;
8. adequate high-output lighting for surgical interventions;
9. other inevitable requirements such as adequate number of power receptacles, gas and suction outlets for both the anaesthesia machine and the cardiopulmonary bypass (CPB) system, and hot and cold water outlets for the CPB;
10. equipment: high-definition displays and monitors, oxygen (O_2) analyser, suction, O_2 supply, defibrillator/resuscitation cart, echocardiographic equipment, sonographers, anaesthesia equipment, CPB equipment, syringe pumps, radiation protection (along with the imaging system), blood warmers and blood bank access, point-of-care laboratory monitoring for blood gases and coagulation parameters, and so on. Because of the life-threatening complications that may be encountered during the procedure, ready-made crash carts consisting of any equipment necessary in an emergency must be available;
11. a complete sterile environment.

MULTIDISCIPLINARY TEAM

One of the key advantages of the HR is its ability to facilitate interdisciplinary collaboration. In addition to its clinical utility, the HR also offers practical advantages in terms of workflow efficiency and resource utilization. By consolidating imaging and surgical capabilities into a single space, hospitals can streamline patient care pathways, reduce procedural delays, and optimize resource allocation (Figure 1.2.2).

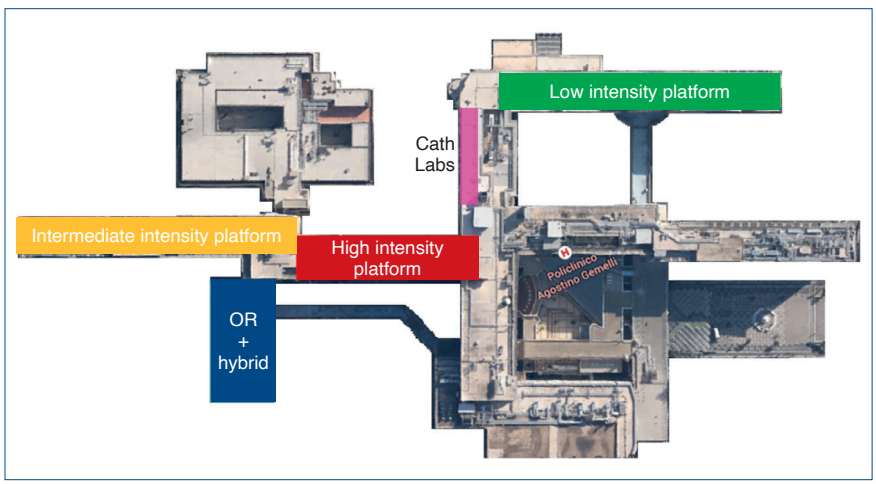


FIGURE 1.2.2 ● Cardiovascular Department of the Hospital Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy. It is divided in three Care Units, where the patient is admitted and assisted according to the level of care needed (high, intermediate, and low). Medical and surgical patients, both pre- and postoperative, are managed by the same specialists. In this way the Cardiovascular Specialists are forced to work together in a multidisciplinary team.

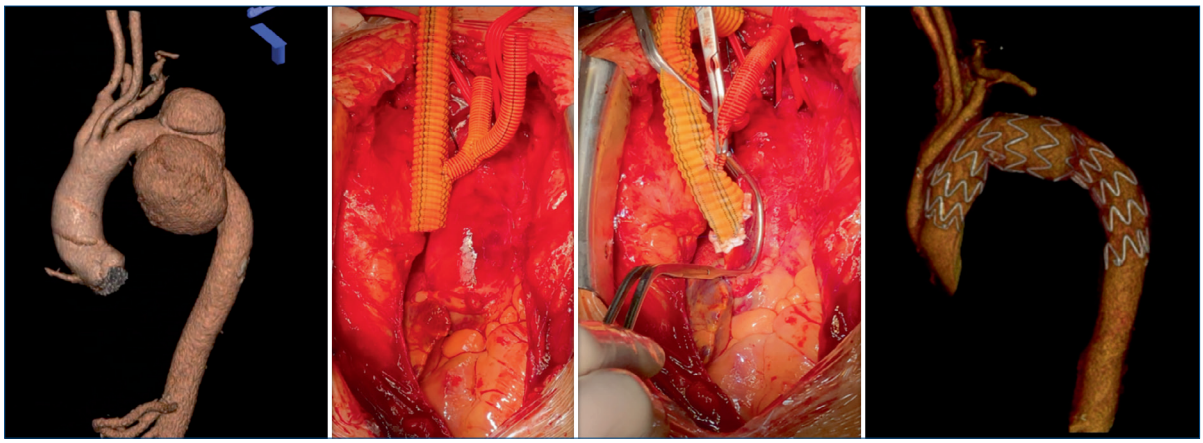


FIGURE 1.2.3 ● Personalized treatment of a giant penetrating aortic ulcer of the aortic arch with total arch debranching and TEVAR in Ishimaru Proximal Landing Zone 0 in the hybrid room setting.

This holistic approach to healthcare delivery enhances patient satisfaction and operational efficiency, ultimately benefiting both patients and healthcare providers. Furthermore, the HR's integrated communication systems enable real-time collaboration and decision-making, ensuring optimal patient care while minimizing procedural risks. Vascular surgeons, cardiac surgeons, anaesthesiologists, interventional radiologists, cardiologists, and other specialists can work together seamlessly, leveraging their respective expertise to develop personalized treatment strategies and optimize patient care.

By providing a centralized platform for multidisciplinary teams to collaborate, the HR enhances efficiency, accuracy, and safety in vascular interventions, ultimately improving patient outcomes and satisfaction.

ADVANCED CARDIOVASCULAR IMAGING

Advanced cardiovascular imaging plays a pivotal role in modern medicine, revolutionizing the diagnosis, treatment, and management of cardiovascular diseases. Through cutting-edge techniques and technologies, it provides clinicians with detailed insights into the structure and function of the aorta and its vessels enabling more accurate diagnosis, personalized treatment plans, and better patient outcomes.

One of the key benefits of advanced cardiovascular imaging is its ability to detect cardiovascular diseases at earlier stages, often before symptoms manifest. This early detection empowers healthcare providers to intervene proactively, potentially preventing the progression of diseases and reducing the risk of complications.

Moreover, advanced cardiovascular imaging techniques allow for a comprehensive assessment of cardiac and aortic function, including measures of cardiovascular anatomy, blood flow dynamics, and tissue characteristics. This holistic approach aids in the precise evaluation of cardiovascular conditions, facilitating the selection of optimal treatment strategies tailored to each patient's unique needs (Figure 1.2.3).

Furthermore, the continuous advancement of cardiovascular imaging technologies has led to improvements in imaging resolution, speed, and safety. In addition to diagnosis and treatment planning, advanced cardiovascular imaging plays a crucial role in guiding interventions. Real-time imaging, like the fusion imaging technique, cone-bone technique, CO_2 DSA, intravascular ultrasound during these procedures, in a HR setting, enhances their safety and efficacy, leading to better outcomes for patients. From the comprehensive characterization of vascular pathology to the precise sizing and deployment of endovascular devices, advanced cardiovascular imaging technologies play a pivotal role in optimizing procedural outcomes and minimizing the risk of complications.[4, 5]

Imaging fusion technique

Fusion imaging is a technique that allows three-dimensional (3D) visualization of intraoperative landmarks by projecting 3D images derived from the preoperative computed tomography (CT) angiography (CTA) scan onto the two-dimensional (2D) intraoperative fluoroscopic image (2D-3D fusion imaging). Registration can be either 2D-3D, which is performed by superimposing the 3D bone model obtained from the CTA onto the bony structures on 2D fluoroscopic images (which requires two perpendicular 2D images), or 3D-3D by superimposing the CTA 3D bone model and aortic calcifications on to a 3D bone model obtained from an on-table cone-beam CT.[4]

Image fusion of aortic 3D volume rendering on live 2D fluoroscopy provides an accurate imaging guidance during endovascular procedures (Figure 1.2.4). As the fused aortic 3D model automatically follows table and detector movements, anatomy centering does not require fluoroscopy. In our experience, before each procedure, a bone and an aortic 3D model are reconstructed from the preoperative CTA on a workstation and then fused with live fluoroscopy. The registration of this 3D preoperative model is performed using bone landmarks visible on two

fluoroscopic orthogonal shots (anterior–posterior and lateral) of the spine. In case of redo aortic procedures, registration of the 3D preoperative model was performed using stent grafts, vascular plugs, coils, or other radio markers from a previous endovascular procedure visible on two fluoroscopic orthogonal shots (anterior–posterior and lateral) of the spine (redo fusion technique)[6] (Figure 1.2.5).

During the procedure, this layout is then used to centre the region of interest and to identify the critical vessels origins. Position of the target vessels is confirmed by a 7 cc contrast-medium injection at 30 cc/s, and if necessary, registration can be refined at any time by the operator. It is reported that this intraoperative guidance by preoperative CTA fusion significantly reduces radiation exposure for both patient and operator during standard and complex EVAR.[7, 8]

Cone-beam computed tomography

Cone-beam computed tomography (CBCT) is an advanced 3D imaging technology that is currently available on state-of-the-art flat panel–based angiography systems. CBCT is a computed tomography-like acquisition performed through rotational angiography. Post-procedural CBCT has recently been proved to be adequate for assessment of incorporated vessel patency and stent-graft integrity.[4]

In our centre, CBCT is performed at the end of complex endovascular procedure to evaluate technical success, defined as successful deployment of the endoluminal graft, absence of a type I or type III endoleak, patent target vessels and endoluminal grafts without significant twist, kinks or obstruction (Figure 1.2.6).

This technique allows immediate treatment and potentially decreases the subsequent need for re-intervention. It may also potentially supplant follow-up CTA in the short-term period, minimizing the amount of radiation and contrast media delivered to the patient. Several studies have reported that endoleaks and kinking were detected intraoperatively with a better sensitivity than with 2D completion angiograms, possibly leading to immediate correction and reduction of early reintervention rate.

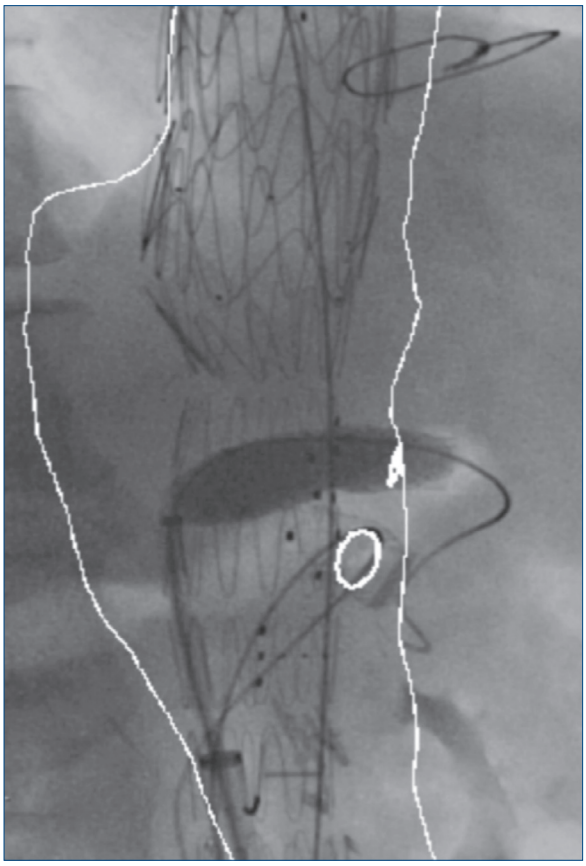


FIGURE 1.2.4 ● Use of fusion Imaging during complex aneurysm endovascular repair.

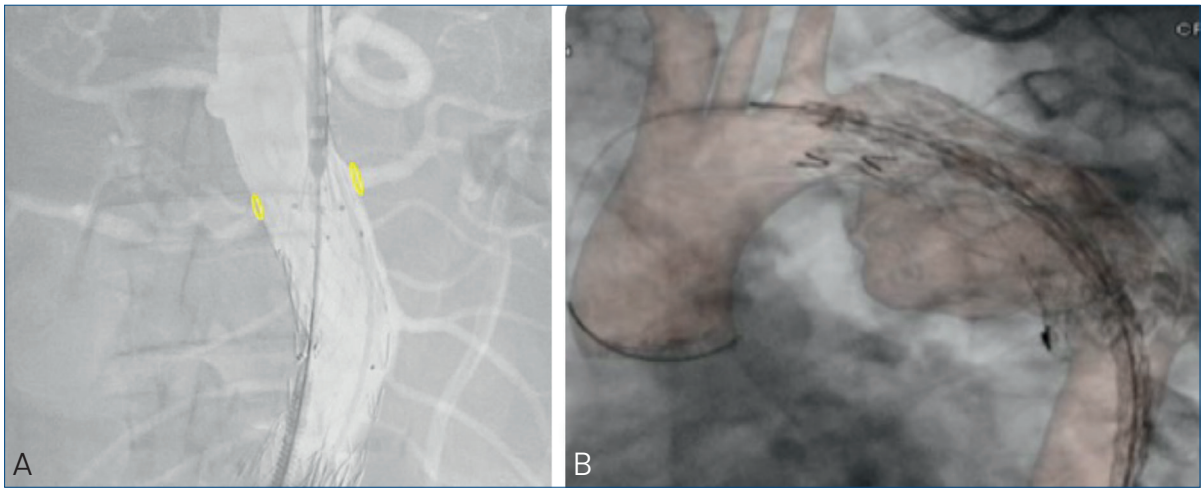


FIGURE 1.2.5 ● Proximal relining for type IA endoleak in a previous EVAR (A) and TEVAR (B) under redo fusion technique. Accuracy of the yellow markers on bilateral renal arteries after shaft device insertion and in the thoracic aorta.

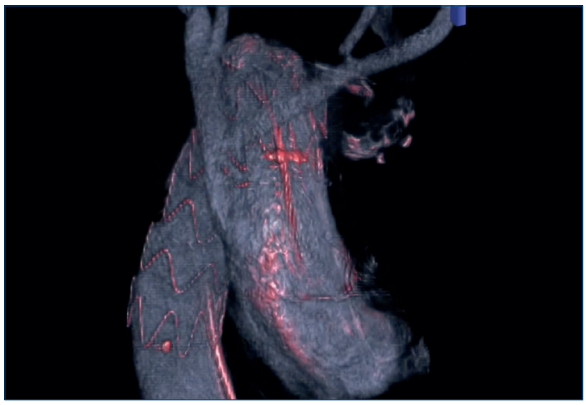


FIGURE 1.2.6 ● A contrast-enhanced cone-beam computed tomography is performed at the end of the procedure to check target vessel patency, stent-graft integrity and absence of endoleaks (3D volume rendering and maximum intensity projection reconstructions of total debranching TEVAR for Kommerel diverticulum in right aortic arch repair).

Intravascular ultrasound

During endovascular procedures, intravascular ultrasound (IVUS) serves as an invaluable adjunct to fluoroscopic guidance, providing real-time visualization of vessel morphology and device deployment. It offers valuable information about plaque morphology, vessel diameter and lesion severity, lumen area, detection of calcium severity and thrombus, detection of dissections, stent apposition and expansion. IVUS uses a piezoelectric transducer generating sound waves after electrical stimulation at the tip of the catheter. Propagation of the waves into different tissues produces a reflection image based on the acoustic properties of each tissue. IVUS catheters sizes range from 2- to 4-French (Fr) and can be easily guided through a 5- or 6-Fr sheath. The larger IVUS catheters come over 0.035-inch guidewires, and the smaller ones that are more often used for infra-inguinal procedures require 0.018-inch or 0.014-inch guidewires. The length of IVUS catheters ranges from 90 to 150 cm.[9, 10]

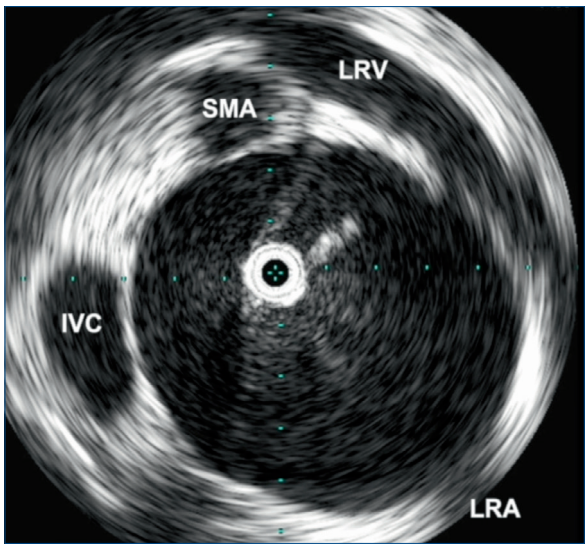


FIGURE 1.2.7 ● Use of IVUS during endovascular repair of thoraco-abdominal aortic dissection, showing the location of superior mesenteric artery (SMA), left renal vein (LRV), left renal artery (LRA), and inferior vena cava (IVC).

By offering cross-sectional images of the vessel lumen and surrounding structures, IVUS enhances procedural accuracy and facilitates optimal device positioning. Furthermore, IVUS-guided assessment of stent expansion and apposition allows for immediate detection of suboptimal results, enabling timely corrective measures to be undertaken. The dynamic feedback provided by IVUS during the procedure empowers clinicians to make informed decisions and refine their approach in real time, thereby optimizing patient outcomes and minimizing procedural complications (Figure 1.2.7).

iFlow

Parametric color coding (PCC) is a developed tool for measuring flow dynamics in a digital sub- traction angiography (DSA) series and can pro- vide quantitative information. In a single image, the quantitative DSA (Q-DSA; software syngo iFLOW; Siemens, Forchheim, Germany) displays objective information on the history of contrast medium through vessels (Figure 1.2.8).[11]

Carbon dioxide

The use of carbon dioxide (CO_2) as a contrast agent in endovascular procedures has emerged as a pivotal innovation, especially for patients with renal insufficiency or allergies to iodinated contrast media. CO_2 is advantageous due to its low viscosity and high solubility, allowing for excellent visualization of vascular structures without the nephrotoxic risks associated with traditional contrast agents. When injected intravascularly, CO_2 rapidly dissolves and is expelled through the lungs, minimizing systemic side effects.

Usually, diagnostic CO_2 angiography is performed in the anteroposterior and 90-degree lateral projections from a 5F angiographic pigtail catheter, positioned in the aorta at the level of the target vessel origin by an automated CO_2 injector. The injection pressure and volume are usually set at 600 mm Hg and 80 to 100 mL, respectively. CO_2 angiography is repeated step by step after the device introduction and during its deployment.[12]

The real-time imaging capability afforded by CO_2 angiography aids in precise catheter navigation and the identification of stenoses or occlusions, ultimately enhancing the safety and efficacy of endovascular interventions. However, careful technique and monitoring are essential to mitigate risks such as air embolism and to ensure optimal imaging outcomes.

Fiber optic real shape

The advent of fiber optic real shape (FORS) technology represents a groundbreaking leap forward in procedural

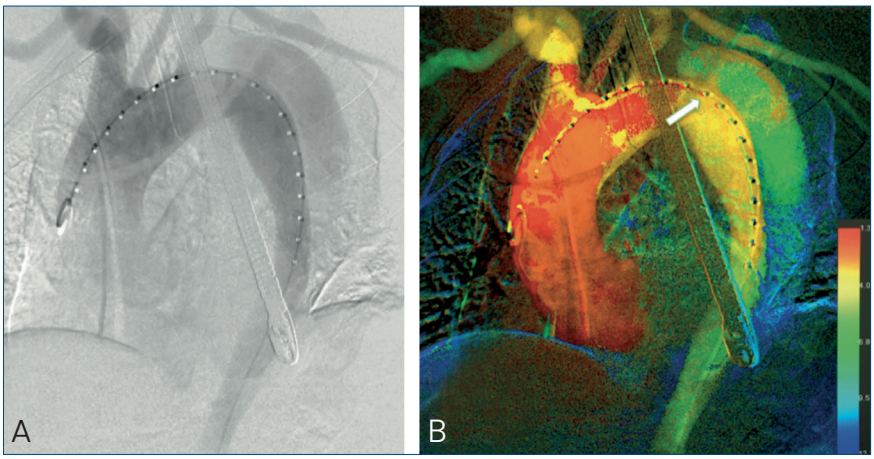


FIGURE 1.2.8 ● Maximum intensity peak of thoracic aorta DSA with the device in pre-deployment position in zone 2 (carotid-subclavian bypass previously): good opacification of distal ascending aorta, entire arch and proximal part of descending thoracic aorta (A). The Q-DSA elaboration shows more details: the proximal ascending aorta, the distal part of descending aorta, the false lumen with the position of the proximal entry tear (white arrow) (B).

precision and efficacy. FORS, a cutting-edge imaging modality, utilizes miniature fiber optic sensors embedded within catheters to provide real-time, three-dimensional visualization of vascular anatomy with unprecedented accuracy and detail. The necessary equipment consists of a desktop workstation, the FORS engine that contains the light source and hardware to generate the reconstruction, and a detachable bedside docking hub to which FORS-enabled devices within the sterile field interface. The initial offering of wires and catheters has been engineered to use a 0.035-inch platform; this may change as additional devices are introduced to the market in the future. Currently, there are three FORS-enabled devices available: an angled hydrophilic guidewire (120-cm length, not back-loadable), a 5.5-F Cobra C2 catheter (80-cm length), and a 5.5-F Berenstein catheter (80-cm length). FORS-enabled devices can be used either alone or in combination with conventional wires, catheters, and sheaths.[13, 14] Pairing with a conventional device, such as a non-FORS–enabled selection catheter, does not impair shape reconstruction of FORS-enabled devices. Current use of FORS guidance in complex aortic interventions has primarily been for navigational tasks. FORS technology presents a new alternative to fluoroscopic guidance in endovascular surgery. It aims to offset the complexity of interventions and reduce dependence on ionizing radiation.

RADIATION EXPOSURE

From rigorous pre-procedural planning encompassing patient-specific radiation dose calculations to the strategic implementation of lead shielding and real-time dose monitoring systems, every facet of the HR's operation must be finely tuned to safeguard both patient welfare and healthcare personnel. As the boundaries of medical technology continue to expand, the imperative to refine radiation safety protocols in the HR remains an enduring pursuit aimed at elevating the standard of care. New imaging systems are equipped with half-dose or low-dose modes to reduce radiation exposure with no impairment of image quality. Use of appropriate collimation allows accurate focus on the area of interest, reduces exposure of surrounding tissues for the patient and scattered radiation for the staff and increases image accuracy. Magnification induces higher exposure, with an increase of the exposure by the square of the magnification factor. To limit the need for magnification, late generation HRs are equipped with high-definition large display monitors that provide large size images without magnification. The pulse mode, opposed to continuous fluoroscopy, is associated with a 90% reduction of produced images. Typical frame rate of 3.75 or 7.5 images/s is sufficient to perform aortic procedures in our daily practice. Moreover, correlating dose rate measurements with the positions of medical staff within the operating room, can significantly reduce the absorbed dose. Implementing real-time dose measurements would greatly enhance this process through continuous monitoring and automatic data recording. Every surgeon and specialist performing endovascular procedures must undergo a dedicated radiation training program.[15, 16]

HYBRID ROOM 3.0

The future of the HR unfolds at the intersection of technological advancement and patient-centric care. As we gaze into the horizon of possibilities, several promising avenues emerge, heralding a new era of transformative potential. Enhanced imaging modalities, such as Artificial Intelligence (AI)-augmented image processing algorithms and three-dimensional volumetric rendering techniques (Figure 1.2.9), promise to revolutionize procedural guidance and anatomical visualization, facilitating greater precision and efficiency in therapeutic interventions.[17] Furthermore, the integration of robotics and telepresence technologies holds the promise of expanding the reach of HR capabilities, enabling remote collaboration and teleproctoring, particularly in underserved regions.

Moreover, the convergence of nanotechnology and targeted drug delivery systems may usher in a new era of

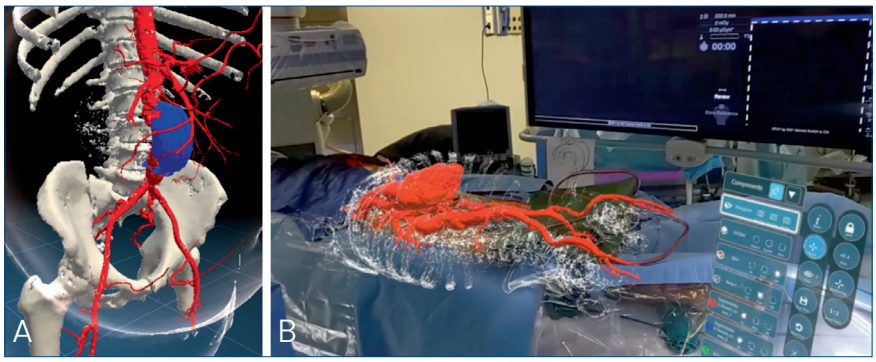


FIGURE 1.2.9 ● Visualization of the hologram with computed tomography reconstruction, and placement of the hologram on the patient lying on the operating table.

theragnostic, where diagnostic imaging and therapeutic interventions are seamlessly integrated within the HR environment. As we embark on this journey of innovation and discovery, the HR stands poised to evolve into a hub of interdisciplinary collaboration, where cutting-edge technologies converge to redefine the boundaries of what is possible in the pursuit of optimal patient outcomes.

CONCLUSIONS

The hybrid operating rooms represents a significant advancement in the field of vascular surgery, particularly during complex procedures.

By integrating advanced imaging, surgical instrumentation, and communication technologies, the HR empowers clinicians to deliver high-quality care with precision, efficiency, and compassion, ultimately improving outcomes and enhancing patient experiences. Providing real-time imaging guidance, facilitating interdisciplinary collaboration, and leveraging cutting-edge technologies, hybrid operating rooms play a vital role in advancing the field of vascular surgery and improving patient outcomes. As technology continues to evolve, the future holds tremendous promise for further enhancing the capabilities and impact of HR settings in vascular interventions. Continued innovation and collaboration will be key drivers of progress in the field of vascular surgery. Using emerging technologies such as robotic-assisted surgery and artificial intelligence, clinicians can further enhance procedural precision, efficiency, and safety, ultimately improving patient outcomes and shaping the future of surgical practice.

By harnessing the full potential of the HR and embracing a culture of continuous learning and improvement, we can revolutionize vascular surgery and pave the goal of advancing patient care and safety.

REFERENCES

1. Nollert G, Wich S. Planning a cardiovascular hybrid operating room: the technical point of view. Heart Surg Forum 2009;12:E125–30.
2. The Cardiovascular Hybrid OR-Clinical & Technical Considerations – published on CTSNet.org
3. Waseem ZA, Joerg KE. Procedures in the Hybrid Operating Room. In: Kaplan JA editor. Kaplan's Essentials of Cardiac Anesthesia (Second Edition); 2018. p. 534–50.
4. Tinelli G, Maurel B, Spear R, *et al*. Endovascular Management of complex aortic aneurysms. Chapter Vascular Surgery: Principles and Practice in Vascular Surgery – 4th Edition.
5. Tinelli G, Bonnet M, Hertault A, *et al*. Impact of Hybrid Operating Rooms on Long-Term Clinical Outcomes Following Fenestrated and Branched Endovascular Aortic Repair. J Endovasc Ther 2021;28:415–24.
6. Minelli F, Sica S, Salman F, *et al*. "Redo" 2D-3D Fusion Technique during Endovascular Redo Aortic Repair. Diagnostics (Basel) 2023;13:635.
7. Maurel B, Hertault A, Sobocinski J, *et al*. Techniques to reduce radiation and contrast volume during EVAR. J Cardiovasc Surg (Torino) 2014;55:123–31.
8. Hertault A, Maurel B, Sobocinski J, *et al*. Impact of hybrid rooms with image fusion on radiation exposure during endovascular aortic repair. Eur J Vasc Endovasc Surg 2014;48:382–90.
9. Kpodonu J, Ramaiah VG, Diethrich EB. Intravascular ultrasound imaging as applied to the aorta: a new tool for the cardiovascular surgeon. Ann Thorac Surg 2008;86:1391–8.
10. Loffroy R, Falvo N, Galland C, *et al*. Intravascular Ultrasound in the Endovascular Treatment of Patients With Peripheral Arterial Disease: Current Role and Future Perspectives. Front Cardiovasc Med 2020;7:551861.
11. Tinelli G, Hertault A, Martin Gonzalez T, *et al*. Evaluation of a new imaging software for aortic endograft planning. Eur Rev Med Pharmacol Sci 2017;21:2717–24.
12. Gallitto E, Faggioli G, Vacirca A, *et al*. The benefit of combined carbon dioxide automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting. J Vasc Surg 2020;72:1906–16.
13. Panuccio G, Torrealba J, Rohlffs F, *et al*. Fiber Optic RealShape (FORS) Technology for Endovascular Navigation in Severe Tortuous Vessels. J Endovasc Ther 2023;30:29–33.
14. Jansen M, Khandige A, Kobeiter H, *et al*. Three dimensional visualisation of endovascular guidewires and catheters based on laser light instead of fluoroscopy with Fiber Optic RealShape technology: preclinical results. Eur J Vasc Endovasc Surg 2020;60:135–43.
15. Hertault A, Rhee R, Antoniou GA, *et al*. Radiation Dose Reduction During EVAR: Results from a Prospective Multicentre Study (The REVAR Study). Eur J Vasc Endovasc Surg 2018;56:426–33.
16. Modarai B, Haulon S, Ainsbury E, *et al*. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Radiation Safety. Eur J Vasc Endovasc Surg 2023;65:171–222.
17. Yunoki J, Hayashi N, Osaki J, *et al*. Endovascular aneurysm repair supported by intraoperative holographic image using virtual reality technology. J Vasc Surg 2024;79:418–9.

1.3 DIGITAL TRANSFORMATION IN TRAINING YOUNG VASCULAR SURGEONS AND RESIDENTS: WEB-BASED DISTANCE EDUCATION, ADVANCED SIMULATION, AND VIRTUAL REALITY TOOLS

Gemmi Sufali, Rodolfo Pini, Stefania Caputo, Antonino Di Leo, Betti Shyti, Andrea Vacirca, Enrico Gallitto, Mauro Gargiulo, Gianluca Faggioli

INTRODUCTION: THE IMPACT OF DIGITAL TRANSFORMATION AND THE COVID-19 PANDEMIC HAVE CHANGED THE VASCULAR SURGERY RESIDENCY PROGRAMS

In the ever-evolving landscape of medical education, as in any other aspect of life, the integration of digital technologies has become imperative, revolutionizing the way aspiring surgeons and residents are trained. In line with this, vascular surgery residency has profoundly changed, enriched by learning experiences and digital instruments that incredibly expand knowledge opportunities. The field of vascular surgery demands a comprehensive understanding of complex anatomical structures, demanding surgical procedures, and evolving endovascular techniques. Traditionally, this knowledge was imparted through didactic lectures, hands-on training, and observation in clinical settings. However, the limitations of these conventional methods were clearly shown during the period of forbidden in-person activities introduced during the COVID-19 pandemic.[1].Due to the restrictions of the pandemic courses, conferences and congresses were canceled, and the training programs were also affected by the reduction of the surgical activities. On the other hand, these difficulties have strongly stimulated the adoption of innovative digital solutions to enhance the educational experience and to bridge the gap between theoretical knowledge and practical application.[2, 3] This chapter explores the recent digital transformation within the training of young vascular surgeons, focusing on web-based distance education, advanced simulation techniques, and the utilization of virtual reality tools.

WEB-BASED DISTANCE EDUCATION AND OTHER TOOLS

Web-based distance education has emerged as a pivotal component in the training curricula, offering accessibility and flexibility to learners irrespective of geographical constraints. Through online platforms and virtual classrooms, aspiring vascular surgeons and residents can engage in interactive lectures, participate in case discussions, and access a vast repository of educational resources curated by experts in the field. Making information and knowledge accessible to everyone fosters continuous learning and facilitates collaboration among peers and mentors on a global scale.

The accessibility and flexibility afforded by web-based platforms ensure inclusivity, transcending barriers of time and space. Additionally, archived recordings enable asynchronous learning, allowing learners to revisit lectures at their convenience and reinforce key concepts at their own pace. Among a variety of digital tools, the most prominent are e-Learning platforms, webinars and live cases, mobile applications, podcasts and social media, technologically advanced simulators and virtual-reality devices. Each of these, offers unique advantages and broadens the boundaries of knowledge.

eLearning platforms

Online eLearning platforms offer structured and interactive educational modules covering a wide range of topics in vascular surgery, from surgical anatomy to diagnostic imaging, from preoperative assessment to best medical therapy, from intraoperative steps of both surgical and endovascular procedures to perioperative care and follow-up. These platforms typically include multimedia content, interactive quizzes, and case-based scenarios thought to facilitate learning while engaging the auditors.

Webinars and live cases

Live or recorded webinars hosted by vascular surgery societies, institutions, and industry partners provide residents with opportunities for real-time engagement, interactive discussions, and expert insights. Webinars may cover every topic, including surgical techniques, emerging technologies, and challenging cases. Live streaming of surgical interventions from the operating rooms permits the sharing of the highest expertise and represents a high-value educational resource. Many recorded live surgeries are also nowadays available and provide a valid source for the study.

Participants are exposed to a diverse array of perspectives and approaches, broadening their clinical acumen and equipping them with the versatility required to tackle complex cases effectively.

Mobile applications

There are various mobile applications specifically designed for vascular surgery, usually providing usually access to anatomy atlases, surgical technique videos, interactive games on case scenarios, and guidelines. These applications allow everyone to study and stay updated conveniently on smartphones and tablets, offering access to a wealth of information at the fingertips.

Social media and podcasts

Social media serves as a powerful tool for vascular surgery residents by facilitating communication and sharing of

experience and information within the vascular community, raising awareness of relevant issues, and also increasing visibility.

Podcasts are usually hosted by experienced vascular surgeons and offer a flexible and alternative way to improve the knowledge of vascular surgery. Podcasts give the opportunity to listen to discussions, interviews with experts, case reviews, and updates on the latest research and advancements in the field. The on-the-go nature of these audio-based educational resources facilitated the popularity of this educational channel in the high-rhythm contemporary world.

"Inter-school specialty lectures"

One notable example within the Italian vascular surgery education landscape is the introduction of the "inter-school specialty lectures" during the COVID-19 pandemic. This innovative approach allows distinguished vascular surgeons from diverse locations to share their expertise to young vascular surgeons and residents across Italy, transcending the limitations of traditional classroom settings.

Through live-streamed sessions, participants gain access to a wealth of specialized knowledge, spanning from basic surgical techniques to emerging trends in vascular surgery. This collaborative model not only enriches the educational experience of the residents, but also fosters a sense of community and camaraderie among learners and mentors alike.

Participants can engage in live interactions, pose questions, and seek clarifications in real-time, fostering an interactive and dynamic learning environment.

The impact of "inter-school specialty lectures" extends beyond the realm of academic enrichment, profoundly influencing the professional development and career trajectories of participants. Exposure to diverse perspectives and innovative approaches ignites a spirit of inquiry and fosters a culture of lifelong learning among aspiring vascular surgeons. Moreover, the networking opportunities facilitated by these sessions pave the way for mentorship, collaboration, and future research endeavors, nurturing the next generation of leaders in vascular surgery.

ADVANCED SIMULATION

Advanced simulation technologies have revolutionized procedural training, providing learners with realistic and immersive experiences in a controlled environment. High-fidelity simulators replicate surgical scenarios with unparalleled accuracy, allowing trainees to refine their technical skills, enhance decision-making abilities, and mitigate errors without compromising patient safety. Moreover, simulation-based training fosters confidence and competence among learners, empowering them to navigate the complexities of vascular surgery with precision and proficiency.

The integration of simulations with virtual reality tools has redefined the boundaries of experiential learning in vascular surgery. By leveraging immersive virtual reality environments, trainees can explore anatomical structures, simulate surgical procedures, and troubleshoot complications in a dynamic and interactive manner. Virtual reality-based training not only enhances spatial awareness and hand-eye coordination but also cultivates a deeper understanding of surgical anatomy and pathology, thereby augmenting the learning curve and proficiency of young vascular surgeons and residents.

Simulation-based curricula in Vascular Surgery

The vascular surgery evolution has seen an increase in endovascular procedures at the expense of traditional surgical ones, accompanied by a simultaneous rise in technical complexity.[4, 5] Endovascular procedures, however, require learning skills that vascular surgeons in training may not fully acquire during their residency. In this scenario, there is a need to introduce alternative learning strategies into the training process that allow vascular surgeons to acquire specific endovascular skills safely and effectively using simulator-based education (SBE).[6] SBE improves the hand-eye coordination, the manipulation of wire, catheters and endoprosthesis, and induces vascular surgery trainees to learn and familiarize with endovascular tools, decision making process and sequence of steps in endovascular procedures.[7] Importantly, SBE allows trainees to practice and to learn from their mistakes without injury real patients.

Driven by the importance of SBE, Nayahangan *et al.*[8] conducted a European general needs assessment to gather consensus across Europe and established vascular surgery technical procedures that should be included in a simulation-based curriculum. Through a three-round modified Delphi method, 34 key opinion leaders from different European countries defined a prioritized list of 30 technical procedures (both surgical and endovascular) that should be included in a simulation-based curriculum.

Vento *et al.*[9] published a paper regarding the effect of EVAR simulations in boosting trainees' learning curve. Vascular surgery residents were randomized into two groups, with the study group allowed to perform more EVAR simulations over a two-week period compared to the control group. After two weeks, the study group significantly reduced the procedural time, the fluoroscopy time and the contrast medium volume used compared to the control group, thus confirming that simulators are a viable and effective option for vascular surgery trainees to improve their skills in EVAR procedures. Similarly, Maertens *et al.*[10] randomized vascular surgery trainees into two groups: the study group (PROSPECT group) with access to the Proficiency based Stepwise Endovascular Curricular Training (PROSPECT) program (consisting of both VRS and e-learning) and the control group with access to the e-learning only. The PROSPECT group performed simulations treating bilateral

iliac artery disease on the ANGIO Mentor simulator. Trainees who completed PROSPECT demonstrated higher technical skills during real life endovascular procedures, thus demonstrating the transferability of simulator-acquired endovascular skills to real life.

Virtual reality simulators

Virtual reality simulators (VRS) allow three-dimensional manipulation of instruments which are viewed on a bi-dimensional screen. The VRS have been widely used to simulate endovascular aortic aneurysm repair (EVAR), carotid artery stenting (CAS) and for the simulated treatment of renal artery stenosis (RAs) and iliac and femoral artery stenosis. The VRS are generally composed by two hardware haptic devices, two screens and a control-console, with some minor differences depending on the specific simulator being considered.

VRS widely reported in the literature are: ANGIO Mentor Dual Slim simulator (3D System/Simbionix, Littelton, CO) and Vascular Intervention System Trainer (VIST) simulator (Mentice AB, Gothenburg, Sweden).

Several studies[11, 12] have analyzed the use of VRS to perform CAS, confirming the high utility of simulators, clearly demonstrated by the improvement of endovascular skills and the reduction of procedure time, fluoroscopy time and contrast medium volume used.

One of the latest developments in endovascular field include the introduction of patient-specific VRS that allows patient specific virtual rehearsal (PsPR), a patient-tailored approach through which trainee can practice and perform real cases on virtual patients just before the real endovascular procedure. The SimbionixPROcedure (Simbionix USA Corp., Cleveland, OH, USA) is a simulation software that convert a patient specific imaging into a simulation giving the possibility to perform the simulation 24 hours before the real operation. Several studies[13, 14] have been published regarding the use of this specific software for PsPR both in cases of CAS and EVAR, and it has emerged that there is a high correspondence between endovascular tools and angiographic projections between the two scenarios. Inexperienced surgeons have reported an improvement in their knowledge and confidence with materials and the endovascular procedure, leading to increased safety in the operating room. However, no correspondence was found in the technical rating between virtual reality and the real setting.[14, 15] The same results were obtained in the treatment of renal artery stenosis by subjecting both a group of medical students and vascular surgery trainees at VRS using the VIST simulator.[15, 16]

3D-modeling and printing

3D-modeling and printing represent a novel technology with huge potential that surgeons and residents can nowadays readily utilize. This technology has been widely known and used in various fields in medicine and surgery, gaining a wider and wider role in trainee's education.[17-19]

The integration of 3D-printing technology into the world of vascular surgery has led to significant improvements in preoperative planning, surgical training, and patient-specific device creation (Figure 1.3.1).

This technology finds utility in different anatomical districts and surgical procedures, as for the femoral access, which is the cornerstone of every endovascular procedure, where the combination of 3D-printing with DUS can contribute to skill development in this area.[20]

It has been studied that use of 3D models increases the understanding of anatomy in aortic diseases.[21] While nowadays most procedures are planned based on computed tomography angiography, 3D-printing can play a role in planning, giving more complete and detailed anatomical details, even though advancements are needed to enhance capability to replicate minor anatomical deformities and variations in tissue density.[22] Moreover, 3D-modeling serves as a valuable adjunct in planning endovascular procedures involving complex anatomies, such as visceral artery aneurysms, by facilitating a deeper understanding of the often-tortuous visceral arterial anatomy.[23]

Expanding from arterial to venous territories, 3D-printing holds promise as a tool to elucidate the hemodynamics of venous diseases.[24]

Looking ahead, 3D-printing can play a pivotal role in aiding vascular surgeons not only in endovascular procedures but also in complex open surgery interventions, including oncovascular surgery. In this field, the utilization

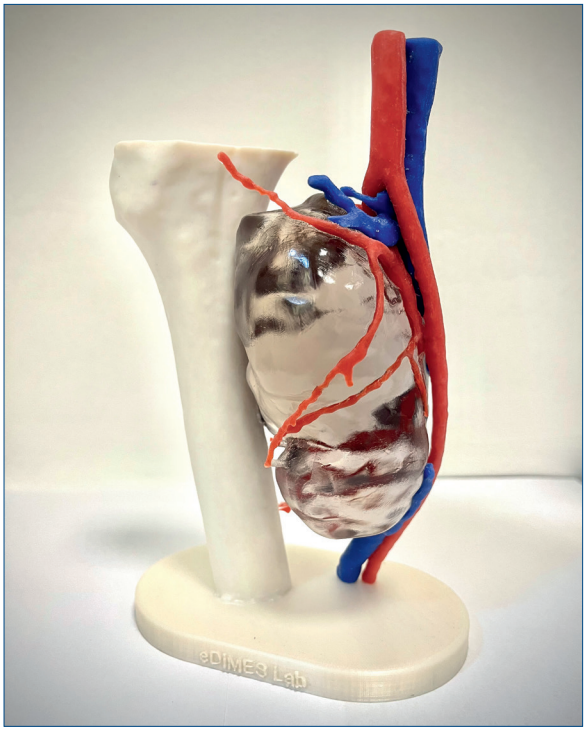


FIGURE 1.3.1 ● 3D-printing technology for preoperative planning of a rhabdomyosarcoma, photo courtesy of DimesLab.

FIGURE 1.3.2 ● Utilization of HoloLens (Microsoft Corporation, Redmont, WA, USA) by a vascular surgery resident (with the permission of the subjects present in the picture).

of 3D-printing and modeling could enhance the comprehension of correlations between vessels and tumor.

In conclusion, this technology is gaining a wider role in vascular surgery training, indeed it is well established that the use of 3D print allows better understanding and mastering of complicated surgery diseases and in particular anatomy and pathophysiology.[25] Additionally, it provides a platform for young vascular surgeons to hone their endovascular techniques and surgical skills in a controlled environment, progressively tackling challenges of escalating difficulty and reducing the risk of errors.[26]

However, challenges such as the additional cost and time associated with current 3D printing technologies, as well as resource availability, must be addressed in the coming years.

Head-mounted displays and smart glasses

Head-mounted displays (HDM) are devices worn like helmets, with a visor consisting of a display through which virtual images are projected.

Smart glasses are devices that allow the projection of information within the person's field of view.[27, 28]

Augmented reality consists of a fusion between the real world and the virtual world in which the subject can move and interact. The possibility of interaction is what differs augmented reality from mere virtual reality.[29-31]

Several devices have been introduced to permit augmented-reality experiences: Google Glass (Google, Mountain View, CA), Meta Glass (Meta Company, San Mateo, CA, USA), HoloLens (Microsoft Corporation, Redmont, WA, USA, shown in Figure 1.3.2), Oculus (Oculus VR, Meno Park, CA, USA), Optinvent (Rennes, France), Vuzix (Vuzix, Rochester, NY, USA), or HTC Vive.

They can be used in teaching surgical techniques for residents by using this HMD and augmented reality in simulation.[27, 30, 32]

The lead surgeon in the operating room can wear the HDM as a pre-set camera that records the operating field, and this footage is projected on a screen outside the operating room, allowing the audience to see exactly what the lead surgeon sees. These devices can be use as well by residents during training sessions with simulator.

In the literature, there is limited data regarding the practical utility of the aforementioned devices, given their recent implementation in clinical practice. However, they can be used in the preoperative planning phase, or in the intraoperative phase.

In vascular surgery, as reported by Taoran Jiang *et al.*,[33] they can be used intraoperatively to identify structures with extreme precision. As shown in their study, utilizing a 3D-printed model of soft tissue with a vascular network inside has allowed for the analysis of how the use of HoloLens enables precise localization of structures, with acceptable static and dynamic errors. This may allow for an increase in the surgical precision and technical success of the procedure, reducing operative times.

By an endovascular means, these devices had been employed in aortic procedures, with reduction of radiations and iodinated contrast medium, thanks to the more precise and easier tridimensional anatomy visualitazion.[34, 35]

The everyday clinical use of these devices is limited by the need for further studies and scientific data before they can be routinely used in the operating room. Additionally, some limitations of these devices include their weight and battery durability.[30, 33]

Although their use in clinical practice requires further data and scientific support, HMDs and smart glasses are certainly advantageous tools in learning both inside and outside the operating room.

CONCLUSIONS AND FUTURE PERSPECTIVES AND CHALLENGES

In recent times, the convergence of digital transformation and the global COVID-19 pandemic has significantly changed vascular surgery residency programs. Particularly, the pandemic gave us the opportunity to realize in a deeper way how innovative technologies can aid and enhance the learning paradigms for aspiring vascular surgeons.

It became evident that the combined-use of web-based distance education, advanced simulation, and virtual reality tools holds immense potential in training vascular residents.

Web-based distance education facilitate the learning process and global collaboration.

Advanced simulation technologies and virtual reality tools provide realist experiences in a controlled environment where the trainees can acquire and refine technical skills as well as enhance decision-making abilities, without any risk for the patients.

By embracing these innovative technologies, educators and institutions can empower learners to excel in an ever-evolving healthcare landscape, ultimately enhancing patient outcomes and advancing the field of vascular surgery.

REFERENCES

1. Faggioli G, Chakfé N, Imray C. Maintaining Safe Elective Aneurysm Surgery in the COVID-19 Era. Eur J Vasc Endovasc Surg 2021;62:675–7.
2. Nickinson ATO, Carey F, Tan K, *et al.* Has the COVID-19 Pandemic Opened Our Eyes to the Potential of Digital Teaching? A Survey of UK Vascular Surgery and Interventional Radiology Trainees. Eur J Vasc Endovasc Surg 2020;60:952–53.
3. Vervoort D, Dearani JA, Starnes VA, *et al.* Brave New World: Virtual conferencing and surgical education in the Coronavirus Disease 2019 era. J Thorac Cardiovasc Surg 2021;161:748–52.
4. Reznick RK, MacRae H. Teaching surgical skills--changes in the wind. N Engl J Med 2006;355:2664–9.
5. Joels CS, Langan EM 3rd, Cull DL, *et al.* Effects of increased vascular surgical specialization on general surgery trainees, practicing surgeons, and the provision of vascular surgical care. J Am Coll Surg 2009;208:692–7, quiz 697.e1; discussion reply 697-9.
6. Bismuth J, Donovan MA, O'Malley MK, *et al.* Incorporating simulation in vascular surgery education. J Vasc Surg 2010;52:1072–80.
7. Aggarwal R, Black SA, Hance JR, *et al.* Virtual reality simulation training can improve inexperienced surgeons' endovascular skills. Eur J Vasc Endovasc Surg 2006;31:588–93.
8. Nayahangan LJ, Van Herzeele I, Konge L, *et al.* Achieving Consensus to Define Curricular Content for Simulation Based Education in Vascular Surgery: A Europe Wide Needs Assessment Initiative. Eur J Vasc Endovasc Surg 2019;58:284–91.
9. Vento V, Cercenelli L, Mascoli C, *et al.* The Role of Simulation in Boosting the Learning Curve in EVAR Procedures. J Surg Educ 2018;75:534–40.
10. Maertens H, Aggarwal R, Moreels N, *et al.* A Proficiency Based Stepwise Endovascular Curricular Training (PROSPECT) Program Enhances Operative Performance in Real Life: A Randomised Controlled Trial. Eur J Vasc Endovasc Surg 2017;54:387–96.
11. Hsu JH, Younan D, Pandalai S, *et al.* Use of computer simulation for determining endovascular skill levels in a carotid stenting model. J Vasc Surg 2004;40:1118–25.
12. Williams EC, MacDonald S, Fox WC, *et al.* A Scoping Review of Simulation-Based Training Paradigms for Carotid Artery Endarterectomy and Carotid Artery Stenting. Ann Vasc Surg 2023;95:271–84.
13. Willaert WI, Aggarwal R, Nestel DF, *et al.* European Virtual Reality Endovascular Research Team, EVEResT. Patient-specific simulation for endovascular procedures: qualitative evaluation of the development process. Int J Med Robot 2010;6:202–10.
14. Desender L, Rancic Z, Aggarwal R, *et al.* EVEREST (European Virtual Reality Endovascular RESearch Team). Patient-specific rehearsal prior to EVAR: a pilot study. Eur J Vasc Endovasc Surg 2013;45:639–47.
15. Van Herzeele I, O'Donoghue KG, Aggarwal R, *et al.* Visuospatial and psychomotor aptitude predicts endovascular performance of inexperienced individuals on a virtual reality simulator. J Vasc Surg 2010;51:1035–42.
16. Van Herzeele I, O'Donoghue KG, Aggarwal R, *et al.* Visuospatial and psychomotor aptitude predicts endovascular performance of inexperienced individuals on a virtual reality simulator. J Vasc Surg 2010;51:1035–42.
17. Biglino G, Capelli C, Koniordou D, *et al.* Use of 3D models of congenital heart disease as an education tool for cardiac nurses. Congenit Heart Dis 2017;12:113–8.
18. Yushkevich PA, Piven J, Hazlett HC, *et al.* User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31:1116–28.
19. O'Brien EK, Wayne DB, Barsness KA, *et al.* Use of 3D Printing for Medical Education Models in Transplantation Medicine: a Critical Review. Curr Transpl Rep 2016;3:109–19.
20. Sheu AY, Laidlaw GL, Fell JC, *et al.* Custom 3-Dimensional Printed Ultrasound-Compatible Vascular Access Models: Training Medical Students for Vascular Access. J Vasc Interv Radiol 2019;30:922–7.
21. Spinelli D, Marconi S, Caruso R, *et al.* 3D printing of aortic models as a teaching tool for improving understanding of aortic disease. J Cardiovasc Surg (Torino) 2019;60:582–8.
22. Bonvini S, Raunig I, Demi L, *et al.* Unsuspected Limitations of 3D Printed Model in Planning of Complex Aortic Aneurysm Endovascular Treatment. Vasc Endovascular Surg 2024 Feb 9:15385744241232186. doi: 10.1177/15385744241232186. Epub ahead of print. PMID: 38335135.
23. Soliński DG, Celer M, Dyś K, *et al.* 3D printing in the endovascular treatment of visceral artery aneurysms. Medicine (Baltimore) 2023;102:e35844.
24. Cervi E, Bissacco D, Ginestra PS. Varicose vein three-dimensional printing model from duplex scan analysis images. J Vasc Surg Venous Lymphat Disord 2023;11:1289–90.
25. Li W, Liu Y, Wang Y, *et al.* Educational value of mixed reality combined with a three-dimensional printed model of aortic disease for vascular surgery in the standardized residency training of surgical residents in China: a case control study. BMC Med Educ 2023;23:812.
26. Foresti R, Fornasari A, Bianchini Massoni C, *et al.* Surgical Medical Education via 3D Bioprinting: Modular System for Endovascular Training. Bioengineering (Basel) 2024;11:197.
27. Starner T. Wearable computing: meeting the challenge. In: Barfield W editor. Fundamentals of Wearable Computers and Augmented Reality. 2nd edition. p.13–30.
28. Lareyre F, Chaudhuri A, Adam C, *et al.* Applications of Head-Mounted Displays and Smart Glasses in Vascular Surgery. Ann Vasc Surg 2021;75:497–512.
29. Cipresso P, Giglioli IAC, Raya MA, *et al.* The Past, Present, and Future of Virtual and Augmented Reality Research: A Network and Cluster Analysis of the Literature. Front Psychol 2018;9:2086.
30. Samant S, Bakhos JJ, Wu W, *et al.* Artificial Intelligence, Computational Simulations, and Extended Reality in Cardiovascular Interventions. JACC Cardiovasc Interv 2023;16:2479–97.
31. Riva G, Wiederhold BK. The New Dawn of Virtual Reality in Health Care: Medical Simulation and Experiential Interface. Stud Health Technol Inform 2015;219:3–6.
32. Yoon JW, Chen RE, Kim EJ, *et al.* Augmented reality for the surgeon: Systematic review. Int J Med Robot 2018;14:e1914.
33. Jiang T, Yu D, Wang Y, *et al.* HoloLens-Based Vascular Localization System: Precision Evaluation Study With a Three-Dimensional Printed Model. J Med Internet Res 2020;22:e16852.
34. Rynio P, Witowski J, Kamiński J, *et al.* Holographically-Guided Endovascular Aneurysm Repair. J Endovasc Ther 2019;26:544–7.
35. García-Vázquez V, von Haxthausen F, Jäckle S, *et al.* Navigation and visualisation with HoloLens in endovascular aortic repair. Innov Surg Sci 2018;3:167–77.

1.4 THE ROLE OF LARGE LANGUAGE MODELS IN DISSEMINATING VASCULAR SCIENTIFIC KNOWLEDGE TO THE GENERAL POPULATION

Walter Dorigo, Claudia Pacciani, Mario D'Oria, Elena Giacomelli, Sara Speziali, Sandro Lepidi, Aaron Thomas Fargion, Raffaele Pulli

INTRODUCTION TO LARGE LANGUAGE MODELS

Large Language Models (LLMs) are sophisticated neural network architectures that have been trained on vast amounts of text data to understand and generate human-like language.

LLMs are designed to comprehend and generate text in a way that closely resembles human communication and they can perform a wide range of language-related tasks, such as language translation, text summarization, question answering, sentiment analysis, and more. LLMs have significantly improved the capabilities of AI systems to understand and generate natural language, enabling them to handle increasingly complex tasks with remarkable accuracy. Overall, large language models represent a groundbreaking achievement in AI, offering previously unknown tools for understanding and generating human-like language.[1]

However, while LLMs have tangible and remarkable capabilities, they also come with challenges and ethical considerations. Concerns regarding biases in training data, potential misuse for spreading misinformation or generating harmful content are areas of ongoing research and debate.[2]

APPLICATION OF LLM TO THE HEALTHCARE

In recent years, the integration of LLMs into the healthcare and medical domains has generated considerable interest. These advanced language models hold great potential to revolutionize various aspects of medical practice, research, and education.

One of the primary advantages of LLMs is their versatility and applicability in completing different medical tasks. From assisting in clinical and laboratory diagnosis to aiding medical professionals in staying updated with the latest developments in their fields, LLMs' potential applications are vast. Moreover, they can speed the research process by helping identify potential research topics, generating research articles and writing cover letters for scientific papers.[3]

However, with these advantages come significant limitations and ethical considerations. Concerns about accuracy, plagiarism, and biases in AI-generated content raise important questions about the use of LLMs in medical writing. Moreover, the issue of authorship in research papers generated with the assistance of LLMs adds another layer of complexity, necessitating clear guidelines and transparency.

The role of LLMs can extend beyond professional settings to patient care. For example, LLMs are capable of generating virtual assistants that can help patients manage their health by providing automated summaries of interactions, medication reminders, and information about diagnoses and treatments.[4, 5] As an example, Zaretsky *et al.*[6] recently demonstrated that LLMs can be used to translate discharge summaries into patient-friendly language and formats that are significantly more readable and understandable than discharge summaries as they appear in electronic health records. However, those summaries required improvements in accuracy, completeness, and safety and, given the safety concerns, initial implementation will require physician review.

LLM AND VASCULAR SURGERY

In the field of vascular surgery, LLMs could help patients face the task of navigating through a vast pool of resources to understand their condition and treatment options. However, the quality and reliability of this information can vary significantly, making it a crucial focal point to ensure access to high-quality educational material to facilitate the comprehension of medical conditions and their implication in order to ease the patient's decision-making process.

For what concerns vascular surgery, research exploring AI's potential applications has focused on diagnostics, risk stratification, and outcome prediction. However, little attention has been given to AI's role in patient health information acquisition, highlighting a gap in the literature. Supplementary materials, such as patient information leaflets and educational videos, have traditionally been used to educate patients. However, the quality of information available online has been questioned, with studies revealing poor readability and reliability. As LLMs claim to present information in a readable and conversational manner, their potential in educating vascular surgery patients still has to be tested. In the literature, studies comparing AI-generated responses to human-written patient information leaflets, found notable differences in readability and quality. AI-generated responses scored lower across various readability metrics and were deemed inferior in quality compared to information leaflets, so despite AI's potential, its current limitations suggest that direct clinician contribution remains crucial in patient education.

In fact, whereas many individuals already trust LLMs for accurate information in healthcare, where reliability is crucial, the same innovative and revolutionary tool can be deleterious if used improperly, and users must be aware of the possibility of encountering inaccurate information. Recently, Melissano *et al.*[7] reported a pilot study involving a web-based community with particular

interest in aortic disease, whose members interrogated the LLMs with questions that an aortic patient, seeking information on the disease, might ask and found that more of 50% of the answers were inaccurate and that, in several cases, the exact same question led to an array of different replies. Moreover, Haidar *et al.*[8] pointed out substantial unreliability and inaccuracy of ChatGPT-generated summaries of information documents created by the United Kingdom's Vascular Society and reserved for patients with vascular disease of surgical interest and confirmed the primary role of vascular physicians in developing the empowerment and the engagement of patients with diseases requiring vascular interventions. Vascular surgeons should not be directing patients to AI LLMs for further information. patient information from reputable professional bodies should remain the standard for supplementary patient education. These limits could be potentially overcome by the use of new versions of LLMs; nowadays GPT-4 is disposable online at a monthly cost ranging between 20 and 25 USD (whereas the basic version 3.5 is available online for free) and it has been reported to outperform the previous version "to create increasingly sophisticated and capable language models".[9] Recently, Javidan *et al.*[10] explored the capability of GPT-4 to answer to a set of 40 questions spanning 4 domains of vascular surgery (carotid artery disease, visceral artery aneurysms, abdominal aortic aneurysms, chronic limb-threatening ischemia) generated by clinical experts. They found that ChatGPT-4 significantly outperformed ChatGPT-3.5 by providing appropriate recommendations in 38 of 40 questions (95%) as compared with 13 of 40 (32.5%) by ChatGPT-3.5, despite longer response lengths.

LLM AND DISSEMINATION OF VASCULAR SCIENTIFIC PAPERS

With the growing interest of the world's population in learning about news, novelties and technological advances in the world of medicine and health, the ability to make complex scientific research clear and accessible becomes increasingly important.[11] The European Union, for example, specifically requires that all randomized controlled trials (RCTs) be accompanied by a layperson's summary.[12] Although there are numerous pointers and strategies for making the summary simple, clear, readable, and understandable by an extremely large and diverse audience,[13] recent studies show that layperson's summaries may not meet the recommended reading level for medical literature.[14]

LLMs have been proposed as a tool to generate summaries from scientific papers. Eppler *et al.*[15] demonstrated excellent results in creating layperson summaries from abstracts of leading urological scientific journals, and Kuckelman *et al.*[16] showed that AI was effective in generating patient-friendly summaries of radiology reports. On the other hand, Hwang *et al.*[17] showed that AI-generated summaries of abstracts from RCTs of various specialties, even if more readable than the originals, had significantly lower quality. As previously stated, there is a lack of studies in the literature concerning the capability of chatbots in making more accessible the results of scientific papers in the field of vascular surgery. One must consider that, due to its high clinical and technical complexity, the readability of the scientific literature in the field of vascular surgery is generally low, even in those parts, such as the abstract, that are often the only part of the research to be read and to be easily accessible during web searches. Whereas an improvement of readability and clarity of the scientific text can be expected following the implementation provided by the LLMs, they could lack in the consistency and accuracy with respect to the original scientific findings, differently from what reported in other specialties.[1] This discrepancy indicates potential specialty-dependent inconsistencies in the quality of data used to inform answers. It is our opinion that AI should be used cautiously in disseminating the results of complex scientific research, which is not easily interpretable and may involve advanced technologies not commonly understood by the general population. As previously described, it is plausible that the use of such tools could be very useful in making simple, generic content accessible, which generally regards the promotion and preservation of health in the population, while, when dealing with the large-scale diffusion of high-specialized scientific studies, they still should be evaluated and improved by expert physicians and researchers. For such reasons, an attitude characterized by substantial interest in this new technology, combined, however, with a high degree of caution and scientific rigor, is in our view even more necessary at a time in history when, in the literature, papers are beginning to appear comparing the role of humans versus AI in the writing of cover letters and more or less extensive portions of clinical notes and research papers.[18, 19] The large-scale diffusion of AI in the health care world will inevitably tend to shift the "ethical dilemma"[20] of its use from how to preserve "academic integrity" to the need to protect the citizen and patient from receiving inaccurate, often misleading, sometimes dangerous information.

PILOT STUDY

Two academic vascular centers were involved in a preliminary study to assess the efficacy of ChatGPT 3.5 in generating readable and accurate layperson's summaries from abstracts of vascular surgery studies.

We collected the articles published in four leading vascular surgery journals from October 2023 to December 2023. Editorials, Commentaries, Letters to Editor, Case reports and Short presentations, Special Communications, Image articles and Historical articles were excluded from the selection. The abstracts of the selected papers were then exported into a Microsoft Excel database.

To convert an original scientific abstract input into a ChatGPT-generated layperson's summary, we followed the method reported by Eppler *et al.* (Box 1.4.1).[15] We then transferred the layperson's summary output gene-

Box 1.4.1 ChatGPT prompt used to write layperson's summaries from vascular scientific papers.

ChatGPT prompt

Translate the preceding abstract into a layperson summary that is understandable by or below a sixth-grade level, incorporating the following elements if available:

- *Population of subjects/participants*
- *Aim of the study*
- *Results of the study*
- *Comments on outcome(s) of the study*
- *Conclusion supported by the findings*
- *Indication if follow-up studies are foreseen*

Moreover, the summary should adhere to the subsequent guidelines:

- *Mean sentence length less than 20 words*
- *Proportion of passive verbs <10%*
- *Spell out any acronym*

For any mention of medication, treatment, health-related outcome, or anything else medically related that the general public or patient might not understand, please explain it, put it in context, and/or define it.

rated by ChatGPT into the database. All measures of readability and grade-level assessments (RRGLIs) were automatically computed using the Web FX tool, as conducted previously.[8,15] This online platform provides evaluations such as the Global Readability Score (GS), Flesch Reading Ease, Flesch-Kincaid Grade Level, Gunning Fog Score (GFS), Smog Index (SI), Coleman-Liau Index (CLI), and Automated Readability Index (ARI), which are widely recognized metrics. While a higher score indicates easier readability for GS and the Flesch-Kincaid Reading Ease, the other indices correlate a lower score with easier readability.[21] Two vascular surgeons (MD and EG) belonging to two different academic hospitals, with >10 year academic experience, independently reviewed a randomized selection (15%) of ChatGPT-generated summaries for clarity and correctness. They used a five-point Likert scale to rate the summary in comparison to the original abstract. The score rated from 1 (completely inaccurate) to 5 (completely accurate). A mean score ≥4 was considered as the cut-off to define the layperson's summary accurate and complete. The analysis compared the readability scores of original abstracts with ChatGPT-generated layperson's summaries, using a t-test. Interrater reliability for evaluating accuracy and clarity of the summaries was measured with Cohen's k. Scores were presented as means with standard deviations. A sub-analysis categorized abstracts by topic. All analyses used SPSS software with a significance level of <0.05.

One-hundred and fifty papers were included in the database, 69 (46%) from the Journal of Vascular Surgery, 36 (24%) from the European Journal of Vascular and Endovascular Surgery, 26 (17%) form the Journal of Endovascular Therapy and 19 (13%) from the Journal of Vascular Surgery Venous and Lymphatics Disorders. Sixteen articles were reviews with or without meta-analysis, whereas two articles were subgroup analysis from previously published RCTs. We did not find any article with a patient summary. In Table 1.4.I we reported the topics of the articles. The mean time for ChatGPT to generate the layperson's summary was 7.5 seconds (SD 1.3 seconds). The cumulative analysis of all 150 abstracts showed a statistically significant difference for the majority of RR-GLIs between the ChatGPT-generated layperson's summaries and the original abstracts (Table 1.4.II), with a significant improvement of readability and grade level parameters among ChatGPT-generated summaries. The results remained the same when analyzing the readability scores on the basis of

Table 1.4.I ● Topics and characteristics of the included abstracts.

Topic	N. (%)	Review	Randomized controlled trial
Cerebrovascular disease	9 (6)		
Thoracic aorta disease	23 (15)	4	
Abdominal aortic aneurysm	38 (25)	2	
Peripheral artery obstructive disease	38 (25)	3	1
Venous and lymphatic disease	26 (17.5)	5	1
Visceral artery disease	4 (3)	1	
Vascular access for hemodialysis	5 (3.5)		
Others	7 (5)	1	

Table 1.4.II ● Readability scores of both original abstracts and ChatGPT-generated layperson's summaries.

Readability index	Original abstract (mean, SD)	ChatGPT summary (mean, SD)	P
Global score	36.6 (13.8)	50.5 (11.1)	<0.001
Flesch Reading Ease	36.6 (13.8)	50.5 (11.1)	<0.001
Flesch-Kincaid Grade Level	11.7 (2.8)	10.9 (1.9)	0.01
Gunning Fog Score	14.5 (2.9)	13.7 (2.4)	0.01
Smog Index	10.6 (2.1)	9.8 (1.8)	0.003
Coleman-Liau Index	13.7 (2.7)	13.7 (1.8)	0.8
Automated Readability Index	9.3 (3.8)	11.8 (2.1)	<0.001

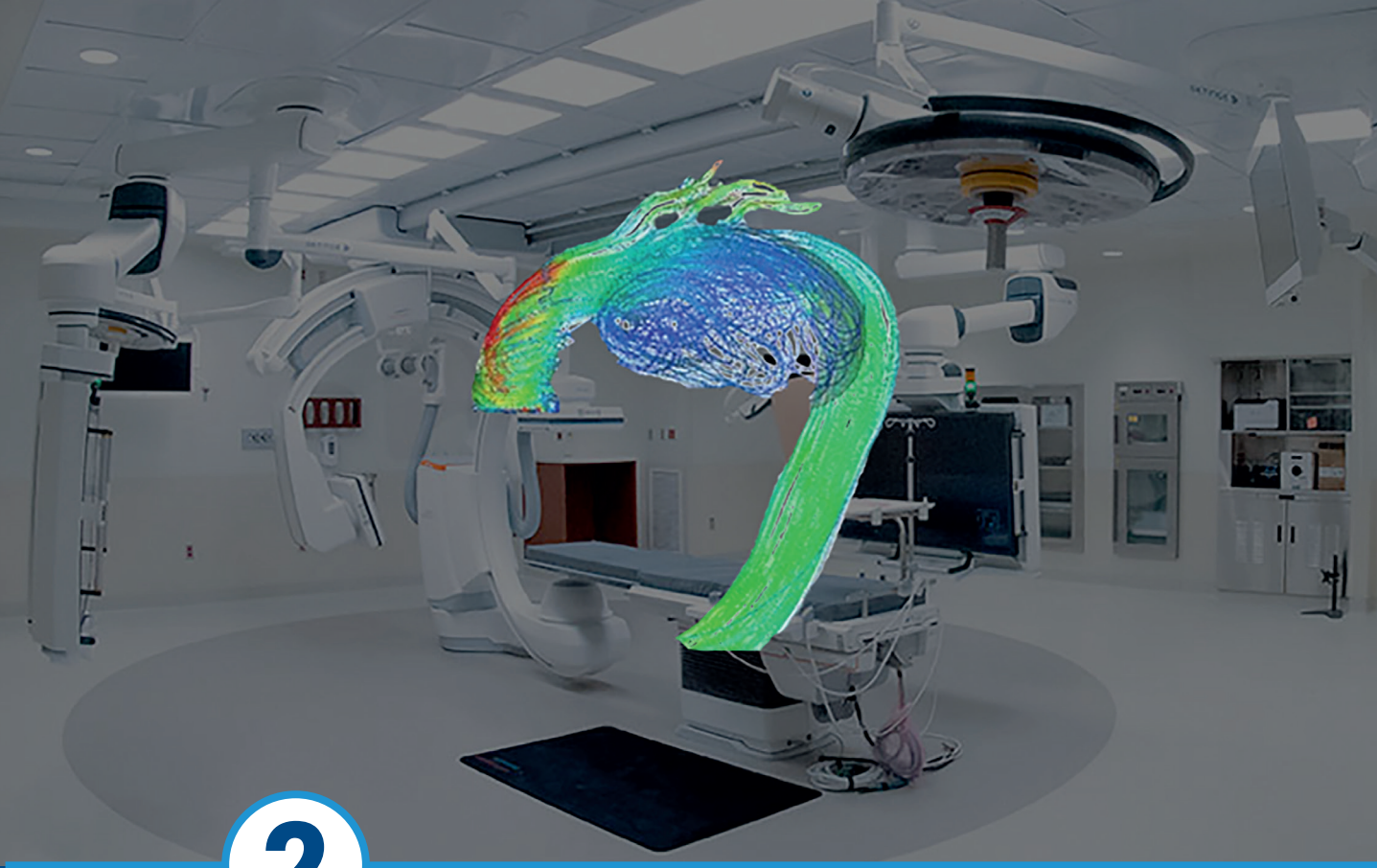
the topic of the abstract, except for papers dealing with cerebrovascular disease, where, in spite of a mild improvement of the GS for the ChatGPT-generated summaries, we found a slight impairment of all other indicators of readability and grade level parameters in comparison with the original abstract. There weren't significant differences with respect to the outcomes in the whole study group when dividing the abstract and the layperson's summary on the basis of the journal of publication. There were significant inter-observer differences in the evaluation of the correctness and clarity of the selected generated output. The layperson's summaries were rated correct in 100% of the cases by a physician, whereas the other physician found them not correct (score <4) in 32% of the cases. The mean rates for the whole summary were 4 (SD 0.5) and 4.7 (SE 0.3), without any inter-observer agreement (k value=-0.1). When separately analyzing the rating of the sections of the layperson's summaries, there was a mild agreement only when the Introduction section was considered

CONCLUSIONS

LLMs are a useful tool for creating readable, patients-friendly layperson's summaries from abstracts of scientific papers in the field of vascular surgery, improving their readability and RRGLIs. However, scientific vascular studies are intrinsically difficult and complex and the readability of AI-generated summaries is still intermediate, demonstrating the difficulty of AI to generate texts easy to read and to understand. Moreover, the level of accuracy, clarity and quality of the AI-generated summaries is still controversial, in our opinion making the intermediary role exercised by the physician between computer outcome and patient still fundamental. While the potential of LLMs in healthcare is promising, several challenges need to be addressed, including ensuring patient privacy and data security, mitigating biases in data and algorithms, validating model performance in clinical settings, and integrating LLMs seamlessly into existing scientific evidences. Collaboration between AI researchers, healthcare professionals, academic institutions, regulatory bodies, and technology developers is essential to harness the full potential of LLMs while addressing these challenges and ensuring their responsible and ethical deployment in healthcare settings.

REFERENCES

1. Dave T, Athaluri SA, Singh S. ChatGPT in medicine: an overview of its applications, advantages, limitations, future prospects, and ethical considerations. Front Artif Intell 2023;6:1169595.
2. Kitamura FC. ChatGPT Is Shaping the Future of Medical Writing But Still Requires Human Judgment. Radiology 2023;307:e230171.
3. Raghu Subramanian C, Yang DA, Khanna R. Enhancing Health Care Communication With Large Language Models-The Role, Challenges, and Future Directions. JAMA Netw Open 2024;7:e240347.
4. Mondal H, Dash I, Mondal S, *et al.* ChatGPT in Answering Queries Related to Lifestyle-Related Diseases and Disorders. Cureus 2023;15:e48296.
5. Dhar S, Kothari D, Vasquez M, *et al.* The utility and accuracy of ChatGPT in providing post-operative instructions following tonsillectomy: A pilot study. Int J Pediatr Otorhinolaryngol 2024, Epub ahead of print.
6. Zaretsky J, Kim JM, Baskharoun S, *et al.* Generative Artificial Intelligence to Transform Inpatient Discharge Summaries to Patient-Friendly Language and Format. JAMA Netw Open 2024;7:e240357.
7. Melissano G, Tinelli G, Soderlund T. Current Artificial Intelligence Based Chatbots May Produce Inaccurate and Potentially Harmful Information for Patients With Aortic Disease. Eur J Vasc Endovasc Surg 2024;67:683–4.
8. Haidar O, Jaques A, McCaughran PW, Metcalfe MJ. AI-Generated Information for Vascular Patients: Assessing the Standard of Procedure-Specific Information Provided by the ChatGPT AI-Language Model. Cureus 2023;15:e49764.
9. Bhattacharya K, Bhattacharya AS, Bhattacharya N, *et al.* ChatGPT in Surgical Practice–a New Kid on the Block. Indian J Surg 2023;85:1346–9.
10. Javidan AP, Feridooni T, Gordon L, *et al.* Evaluating the progression of artificial intelligence and large language models in medicine through comparative analysis of ChatGPT-3.5 and ChatGPT-4 in generating vascular surgery recommendations. JVS-Vascular Insights 2024;2:100049.
11. Maurer M, Siegel JE, Firminger KB, *et al.* Lessons Learned from Developing Plain Language Summaries of Research Studies. Health Lit Res Pract 2021;5:e155-e161.
12. European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC Text With EEA Relevance. https://eur-lex.europa.eu/legal- content/EN/TXT/?uri5celex-%3A32014R0536
13. Good Lay Summary Practice. 2023. https://health.ec.europa.eu/system/files/2021-10/glsp_en_0.pdf
14. Shiely F, Daly A. Trial lay summaries were not fit for purpose. J Clin Epidemiol 2023;156:105–12.
15. Eppler MB, Ganjavi C, Knudsen JE, *et al.* Bridging the Gap Between Urological Research and Patient Understanding: The Role of Large Language Models in Automated Generation of Layperson's Summaries. Urol Pract 2023;10:436–43.
16. Kuckelman IJ, Wetley K, Yi PH, *et al.* Translating musculoskeletal radiology reports into patient-friendly summaries using ChatGPT-4. Skeletal Radiol 2024;53:1621–4.
17. Hwang T, Aggarwal N, Khan PZ, *et al.* Can ChatGPT assist authors with abstract writing in medical journals? Evaluating the quality of scientific abstracts generated by ChatGPT and original abstracts. PLoS One 2024;19:e0297701.
18. Deveci CD, Baker JJ, Sikander B, *et al.* A comparison of cover letters written by ChatGPT-4 or humans. Dan Med J 2023;70:A06230412.
19. Sikander B, Baker JJ, Deveci CD, *et al.* ChatGPT-4 and Human Researchers Are Equal in Writing Scientific Introduction Sections: A Blinded, Randomized, Non-inferiority Controlled Study. Cureus 2023;15:e49019.
20. Miao J, Thongprayoon C, Suppadungsuk S, *et al.* Ethical Dilemmas in Using AI for Academic Writing and an Example Framework for Peer Review in Nephrology Academia: A Narrative Review. Clin Pract 2023;14:89–105.
21. https://www.webfx.com/tools/read-able/



2

TECHNOLOGY BOOSTED DIAGNOSIS AND ADVANCED PROCEDURAL PLANNING IN ENDOVASCULAR SURGERY

2.1 ROBOT-MEDIATED VASCULAR ULTRASOUND IMAGING: A PROMISING TECHNOLOGY FOR VASCULAR DIAGNOSIS AND SCREENING PROGRAMS

Paolo Zamboni, Giulia Baldazzi, Anselmo Pagani, Alessandro Bertagnon, Saverio Farsoni, Marcello Bonfè

SUSTAINABILITY OF NATIONAL HEALTH SYSTEM IN ITALY

The Italian National Health System (NHS) is currently in crisis due to a reduction in the number of doctors and health workers, very high management costs, long waiting lists for the execution of exams and a lack of effective vascular screening programs.

Since the 2010's, the major national and international institutions underlined the sweeping changes among the health care systems; the European Union (EU) Commission, for example, established a process to help state members to provide modern, responsive and sustainable health systems in 2011.[1] In Italy, in order to face the financial difficulties of the NHS, between 2019 and 2024, a constant annual increase of 2 billion euros was allocated. Nevertheless, as underlined by the journal "Il Sole 24 ore" in December 2023, the healthcare spending borne by Italian citizens has continued to rise, from 28.13 billion in 2016 to 40.26 billion in 2022;[2] considering instead expenses for health cares in private institution, spending increased from 22,815.4 million to 26,243.2 million euros in 2022 with a corresponding average annual growth was 1.6%.[3]

For these reasons, a sustainable health system must include very strong technological innovation that can ideally lead to employing fewer staff, reducing costs and possibly improving the efficiency of the system.

In the vascular field, the most supportive screening tool in vascular diagnostics is Doppler ultrasonography (DUS): it is a non-invasive, repeatable exam and it has been recommended as the first line tool for diagnosis and screening for many vascular diseases; however, its operator dependency represents the chink in its armor.[4]

At the moment, the main obstacles for the Italian NHS are represented by a very high demand for services due to the aging population,[5] the spread of metabolic diseases and the lack of financial public resources and trained operators. Intervening in good time means that the surgeon may be employed in open surgical or endovascular treatments most of the time, reserving screening activities for other figures.

Unfortunately, the figure of the sonographer does not exist in our country and angiology is a dying specialty in the European continent. For this reason, taking into account the recent advances in the field of robotics and Artificial Intelligence (AI) and sharing the statement of a recent article published by the American Heart Association (AHA) "Artificial Intelligence may provide clinical and mechanistic insights, address bias in clinical studies, and facilitate education and implementation science to improve cardiovascular and stroke outcomes"[6] we thought that an anthropomorphic arm would be able to perform screening vascular ultrasound examinations.

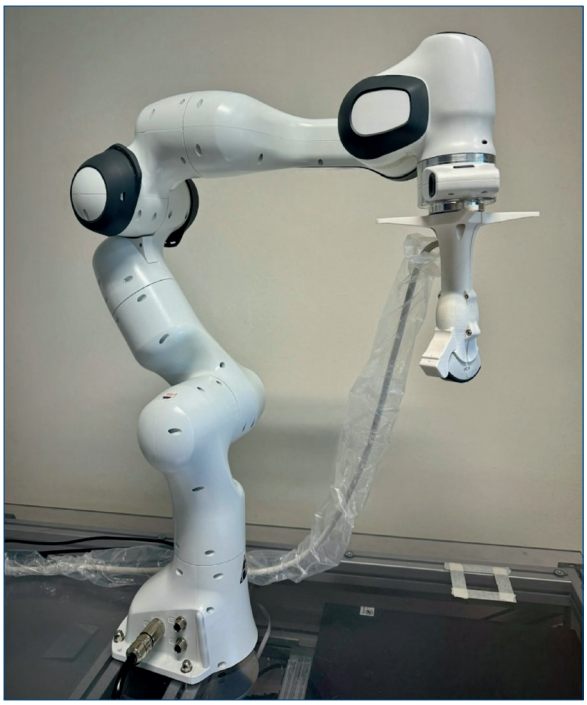


FIGURE 2.1.1 ● Collaborative anthropomorphic robot at 7 axis holding a probe by the means of a 3D printed mount.

To this end, we set up an interdisciplinary team at University of Ferrara composed of vascular surgeons and robotic, automation and computer engineers and computer scientist with expertise in both artificial intelligence and robotics, in order to develop a fully automated vascular screening project (Figure 2.1.1).

NON-OPERATOR DEPENDENT DOPPLER VASCULAR ULTRASOUND

It is well known that operator-dependence remains the biggest stumbling block in ultrasound systems.

For this reason, in the context of this research, we chose to develop a robot with an anthropomorphic arm feature that can be adapted to any ultrasound probe or instrumentation currently on the market, effectively avoiding additional costs related to instrument acquisition. Moreover, we decided to train the robot and artificial intelligence to measure quantitative parameters with well-studied and known cut-offs.

From this point of view, the first model we took inspiration from was the measurement of the diameter of

the abdominal aorta, thinking of a screening program using one of the parameters most easily collected by ultrasound.

Similarly, other values can be measured with Doppler imaging: peak velocity, the sequence of jugular pulse areas or even simple positive/negative tests such as the Compression UltraSound (CUS) maneuver in the diagnosis of deep vein thrombosis.

The aim is to lead the robot and the artificial intelligence to anatomically recognize a vascular structure and measure a single screening parameter which becomes decisive in discarding or selecting a patient for further investigations, without involving the presence of the specialist physician.

The advantage of machine employment is that all these measurements have considerable reproducibility; instead, even a well-trained human operator does not always measure the parameter unequivocally, so there are shortcomings, albeit bearable, in terms of inter- and intra-operator assessment.

Robotics and artificial intelligence, as we will develop later, have a further advantage: the unambiguous methodology in measuring the parameter of interest and the continuous refinement and learning, otherwise known as machine learning, that leads the machine to improve its performance, which appears to be superior to human training.[7]

THE MODEL OF ABDOMINAL AORTA DIAMETER ULTRASOUND ROBOTIC ASSESSMENT

Our team started its research by focusing its interest on measurement of the abdominal aorta (Figure 2.1.2): the abdominal aorta aneurysms (AAA) is defined as a permanent localized dilatation or widening of the aorta in its abdominal tract with an increase of 50% of its expected normal diameter; in clinical practice a fixed threshold diameter of 30 mm or more is used (Figure 2.1.3).

The AAA represents a devastating pathology with a high mortality rate in case of rupture.)

It must be said that all systematic screening programs in this field have failed: while we know that the pathology of abdominal aortic aneurysm increases epidemiologically from the age of 65, it is not certain that individuals who were negative at 65 years of age cannot be positive in subsequent years; thus, forcing the patient to undergo continuous follow-up, the number of examinations required for monitoring the general population is high.

Furthermore, the optimal age of screening at which most lives are saved, and which is cost beneficial has not been assessed formally and with the increasing life expectancy in Europe, screening at older ages might be of benefit.[4]

An undeniable advantage of robotic screening is the tirelessness of the machine, which can thus work much harder than a specialist doctor with easily predictable scheduling of the number of patients.

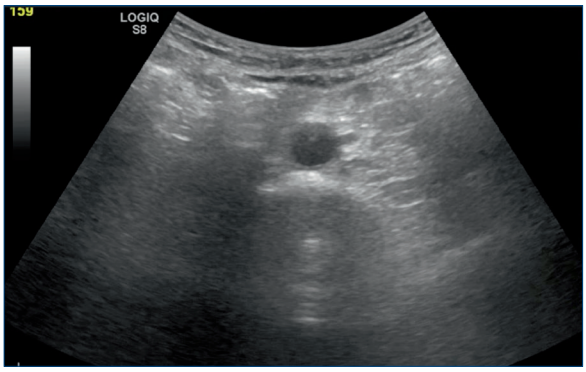


FIGURE 2.1.2 ● Example of hundreds of scan, performed by different human operators, to train the AI in recognize the anatomical landmarks of the abdominal aorta in the transverse aspect.

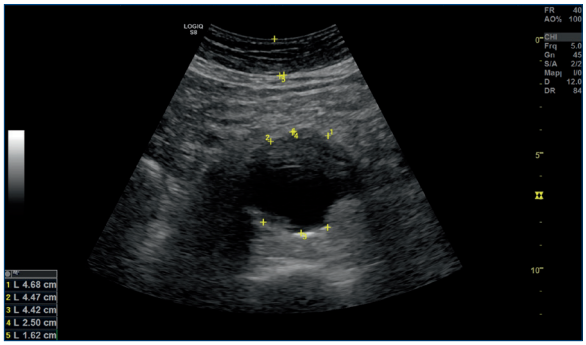


FIGURE 2.1.3 ● Example of hundreds of scan of patient with aneurism of the abdominal aorta in transverse view. The HUMAN protocol included aortic diameter and other measurement. The latter, quantifies subcutaneous thickness, skin surface-aortic wall distances etc. related to the individual BMI. The complex of this dataset allowed the AI to elaborate information about the pressure to be applied on the probe in order to obtain the best imaging according to the depth of the aorta.

Two further points of a robotic based screening programs should be highlighted: the first one is the psychological impact of the patient coming face to face with the robot. It should be explained to the patient that a human intermediation is always present; that makes this approach not dissimilar to that of Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) examinations, where the radiologist is in the control room for the report without any direct contact with the patients. In our case we have foreseen that a general health worker politely seats the patient to receive the ultrasound scan, simply pushes a button to start the operation and, at the end, assists the patient to leave the diagnostic area. This is therefore a known impact with no significant differences perceived by the patients.

The second point we wanted to focus on is the fact that the robotic diagnostic system only performs as an alarm screening without any medical diagnosis. In particular, its role is to measure an aortic diameter and distin-

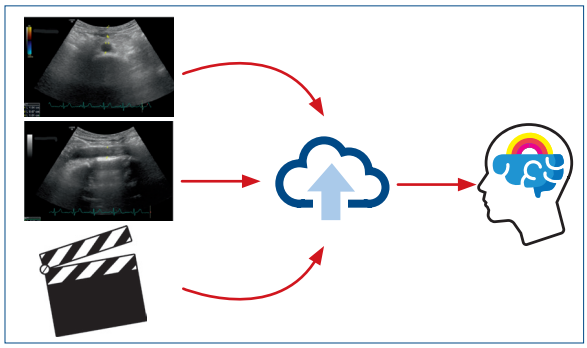


FIGURE 2.1.4 ● Flowchart from data acquisition to AI learning process.

guish patients of possible surgical or specialist interest from the rest of the population that is certainly negative for the pathology sought. Following this rule, we could consider its employment in an ideal screening program.

The human role does not only lie on the end of the process with a specialist signing a report but is the starting point of the learning process pursued by the AI.

The clinical division of the team had a trainer role for the AI; the underlying flowchart was applied.

In the very beginning of the study a repeatable and standardized protocol for data collection through the ultrasound Doppler scan of patient abdominal aorta was defined. Protocol consists of collecting data on age, sex, weight and height and 2 different images of the abdominal aorta in transverse and longitudinal view including aortic diameter and a clip recorded during the vessel's transverse scan.

Every exam, anonymized, was uploaded on a cloud database developed by the engineering division. The images were then extracted and used by AI to learn how to perform the aortic scan and recognize the anatomical vascular structure (Figure 2.1.4).

The image acquisitions were intentionally performed by different human operators, in order to introduce the inter-operative viability in the learning process of the AI.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

At the dawn of the 21st century, Artificial Intelligence (AI) is a discipline that has significantly contributed to technological advancement, effectively becoming a part of our everyday lives and revolutionizing them. The concept of AI, however, is not novel but dates to 1950 when Alan Turing's groundbreaking work "Computing Machinery and Intelligence" was published. Today, we define AI as a combination of disciplines and approaches pursued with the goal of designing machines capable of solving problems and replicating activities inherent to human intelligence. Typical applications of AI systems include natural language processing, speech recognition and computer vision.

The term AI is often mistaken for the term machine learning, although the latter is actually a subset of AI.

Machine learning (ML) involves creating systems that learn or improve their performance autonomously through the data they utilize. An important distinction is that while everything related to ML falls under artificial intelligence, AI includes not only machine learning but also other techniques and methodologies. ML algorithms can be classified according to how each algorithm learns from the data, and although many variations have been developed, the two best known categories are supervised and unsupervised learning. Supervised learning is characterized by the presence of labeled data pairs consisting of input features and corresponding output labels. The goal of supervised learning is to train a model to learn the mapping between input features and output labels, enabling it to make accurate predictions or classifications when presented with new, unseen data. The use of supervised learning therefore requires the labeling of a large amount of data, which is often done manually by human experts. On the other hand, unsupervised learning involves training on unlabeled data without explicit guidance or supervision from external sources. This approach is particularly useful for extracting insights from unstructured data, detecting anomalies, and exploring datasets when true labels are unavailable or difficult to obtain.

In medicine, AI and ML act as catalysts for innovation, offering a glimpse of a future in which health care transcends the boundaries of human capabilities. Imagine a world in which medical decisions are not based solely on the expertise of individual physicians, but rather on the collective intelligence distilled from vast reservoirs of patient data, clinical trials and scientific literature.

In the field of medical imaging, AI and ML have already proven capable of identifying anomalies within radiographs, ultrasounds, MRIs, and CT scans that are imperceptible to the human eye. By leveraging the capabilities of deep learning — a powerful subset of ML employing neural network architectures — AI algorithms can detect early signs of cancer, pinpoint fractures, and even forecast the progression of neurodegenerative diseases long before symptoms appear.

A fully autonomous robotic ultrasound system requires computer vision capabilities to replace the expertise of sonographers. Accurately identifying the aorta and its boundaries in ultrasound images is essential in this project, a task commonly referred to as image segmentation. Deep learning has the potential to effectively segment medical images and extract detailed features. We employed a supervised learning approach based on a Convolutional Neural Network (CNN) with encoder-decoder structure, named U-Net,[9] known for its performance in image segmentation tasks, particularly in medical imaging.

Our implementation utilizes the DenseNet121,[10] architecture for the encoder, while the decoder is implemented using a conditional Generative Adversarial Network (cGAN) known as "pix2pix".[11]

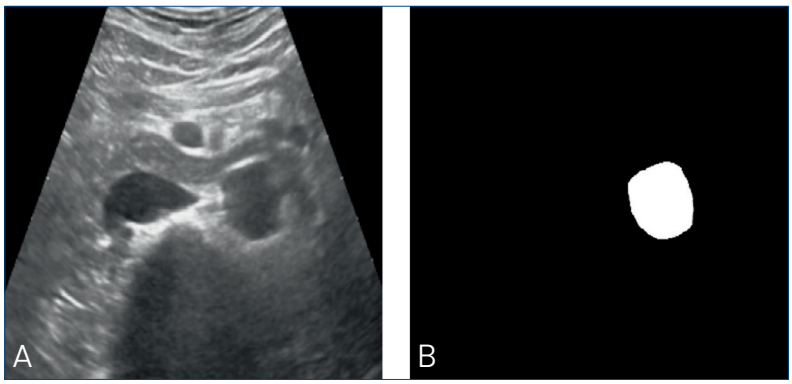


FIGURE 2.1.5 ● An ultrasound image of the abdomen (A), the mask manually drawn by the physician to identify the aorta (B)

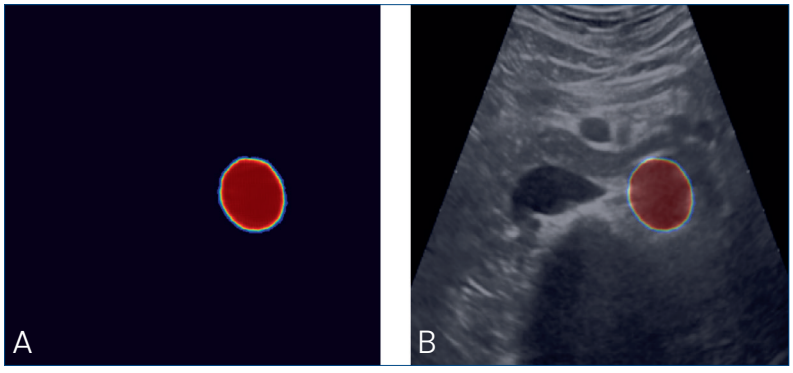


FIGURE 2.1.6 ● Predicted mask from the deep learning model, using a color scale from blue to red, where red indicates higher confidende in assigning that pixel as belonging to the aorta (A). Predicted mask on the original ultrasound image to show the accurate identification of the aorta (B).

As this approach entails supervised learning, it requires labeling of the collected data by trained medical personnel. In our case, labeling consists of drawing a mask over the aorta in the ultrasound images (Figure 2.1.5). The diversity of images that compose the dataset, from different ultrasound machines, from different patients and conducted by various medical professionals, ensures the model's ability to effectively generalize its knowledge.

The model achieved a validation accuracy of 0.9949 and a validation loss of 0.0160 in correctly segmenting the aorta on test set. An example of the model's accuracy is depicted in Figure 2.1.6, where the mask generated by the model is shown followed by its overlay on the original image.

Finally, the trained model was experimentally tested on a real time video stream acquired from the US machine, demonstrating an average inference time of 38 ms, corresponding to a processing capacity of 26 frames per second (FPS). This assessment highlights the model's potential for on-the- fly aorta segmentation during US examinations, as well as its real time applicability and efficiency when used in a realistic clinical scenario.

It is worth noting that U-net has been improved, resulting in models such as Swin-Unet[12] and UNet++,[13] which promise superior results for some imaging applications. Although these approaches offer promising advances, our current implementation has already shown excellent performance in evaluation metrics. In addition, another architecture that is showing significant results in medical imaging, including segmentation, is Transformers,[14] which is likely to become the standard in the coming years. We plan to test it soon.

AI-MEDIATED ROBOTIC AORTIC ULTRASOUND IMAGING

Recently driven by the so-called 4th Industrial Revolution (Industry 4.0), robotic systems have undergone a meaningful development towards human-centered applications, which can include co-working collaboration among robots and humans with Physical Human-Robot Interaction (pHRI). Such a feature has opened perspective scenarios also in medical-related applications.[15] The design of robotic manipulators takes inspiration from the human arm, consisting of a sequence of several joints and bones that confers strong agility in movements. The tool mounted and transported by the robot generally depends on the specific application.

Furthermore, collaborative robots are equipped with on-board force sensors, that enable the implementation of motion algorithms to safely control the forces that the robot applies to the external environment and to the human they are physically interacting with. Considering the above-mentioned considerations, the time has come to study the integration of emerging technology frameworks such as collaborative robotics and artificial intelligence, with the aim of developing an autonomous AI-guided robotic system for ultrasound vascular examinations.

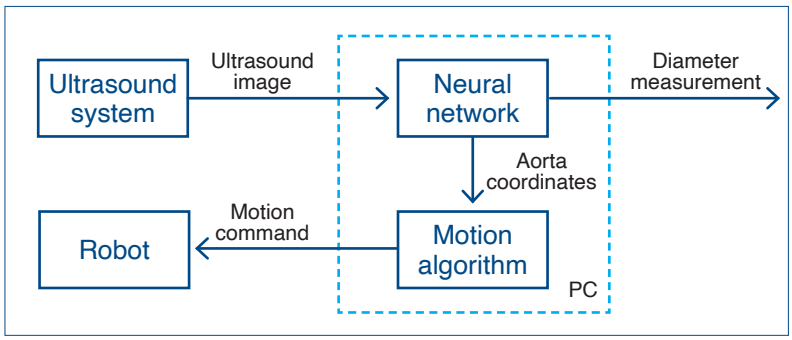


FIGURE 2.1.7 ● The system architecture.

Therefore, we developed the first prototypal demonstration cell making use of the Franka Emika collaborative robot[16] and the MyLab Alpha ultrasound system. We fixed the ultrasound probe to the robot end-effector by means of a custom-made 3D-printed support.

A desktop PC is in charge of acquiring the images from the ultrasound and elaborating the command to move the robot upon the patient's abdomen to search for the aorta. The scheme of Figure 2.1.7 shows the system architecture.

In particular, the operator manually moves the robot to the initial position, where the ultrasound probe is in contact with the patient's abdomen, but the aorta is not necessarily visible. Then, the procedure starts: the robot autonomously moves the probe in a grid of configurable size on the patient's abdomen changing the probe orientation and applying increasing forces while maintaining strict safety constraints. In the meanwhile, the neural network tries to segment the aorta in the ultrasound image and, when detected, transmits its coordinates to the robot. The motion algorithm converts the video coordinates into spatial coordinates, so that the aorta search can be refined to optimize the ultrasound visualization. Finally, the aorta diameter measurement is generated when the aorta is sufficiently at the center of the ultrasound image, where the focus is optimal. Figure 2.1.8 shows the experimental setup of our system.

The first experiments demonstrated the potential of the system. Five healthy volunteers with different Body Mass Index (BMI) have been successfully scanned by our system, which was able to detect the aorta and to provide its diameter measurement within a maximum time of 2 minutes.

FUTURE SCENARIOS AND CONCLUSIONS

The future roadmap includes two different scenarios and a mandatory step. The latter consists in the today complex acquirement of the CE label to permit our prototype to go out of the lab and live in a clinical setting. It is a complex procedure which requires to grant our University of Ferrara patent to an industrial partner. Subsequently, the first scenario consists in a series of comparative and multicentric studies, involving SICVE, ESVS, SVS interested centers.

The second scenario is to perform specific studies validating the use of robotic vascular ultrasound screening in different topics out of abdominal aortic screening, such as deep venous thrombosis[17] and internal carotid artery[18] screening and assessment of ultrasound jugular venous pulse.[19]

Our great hope is to improve the current health sustainability in Italy and possibly in Europe and in the western countries, proposing automated vascular screening aimed to recognize candidate patients for surgery before the happening of vascular disaster like aortic rupture, strokes or pulmonary embolism.

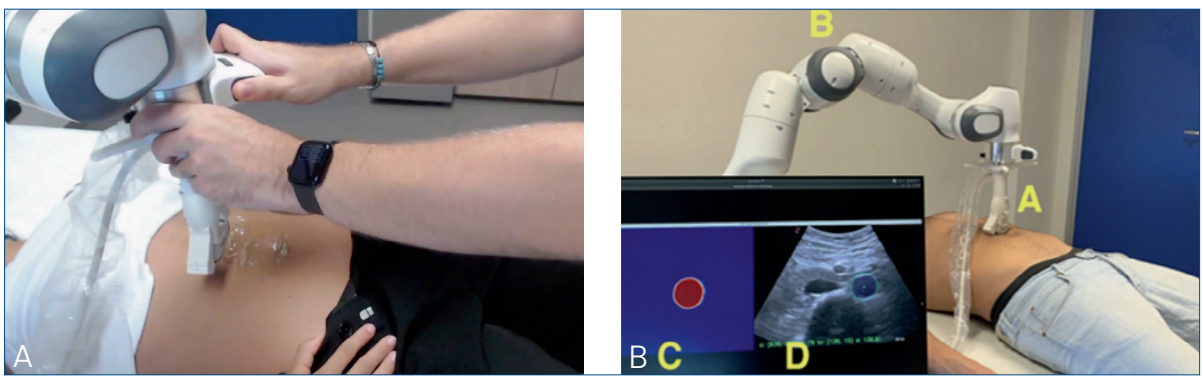


FIGURE 2.1.8 ● A) The initialization procedure executed by non-qualifed operators. B) The autonomous robotic system. A) the ultrasound probe; B) the collaborative robot; C-D) the neural network segmentation of the aorta with diameter measurement.

REFERENCES

1. Agenzia esecutiva per i consumatori, la salute, l'agricoltura e la sicurezza alimentare (Commissione europea). Sweeping changes to upgrade Europe's health systems. DOI 10.2818/690230, 2018
2. Er. Di.. Spesa sanitaria: nel 2022 a carico degli italiani 40,26 miliardi (+8,3%), la metà per visite e interventi. Il sole 24 ore, 21 Dic 2023 https://www.sanita24.ilsole24ore.com/art/dal-governo/2023-12-21/spesa-sanitaria-2022-italiani-hanno-pagato-tasca-propria-4026-miliardi-83percento-192355.php?uuid=AF7a5A9B#&refresh_ce=1
3. Dipartimento della Ragioneria Generale dello Stato, Ministero dell'Economia e delle Finanze. "Il monitoraggio della spesa sanitaria", Rapporto n. 10, Dicembre 2023, https://www.rgs.mef.gov.it/VERSIONEI/attivita_istituzionali/monitoraggio/spesa_sanitaria/index.html
4. Wanhainen A, Van Herzeele I, Bastos Goncalves F, *et al.* European Society for Vaascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2024;67:192–331.
5. Invecchiamento della popolazione e sostenibilità del SSN, Ministero della Salute, Consiglio Superiore di Sanità, Sessione LII (2019-2022), Sezione I; https://www.pnes.salute.gov.it/imgs/C_17_pubblicazioni_3094_allegato.pdf
6. Armoundas AA, Narayan SM, Arnett DK, *et al.*; American Heart Association Institute for Precision Cardiovascular Medicine; Council on Cardiovascular and Stroke Nursing; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular Radiology and Intervention; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; and Stroke Council. Use of Artificial Intelligence in Improving Outcomes in Heart Disease: A Scientific Statement From the American Heart Association. Circulation. 2024 Feb 28. doi: 10.1161/CIR.0000000000001201.
7. May, M. Eight ways machine learning is assisting medicine. Nat Med 2021;27:2–3.
8. Reimerink JJ, van der Laan MJ, Koelemay MJ, *et al.* Systematic review and meta-analysis of population-based mortality from ruptured abdominal aortic aneurysm. Br J Surg 2013;100:1405–13.
9. Ronneberger O, Fischer P, Brox T. U-net: Convolutional networks for biomedical image segmentation. In: N. Navab N, J. Hornegger J, W. M. Wells WM, *et al.* and A. F. Frangi, EdsMedical Image Com- puting and Computer-Assisted Intervention – MICCAI 2015. Cham: Springer International Publishing; 2015. p. 234–41.
10. Huang G, Liu Z, Maaten LVD, *et al.* Densely connected convolutional networks in 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR). Los Alamitos, CA, USA: IEEE Computer Society, jul 2017, pp. 2261–2269. [Online]. Available: https://doi.ieeecomputersociety.org/10.1109/CVPR.2017.243
11. Isola P, Zhu J-Y, Zhou T, *et al.* Image-to-imagetransla-tion with conditional adversarial networks. In 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), 2017. p. 5967–76.
12. Cao H, Wang Y, Chen J, *et al.* Swin-unet: Unet-like pure transformer for medical image segmentation. In Computer Vision – ECCV 2022 Workshops, L. Kar- linsky, T. Michaeli, and K. Nishino, Eds. Cham: Springer Nature Switzerland, 2023. p. 205–18.
13. Zhou Z, Siddiquee MMR, Tajbakhsh N, *et al.* Unet++: Redesigning skip connections to exploit multiscale features in image segmentation. IEEE Transactions on Medical Imaging 2019;39:1856–67.
14. Shamshad F, Khan S, Zamir SW, *et al.* Transformers in medical imaging: A survey. Medical Image Analysis 2023;88:102802.
15. Bertelsen A. Collaborative robots for surgical applications." ROBOT 2017: Third Iberian Robotics Conference: Volume 2. Springer International Publishing, 2018.
16. Haddadin S. The franka emika robot: A reference platform for robotics research and education. IEEE Robotics & Automation Magazine 2022;29.2:46–64.
17. Righini M, Paris S, Le Gal G, *et al.* Clinical relevance of distal deep vein thrombosis. Review of literature data. Thromb Haemost 2006;95:56–64.
18. Jahromi AS, Cinà CS, Liu Y, *et al.* Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. J Vasc Surg 2005;41:962–72.
19. Zamboni P, Malagoni AM, Menegatti E, *et al.* Central venous pressure estimation from ultrasound assessment of the jugular venous pulse. PLoS One 2020;15:e0240057.

2.2 COMPUTER MODELLING AND ADVANCED SIMULATION IN TEVAR

Anna Ramella, Giulia Luraghi, Sara Barati, Giulia De Campo, Jose F. Rodriguez Matas, Jasper de Koort, Tim Mandigers, Irene Fulgheri, Maurizio Domanin, Robin Heijmen, Nabil Chakfe, Frederic Heim, Francesco Migliavacca, Santi Trimarchi

INTRODUCTION

Computational models are widely adopted in the literature to replicate in-silico clinical procedures as they can support preoperative planning and give insights into the mechanical behavior of the anatomical structure of interests or of medical devices or of their interaction. Among them, the Computational Fluid dynamics (CFD), Finite Element Analysis (FEA), and Fluid-Structure Interaction (FSI) simulations are the most used. CFD simulates the *fluidynamics* (*i.e.*, blood flow) in a rigid domain, while FEA allows for modelling the structural mechanics without considering blood flow. As a third, FSI combines both methods and allows for an evaluation of blood-induced wall motion and deformation, coupling *fluidynamics* and structural mechanics.

Recently, engineers societies and regulatory bodies publications highlighted the importance of ensuring the reliability of computational models, particularly if they are related to clinical applications.[1–5] High-fidelity numerical simulations aim at replicating clinical procedures, reflecting real-world scenarios. Therefore, the consistency and accuracy of such models are essential to ensure their effectiveness and trustworthiness in clinical practice. The demonstration of credibility is related to a process that involves rigorous validation and verification (V&V) activities.[2, 6] The ultimate objective is to accurately predict clinical procedure outcomes or facilitate the development of in-silico clinical trials.[4, 7] The concepts of V&V consist, respectively, of determining whether the simulated procedure is representative of the physical reality (validation) and if the adopted mathematical tool is appropriate (verification).

In this framework, the clinical context of use is the thoracic endovascular aortic repair (TEVAR) procedure. TEVAR is now the primary choice to treat thoracic aortic pathologies (aneurysms, acute syndromes, dissections) as it offers an alternative to traditional open surgery.[8–10] In fact, differently from the latter, TEVAR is associated with shorter hospital stays and recovery periods. Following its endorsement by the Food and Drug Administration (FDA) in 2005, clinical studies have documented superior patient outcomes associated with TEVAR when compared with open surgical repair.[11] TEVAR technical success largely depends on the anatomical suitability of the aortic region. Therefore, an extremely accurate pre-operative planning to assess diameters, lengths, angles, three-dimensional morphology, and the presence of thrombus or calcifications is of primary importance. Conventionally, the preferred imaging modalities for both preoperative and postoperative evaluation are computed tomography angiography (CTA), and - less commonly - Magnetic Resonance Imaging (MRI). However, in recent years, a rise in the use of *in silico* approaches to analyze TEVAR scenarios has been documented.[12, 13]

Starting from an already proved methodology, previously reported by our group in 2022,[14] here we aim to summarize and update our current practice for computer modelling and simulation in TEVAR, showing the path line to develop high-fidelity FEA simulations of these complex endovascular procedures. Crucial steps will be outlined as follows: 1) validation of the device model; 2) validation of the TEVAR simulation in rigid domains; 3) validation of the TEVAR procedure with patient-specific anatomies; 4) use of the TEVAR simulation in the pre-operative planning.

DEVICE MODEL VALIDATION

The validation process of the numerical simulation consists of comparing the numerical results with experimental evidence. It aims to validate the stent-graft models first and then the stent-graft implantation procedure.

Experimental crimping tests were performed on commercially available Valiant Captivia (Medtronic Inc., Santa Rosa, CA) thoracic aortic stent-grafts in order to 1) calibrate the material properties of the nitinol (stent) and polyethylene terephthalate (PET,graft fabric) and 2) validate the device numerical model itself. These tests were carried out on the stent-grafts at 37°C ± 2°C (dry air) by using the Blockwise Crimper system (Blockwise Engineering LLC, Figure 2.2.1A). Starting from the initial configuration, each stent-graft was crimped down to 10 mm and then released back to the initial diameter.

On the numerical side, a digital twin of the real device is created. The stent was discretized with beam elements with a circular cross-section (diameter of 0.5 mm). The graft was discretized with triangular elements. Nitinol was modelled with a shape memory formulation, while PET was modelled as a linear isotropic elastic fabric material. A node-to-node connection between the graft and stent elements was imposed to replicate the presence of the suture points. Also, the pre-stress of the stent-graft was recreated for taking into account the oversizing of the manufactured nitinol struts with respect to the graft. As in the crimping experiment, in the simulation, 10 rigid crimping planes were placed around the device, displaced radially to reach the desired crimped diameter and then moved back.

Numerical and experimental data were compared in terms of radial force-vs-diameter history curves. Validation results are reported in Figure 2.2.1B.

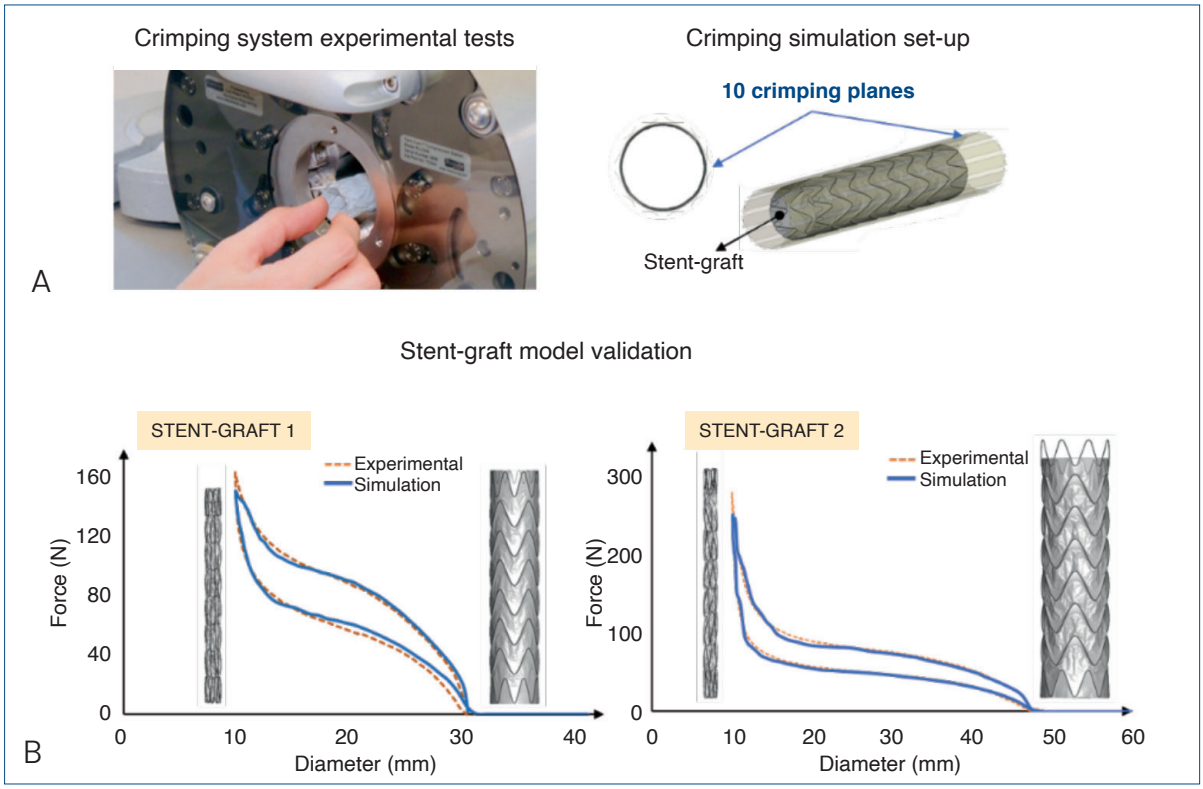


FIGURE 2.2.1. ● A) Experimental and crimping simulation set-up. B) Results of the device validation for two tested stent-grafts: numerical curves (blue) are compared with experimental curves (orange dotted).

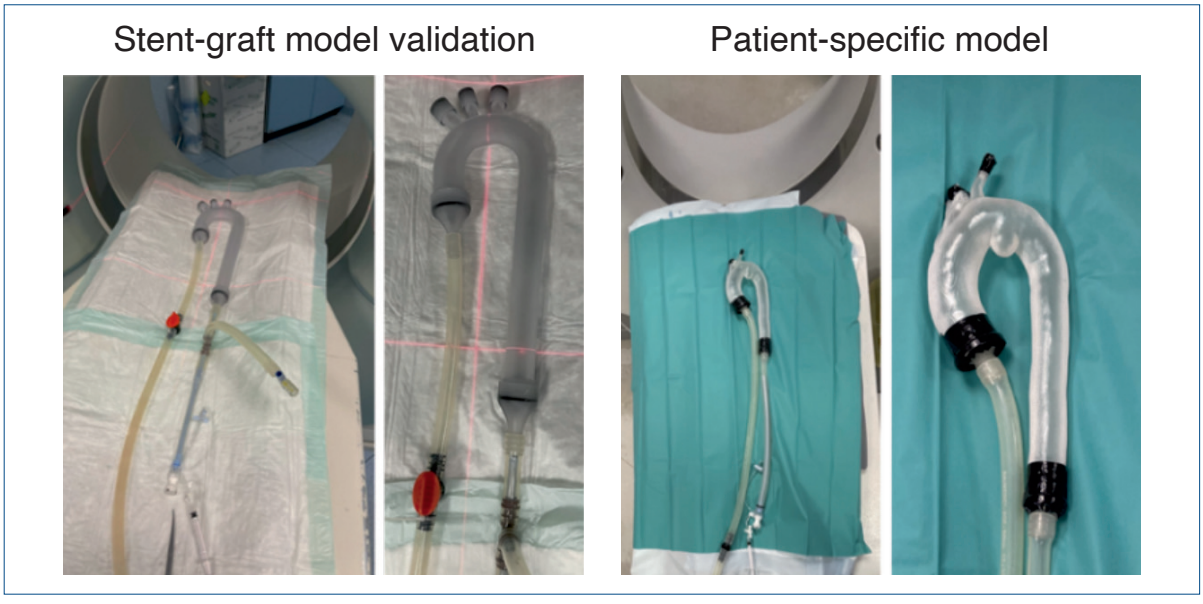


FIGURE 2.2.2 ● 3D-printed rigid models used in the deployment simulation validation process.

TEVAR SIMULATION IN RIGID DOMAINS

When looking for the development of really high-fidelity FEA models, the simulation of the TEVAR procedure has to truthfully replicate the physical stent-graft deployment. For this reason, an *ad hoc* experimental set-up was built. In particular, two aortic models (one idealized and one patient-specific, Figure 2.2.2) were 3D-printed with a rigid transparent polymer (Stratasys VeroClear RGD810). Then, thet Captivia stent-grafts were experimentally implanted by a surgeon into the models. As an

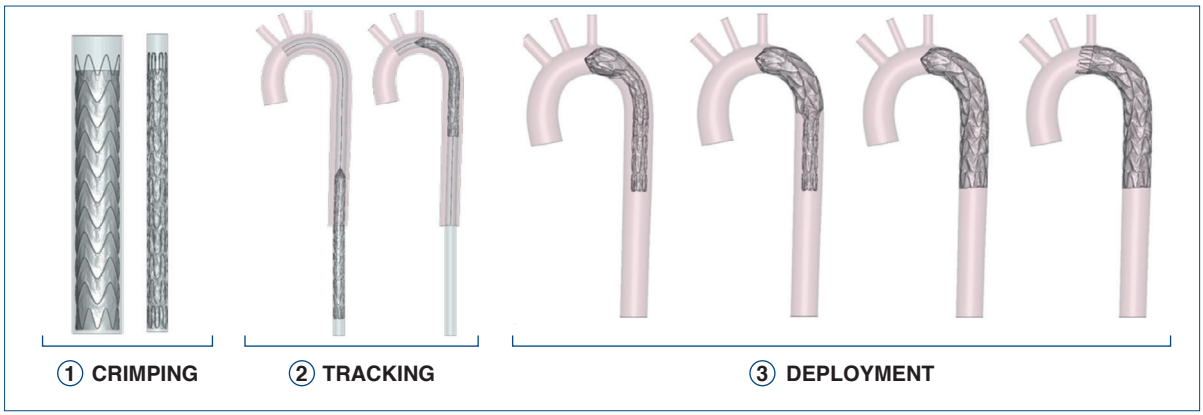


FIGURE 2.2.3. ● Summary of the 3 main steps adopted for general FEA TEVAR simulation (idealized case).

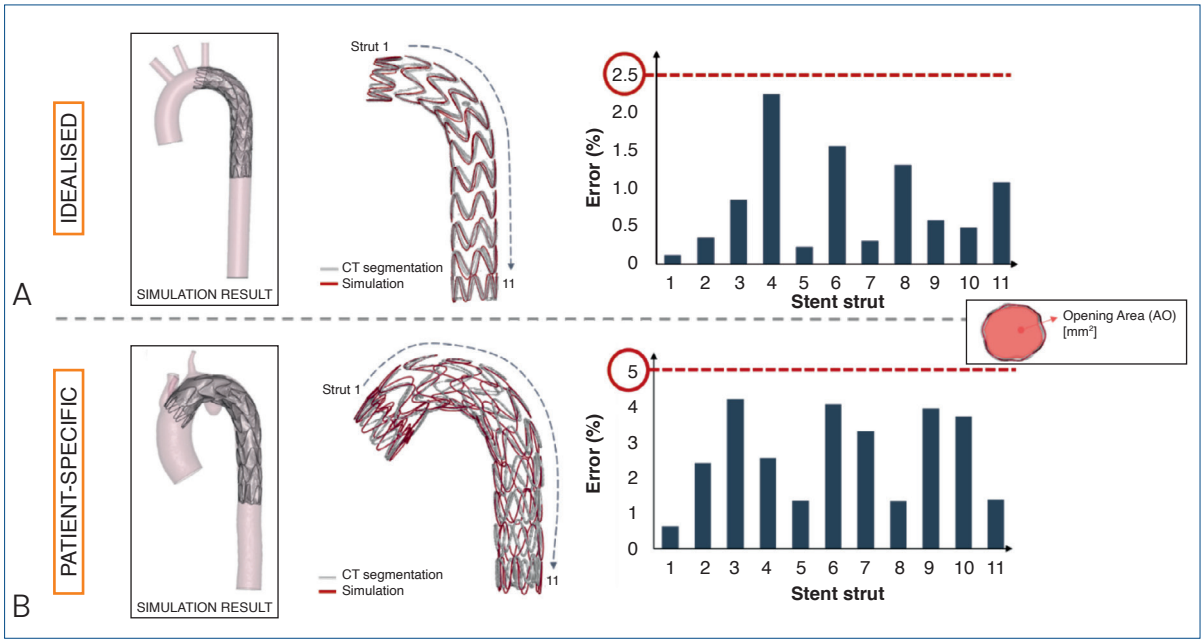


FIGURE 2.2.4. ● Results of the simulation validation process: A) idealized aorta and B) patient-specific aorta. In both cases, on the left, the final instant of the simulation and the qualitative overlap between simulation (red) and segmentation (white) are depicted. On the right, the plot reports the Opening Area (OA) error computed at each stent strut.

example of graft sizing and choosing criteria, if the aortic diameter in the intended landing zone was 30 mm, in both cases, a straight 34-mm, 150-mm long stent-graft was implanted following the manufacturer's instructions for use. The patient-specific anatomy was segmented from his own anonymized CTA images (provided by Policlinico di Milano Hospital). The whole procedure was always performed under CTA monitoring. Aortic models were filled with water at 37 °C to replicate body temperature. Using the VMTK software (Orobix s.r.l.), each stent was segmented from CTA acquisitions, and then used to validate the numerical simulation.

The TEVAR FEA simulations included 3 steps (Figure 2.2.3): 1) stent-graft crimping into a catheter; 2) stent-graft tracking inside a catheter along the vessel centerline; 3) stent-graft gradual deployment into the aorta.

Main results of this validation process are reported in Figure 2.2.4. On top/left, a qualitative overlap between the simulation results (red) and the stent segmented from CTA images (white) is shown. To quantify the errors between the two outputs, the simulation vs. segmentation error on the opening area (OA) is computed. The OA is defined as the area enclosed by a spline fitting the proximal apex of each stent strut.

As for both the cases detailed in Figure 2.2.4, the qualitative overlap generally showed a good agreement between simulation and segmentation. Calculated OA error values were <2.5% for the idealized, and <5% for the patient-specific anatomy. These error values are in both cases, significantly lower than the ones reported

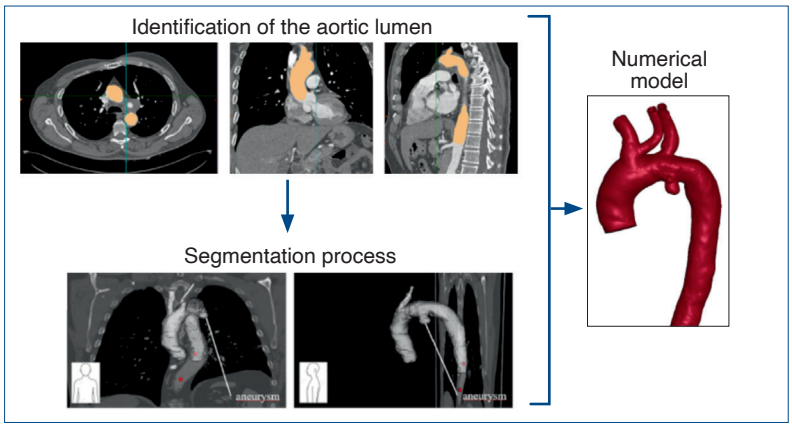


FIGURE 2.2.5. ● General process to obtain the aortic model starting from clinical CTA images.

by previously published studies.[15, 16] Finally, the above mentioned results allowed us stating that the simulation method has been formally validated.

TEVAR SIMULATION IN PATIENT-SPECIFIC ANATOMIES

As the simulation procedure is validated in rigid anatomies, then a further step is consequently required, *i.e.* to confirm its accuracy also in real patient-specific morphologies.[17, 18] For this purpose, patient-specific a aortic anatomies were segmented and post-processed from clinical CTA images to obtain a FEA domain suitable for numerical simulations (Figure 2.2.5).

Differently from the validation process applied to rigid domains, in patient-specific applications the aorta is modelled with deformable linear elastic material. The arterial pre-stress state due to blood pressure is included as well.[19]

To clarify practical aspects of our methods, the validation process of three patient-specific cases (Figure 2.2.6) using post-operative CTA images are presented below. Data regarding Patient-1 was provided by the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, while the other two (Patient-2 and Patient-3) were provided by the St. Antonius Hospital, Nieuwegein, Netherlands. Details regarding patients' pathologies, stent-graft landing zones, and device sizes are listed in Table 2.2.I. Follow-up CTAs performed two months after TEVAR confirmed the accurate position of the thoracic aortic stent-grafts, without unexpected or adverse findings. For validation purposes, at the end of the simulation, the resultant stent configurations are compared to the stent segmented from post-operative images, and OA differences are quantified using the same approach explained above.

As shown in Figure 2.2.6C, a good qualitative overlap between the segmented and simulated stent configurations was achieved for every patient. Then, by evaluating the OA at each stent strut, OA percentage errors between the simulation and CT reconstruction were always found to be below 10%, lower if compared to other literature studies.[16, 20, 21] Error values were higher for Patient-1 at the level of pathology. In all the anatomies, errors below 5% were observed in the proximal ring, which plays a crucial role in guaranteeing the anchoring of the device to the aortic wall.

This patient-specific application has demonstrated the ability of our numerical tool simulation model to faithfully replicate the TEVAR procedure in patient-specific aortas, opening the way for iys wider application in clinical practice as, for example, a planning tool.

PREOPERATIVE PLANNING TOOL

Moving through the above mentioned validation process phases , it has been highlighted that computer simulations can be representative of the real implantation procedure as the quantitative comparison of the simulated and CT reconstruction has minimal differences. Furthermore, as the timing to produce results from a computer simulation is compatible with those required to plan the intervention, pre-procedural planning looks like an actual way to adopt an *in silico* strategy. In fact, apart from the validation process, an important remark is related to the large time that is necessary to carry out this patient-specific workflow after receiving CT images: in one/two working days, the process can

Table 2.2.I ● Information about the three patients included in the study.

Patient ID	Pathology	Landing zone	Implanted stent-graft (proximal diam x distal diam x length)
1	Penetrating aortic ulceration	2	34 x 34 x 100
2	Intramural hematoma	3	36 x 36 x 200
3	Penetrating aortic ulceration	2	38 x 38 x 100

diam: diameter.

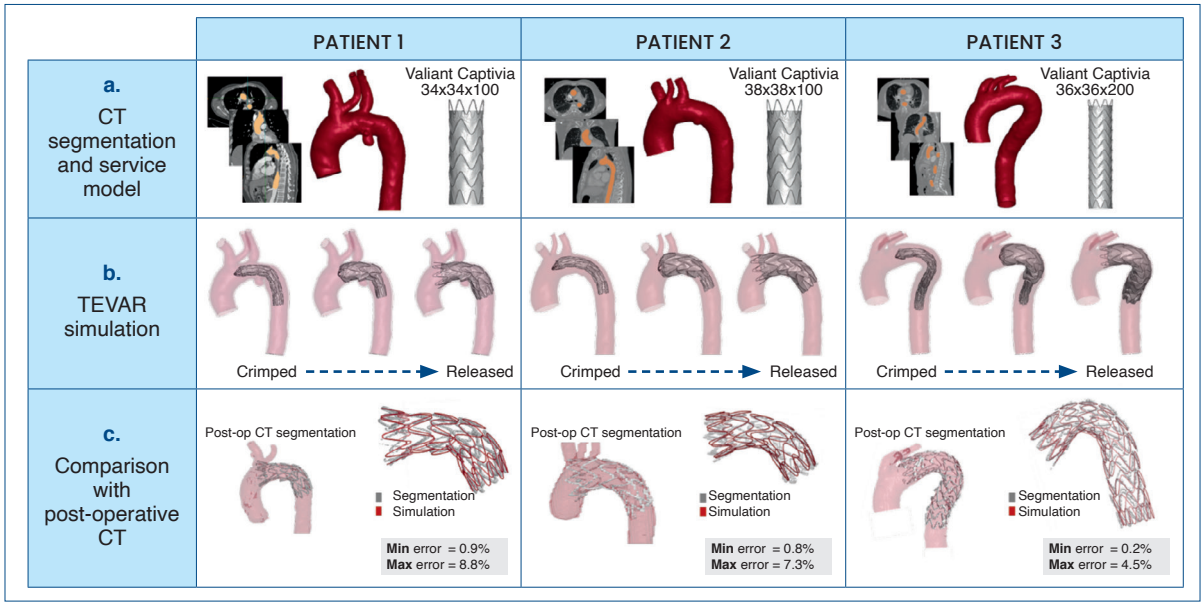


FIGURE 2.2.6 ● Final instant of the simulations for all the patients and comparison with post-operative CT images. Only the maximum and minimum OA errors are reported.

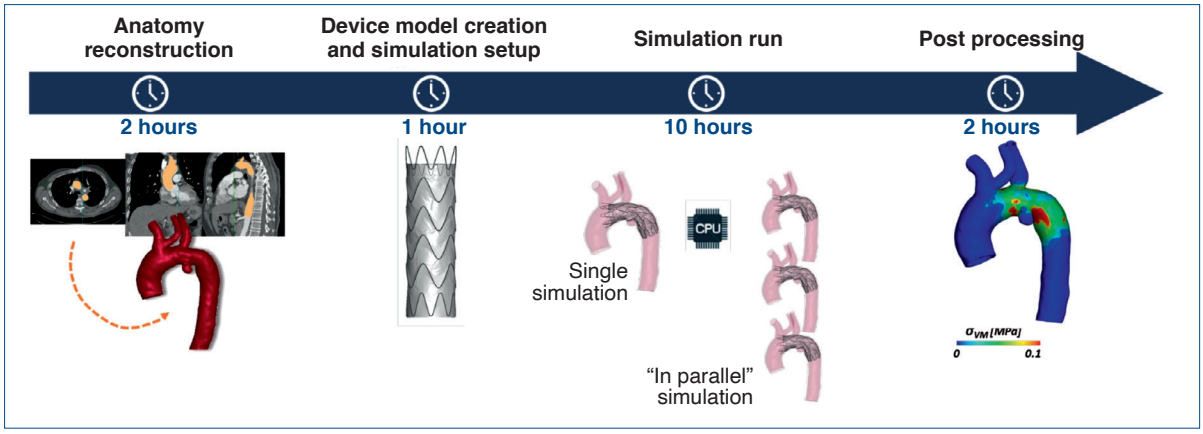


FIGURE 2.2.7 ● Timing to produce results useful for clinicians.

be done (Figure 2.2.7). Once the stent-graft has been characterized (this phase is not included in this timing), the anatomy reconstruction from CT images takes approximately a couple of hours as, for now, a manual intervention is required to fix some geometric and mesh discontinuities. The preparation of the input file to run the FEA simulation takes about one hour. Then, the simulation computational time takes approximately 3-to-10 hours depending on the case (on 28 CPUs of an Intel Xeon64 with 250 GB of RAM), but more than one simulation with different targets (e.g., landing zones, stent-graft sizes) can be run in parallel. The last phase is the elaboration of the results, which takes less time. Starting from simulation results, a report with numerical quantities of interest (e.g., stent-graft apposition, wall stresses) is automatically generated and results can be analyzed together with clinicians.

As an example,[22] we applied this pathway to an 82-year-old lady treated for penetrating aortic ulceration (PAU) in 2 and 3 landing zones (LZ), with maximum diameters of 38 mm. At follow-up, there was an intraluminal floating thrombus located at the outer curvature of the proximal descending aorta (Figure 2.2.8). The patient underwent left common carotid to left subclavian artery (LCCA-LSA) bypass and standard TEVAR in 2 LZ with a Valiant Captivia device (32x32x100 mm). To obtain the 3D reconstruction of the vessel, the pre-operative CTA images were segmented and post-processed to be discretized. The aortic mesh, including the floating thrombus, was realized. The thrombus material was modelled as softer than the vessel wall. TEVAR simulations were carried out considering different stent-graft LZ in zone 2 of the aortic arch. The aim was to identify which location has a better apposition of the stent-graft to the

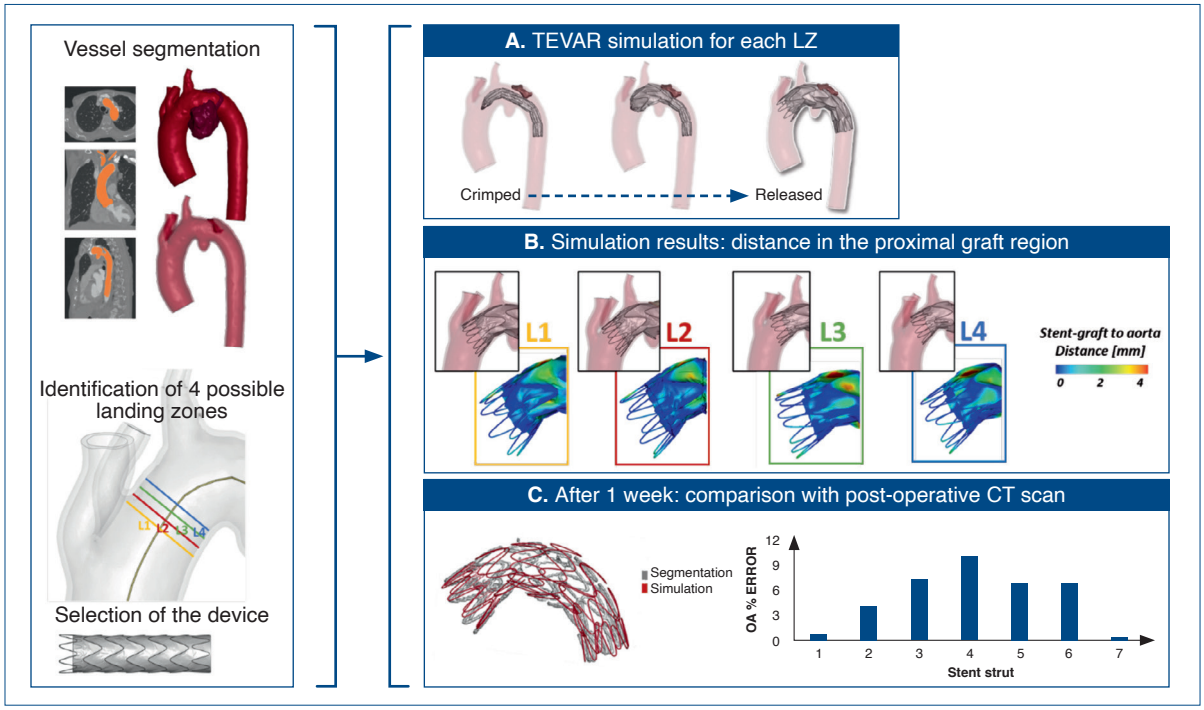


FIGURE 2.2.8 ● Example of planning applied to a patient-specific case.

aortic wall: four LZ in the arch zone 2 have been selected for performing the TEVAR simulation (L1 more proximal, L4 more distal). The results of the simulations (Figure 2.2.8 A, B) were compared in terms of distance between the aorta and stent-graft in the LZ region. Based on our results, the most proximal location (LZ 1) showed the minimal distances, and could have been suggested as the optimal choice and discussed with clinicians before the procedure. To verify the reliability of the process after the operation, the an early (usually 1-week post-operative CTA images were compared with *in silico* prediction, obtaining a good matching (differences in the proximal zone lower than 1% and maximum difference of 10.8% in the area of the floating thrombus) (Figure 2.2.8C).

CONCLUSIONS

In the context of regulatory approval and clinical decision-making, the reliability of computational models becomes a critical factor. Regulatory bodies and healthcare professionals should base their recommendations on credible models , assessing the safety and efficacy of medical devices, and optimizing patient care pathways. Therefore, ensuring the trustworthiness of computational models in clinical practice is imperative for improving procedural outcomes, healthcare delivery, and advancing medical research.

The methodology discussed in this chapter follows the V&V40 guidelines to develop high-fidelity stent-graft models and TEVAR simulations.[5, 14] In particular, given a stent graft, a proper stent and graft material characterization and a device model validation are performed before approaching TEVAR procedure simulations. Then, the TEVAR simulation itself needs to be validated (e.g., by performing the stent-graft implantation under CTA in a rigid phantom) to establish the overall model credibility. Once the model applicability has been proved,[18] the procedure can be applied to patient-specific aortic anatomies: starting with the segmentation and discretization of the aortic model from pre-operative CTA images, the commercial stent-graft size is selected according to the aortic anatomy and the simulation of the TEVAR procedure can be performed. As further model validation, the deployed stent configuration obtained with the simulation can be compared to the stent segmented from post-operative CTA images (if available).

Accordingly, a new workflow might also be used in the pre-procedural planning phase, since it has been proved to help replicating the TEVAR procedural expected outcome in a realistic scenario before the clinical intervention.

REFERENCES

1 Morrison TM, Hariharan P, Funkhouser CM, *et al.* Assessing Computational Model Credibility Using a Risk-Based Framework: Application to Hemolysis in Centrifugal Blood Pumps. ASAIO J 2019;65:349–60.
2 Pathmanathan P, Gray RA, Romero VJ, Morrison TM. Applicability Analysis of Validation Evidence for Biomedical Computational Models. J Verif Valid Uncertain Quantif 2017;2.
3 Santiago A, Butakoff C, Eguzkitza B, *et al.* Design and execution of a verification, validation, and uncertainty quantifica-

tion plan for a numerical model of left ventricular flow after LVAD implantation. PLOS Comput Biol 2022;18:e1010141.
4 Viceconti M, Pappalardo F, Rodriguez B, *et al.* In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods 2021;185:120–7.
5 ASME. Assessing credibility of computational modeling through verification and validation: application to medical devices. Asme V&V 40-2018 2018:60.
6 ASME. Guide for Verification and Validation in Computational Solid Mechanics. Am Soc Mech Eng 2006;(March):1–53.
7 Pappalardo F, Russo G, Tshinanu FM, *et al.* In silico clinical trials: concepts and early adoptions. Brief Bioinform 2019;20:1699–708.
8 Isselbacher EM, Preventza O, Hamilton Black J, *et al.* 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;80:e223–393.
9 Czerny M, Schmidli J, Adler S, *et al.* Current Options and Recommendations for the Treatment of Thoracic Aortic Pathologies Involving the Aortic Arch: An Expert Consensus Document of the European Association for Cardio-Thoracic Surgery (EACTS) & the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2019;57:165–98.
10 Writing Committee, Riambau V, Böckler D, Brunkwall J, *et al.* Management of Descending Thoracic Aorta Diseases: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;53:4–52.
11 Fillinger MF, Greenberg RK, McKinsey JF, *et al.* Reporting standards for thoracic endovascular aortic repair (TEVAR). J Vasc Surg 2010;52:1022–1033.e5.
12 Mandigers TJ, Ramella A, Bissacco D, *et al.* Thoracic Stent Graft Numerical Models To Virtually Simulate Thoracic Endovascular Aortic Repair: A Scoping Review. Eur J Vasc Endovasc Surg 2023;66:784–96.
13 Avril S, Gee MW, Hemmler A, *et al.* Patient-specific computational modeling of endovascular aneurysm repair: State of the art and future directions. Int j Numer Method Biomed Eng 2021;37:e3529.
14 Ramella A, Migliavacca F, Felix J, *et al.* Validation and Verification of High-Fidelity Simulations of Thoracic Stent-Graft Implantation. Ann Biomed Eng 2022 2022:1–13.
15 Kan X, Ma T, Dong Z, *et al.* Patient-Specific Virtual Stent-Graft Deployment for Type B Aortic Dissection: A Pilot Study of the Impact of Stent-Graft Length. Front Physiol 2021;12:1171.
16 Perrin D, Demanget N, Badel P, *et al.* Deployment of stent grafts in curved aneurysmal arteries: Toward a predictive numerical tool. Int j Numer Method Biomed Eng 2015;31:26–36.
17 Ramella A, Migliavacca F, Matas JFR, *et al.* On the validation of patient-specific numerical simulations of the TEVAR procedure. Procedia Struct Integr 2023;49:16–22.
18 Ramella A, Migliavacca F, Felix J, *et al.* Applicability assessment for in-silico patient-specific TEVAR procedures. J Biomech 2023;146(December 2022):111423.
19 Ramella A, Lissoni V, Bridio S, *et al.* On the necessity to include arterial pre-stress in patient-specific simulations of minimally invasive procedures. Biomech Model Mechanobiol 2023;23:525–37.
20 Kan X, Ma T, Lin J, *et al.* Patient-specific simulation of stent-graft deployment in type B aortic dissection model development and validation.pdf. Biomech Model Mechanobiol 2021;20:2247–58.
21 Romarowski RM, Faggiano E, Conti M, *et al.* A novel computational framework to predict patient-specific hemodynamics after TEVAR: Integration of structural and fluid-dynamics analysis by image elaboration. Comput Fluids 2019;179:806–19.
22 Mandigers TJ, Ramella A, Bissacco D, *et al.* Utilizing numerical simulations to prevent stent graft kinking during thoracic endovascular aortic repair. J Vasc Surg Cases, Innov Tech 2023;9:101269.

2.3 3D PRINTING MAY IMPROVE DIAGNOSIS AND PROCEDURAL PLANNING OF ENDOVASCULAR PROCEDURES

Antonio Freyrie, Claudio Bianchini Massoni, Alexandra Catasta, Arianna Mersanne, Chiara Martini, Ruben Foresti, Paolo Perini

INTRODUCTION

Precise diagnosis and meticulous procedural planning are fundamental for achieving successful outcomes in endovascular surgery. Traditionally, these processes have relied heavily on advanced imaging techniques such as computed tomography angiography (CTA) and magnetic resonance imaging (MRI), providing detailed vascular maps that may guide clinicians in navigating complex anatomical structures.[1–3] However, despite the advancements of these imaging modalities, challenges persist in visualizing intricate vascular pathologies and accurately planning interventions.

The advent of 3D printing technology heralds a promising new era in the diagnosis and planning of endovascular procedures.[4] By translating digital imaging data into tangible, patient-specific anatomical models, 3D printing may offer clinicians an unprecedented opportunity to interact with complex vascular pathology in a physical form. This tangible representation may enable a deeper understanding of patient-specific anatomy, enhancing pre-procedural strategizing and potentially reducing intraoperative complications and operating times.[4, 5]

The utilization of 3D printing in endovascular surgery is still emerging but has shown remarkable potential.[6] Early reports in the literature document pioneering efforts where 3D-printed models have been instrumental in resolving challenging clinical scenarios, providing clinicians with novel insights into anatomical nuances that were previously inaccessible through traditional imaging alone.[7, 8] As such, this chapter explores the evolving role of 3D printing technology in improving the diagnosis and preoperative planning of endovascular interventions, highlighting its potential impact on patient care.

CURRENT/AVAILABLE 3D-PRINTERS AND MATERIALS

Additive manufacturing (AM) involves a variety of production processes that differ based on the way they build plastic and metal parts. These processes can differ in terms of material selection, surface finish, durability, manufacturing speed, and cost. In AM, the material is added layer-by-layer with the aim of creating complex shapes that are not obtainable with traditional material subtraction manufacturing processes.[9, 10]

Bioprinting identifies AM processes that involves combining cells, growth factors, and/or biomaterials to create biomedical parts that often mimic natural tissue or its morphology. Biomaterials are substances that have been engineered for medical purposes, either to treat, augment, repair, or replace a tissue function of the body, and can be derived from nature or synthesized in the laboratory.[11]

These materials play a crucial role in ensuring the functionality of the final application because they are exposed to mechanical stresses or chemical reactions that may affect their properties. As such, it becomes essential to study mechanochemical systems and biocompatibility accurately.[12]

To ensure that the final product meets the required specifications, the construction process must be customized based on the material's performance. Post-processing techniques play a crucial role in ensuring the accuracy and precision of additive manufacturing in the medical sector. Some common post-processing techniques include surface smoothing, surface coating, support removal or sterilization.[10]

Bioprinting in vascular surgery is an innovative application of additive manufacturing technology specifically tailored for the field of vascular surgery. This technology allows for the precise layer-by-layer construction of complex anatomical structures, tailor-made to meet the specific needs of individual patients.[13]

This customization involves generating a digital 3D model using either imaging technologies, such as computer tomography or magnetic resonance, or computer-aided design (CAD) software. The customization process and the generated digital 3D model can be carried out using various types of software suitable for all printing technologies typically grouped in 7 families: powder bed fusion, binder jetting, directed energy deposition, VAT polymerization, material jetting, material extrusion, and sheet lamination.[14]

According to the American Society for Testing and Materials and its technical committee (ASTM F42—Additive Manufacturing), in healthcare all the AM families and the related 3D printing technologies are used.[14]

Sheet lamination (SL) – laminated object manufacturing (LOM) or selective deposition lamination (SDL) – employs foils to fabricate 3D-colored objects suitable for teaching activities or phantoms. However, residual material necessitates manual removal, which is not always possible with intricate shapes such an empty sphere. Powder bed fusion (PBF), as selective laser sintering (SLS) technology, and binder jetting (BJ), as multi-jet printing (MJP) or directed energy deposition (DED) technology, selectively fuse or bind powdered (or wired) materials, and are frequently utilized to produce orthopedic implants, prosthetics, or pharmaceutical applications. PBF and BJ are characterized by short production time and the absence of binding agents.[15]

VAT polymerization – stereolithography (SLA) (Figure 2.3.1) or digital light processing (DLP) technologies – or

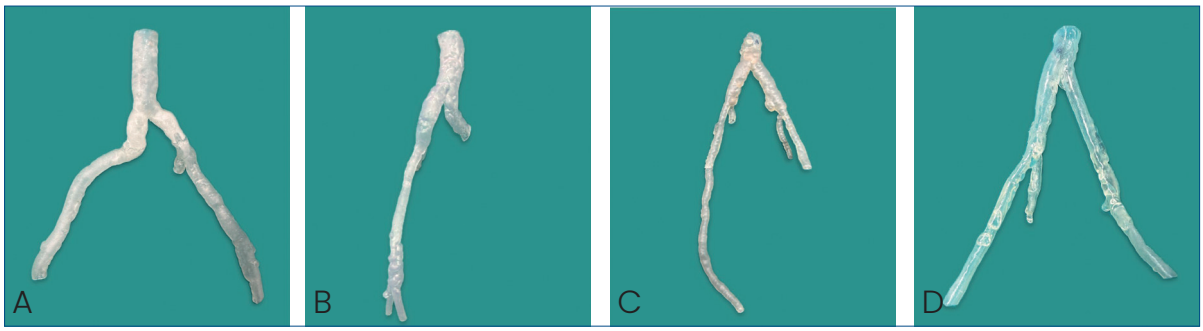


FIGURE 2.3.1 ● Custom-made patient-specific 3D models printed using SLA technology and different materials: A) Dental LT Clear; B) Dental LT Clear V2; C) Flexible 80A; D) Elastic 50A.

material jetting (MJ) – such as PolyJet (PJ) (Figure 2.3.2) – are commonly used approaches to create dental and orthopedic implants for medical applications. Resins react to a specific laser wavelength, building the designed object layer-by-layer. By employing VAT polymerization, it is possible to generate single-material empty objects whereas MJ enables multi-color and multi-material printing.[14]

Finally, material extrusion via fused deposition modelling (FDM) (Figure 2.3.3) or robocasting (RC)/Direct Ink Writing (DIW) is employed to heat or extrude materials to create the final 3D-printed object. Both these families and related technologies offer a wide range of materials that can be used in the same printing process, allowing for the creation of engineered prototypes, medical devices, dental implants using ceramic materials, and even the production of living tissue and organs through bioprinting, which combines biological and synthetic materials.[16]

In light of the advancements in biomedical engineering, particularly with the advent of fused deposition modeling (FDM) in 3D printing, there has been a surge in enthusiasm surrounding Polylactic acid (PLA) due to its advantageous thermoplastic properties. PLA exhibits remarkable resilience as it can be repeatedly heated to its melting point, cooled, and reheated without undergoing significant degradation. PLA paired with FDM technology, facilitates the swift production of tailored structures and the development of platforms for a wide array of applications, spanning from research to surgical practices.[17]

Therefore these families of material processing and related technologies offer a wide range of materials that can be used in the different printing process, allowing for the creation of engineered prototypes, medical devices, dental implants using ceramic materials or 3D model using different types of resins (e.g.photopolymers), thermoplastic polymer (*e.g.* nylon) or plastic.

The healthcare AM technology landscape from 2021 to 2028 is projected to be dominated by several key methods. These include stereolithography, electron beam melting, deposition modeling, laser sintering, laminated object manufacturing, and jetting technology.[18]

In conclusion, 3D printing provides the ability to produce customized models for complex surgeries, enabling the surgical team to enhance preoperative planning. Additionally, 3D printing has the potential to train young surgeons by offering a trial-and-error approach.

To lay the groundwork for large-scale production, it is imperative to identify or innovate new cost-effective biomaterials that are both biocompatible and sterilizable. These materials should be capable of ensuring accuracy, precision, and high quality throughout the device development process and subsequent post-processing/finishing procedures, while also meeting regulatory requirements.

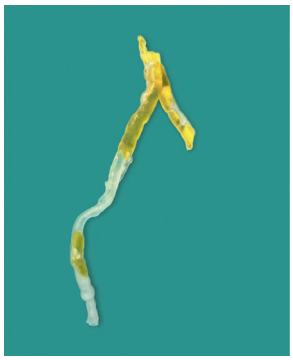


FIGURE 2.3.2 ● Custom-made patient-specific 3D model printed using PolyJet technology and combining rigid and soft materials (respectively VERO YELLOWV RGD 838 and AGILUS30 CLEAR FLX93).

FIGURE 2.3.3 ● Custom-made patient-specific 3D model printed using FDM technology and Polylactic acid (PLA) material.

3D PRINTING TECHNOLOGIES USED FOR VASCULAR SURGERY PURPOSES

When focusing on the use of 3D printing technologies in vascular surgery, it's important to note that not all the technologies discussed in our previous paragraph seem to be currently employed in this field, based on available literature.

The printing of a 3D-model for vascular surgery typically starts by exporting data in DICOM (Digital Imaging and Communications in Medicine) from a CTA.[3, 14] The CTA should be in good, quality, with a slice thickness not greater than 1mm, preferably submillimetric, in order to obtain a precise 3D-model.[19–21]

Subsequently, the process of generating 3D patient-specific or custom-made models moves on to the next step. To obtain a .stl file, a medical imaging software is typically used. The region of interest is isolated, and a surface 3D rendering is obtained. Medical imaging software available for this purpose can be open-source, free, or commercially available. Most used open-source options in literature are 3D Slicer (The Slicer Community, www.slicer.org), and ITK-Snap (www.itksnap.org). Mimics (Materialise NS, Leuven, Belgium) is the most used solution among commercial software. Also Osirix (Pixmeo SARL, Switzerland), and Horos (Horos Project, https://horosproject.org/) can be used to obtain a .stl through a 3D surface rendering.

The .stl file can theoretically be sent directly to a 3D-printer for printing. However, the use of a mesh editing software is strongly advised to correct errors and to optimize and customize the model appearance through mesh refining, surface smoothing, and model scaling. In literature, the most used free option in vascular surgery seems to be Autodesk Meshmixer (San Francisco, CA, USA). Among commercial solutions, it seems the most used is 3matic (Materialise NV, Leuven, Belgium).

Following an in-depth look into current literature on 3D printing in vascular surgery about the specific 3D printers used, Stratasys (Eden Prairie, MN, USA), and 3D Systems Corporation (Rock Hill, SC, USA) emerged as top choices. It is worth noting that the printing time may range widely – from 3 to 72 hours – depending on the complexity of the model and the printing method employed. The costs are also quite variable, usually ranging from 10 to 1500 euros per model.[6, 19]

Interestingly, the most prevalent 3D printing technologies in the available literature were Fused Deposition Modeling (FDM), Stereolithography (SLA), and PolyJet. The choice of materials for 3D printing varies depending on the printing technology employed. For instance, PolyJet and SLA utilize distinct photopolymer resins—PolyJet employs polyurethane (PUR)-based resins, while SLA uses methacrylate-based resins. On the other hand, FDM utilizes thermoplastic materials like PLA (Polylactic Acid) and ABS (Acrylonitrile Butadiene Styrene), sometimes incorporating silicone coatings. Printed models can be rigid, flexible, or elastic; multi-material printers can incorporate both flexible and rigid parts (with different and customizable degrees of flexibility). The models can be transparent or opaque. This illustrates the versatility of 3D printing in creating models that suit specific surgical needs.

Reports in literature generally underscore the high accuracy of these models. The methods used to validate accuracy were diverse, from comparing model data to patient scans using complex algorithms to verifying vessel compatibility with X-rays and angiography. The precision of these models is key, and the research points out that factors like image quality during scanning and the printing process itself play vital roles in achieving this accuracy. For instance, the thickness of each slice during printing can greatly influence the fidelity of the final model.

3D PRINTING FOR DIAGNOSIS AND PLANNING IMPROVEMENT

The utilization of 3D printed models for surgical planning is emerging, and it is starting to demonstrate notable success across various vascular procedures, as evidenced by studies available in literature. At present, a fair number of articles can be found that detail the effective implementation of 3D models in pre-operative planning processes.[4, 5, 19, 21–25]

Among these, seven articles conducted prospective analyses involving patient-specific 3D models, encompassing a cohort of 209 patients. Notably, several studies highlighted significant enhancements in surgical performance and heightened self-confidence among both residents and experienced surgeons when utilizing 3D models for planning and intraoperative guidance.

In one study, residents reported tangible improvements in procedure planning and technical skills, which could potentially translate into improved patient safety.[5] The integration of 3D models into pre-operative planning was consistently associated with therapeutic success and facilitated discussions surrounding treatment strategies and outcomes. Furthermore, studies emphasized the potential of 3D printing technology to reduce operating times and guide decisions on treatment approaches, particularly in complex cases like aortic arch aneurysms and fenestrated-EVAR procedures.

Complications were documented in a subset of cases, yet technical success without major procedure-related issues was reported in several instances, underlining the value of meticulous pre-operative planning with 3D models. Notably, the adoption of 3D printing facilitated critical decision-making, such as shifting from endovascular to open repair strategies based on anatomical considerations.

In fact, the vast majority of the studies about vascular surgery and 3D-printing are related to endovascular procedures. Additionally, the use of 3D models in robotic-assisted abdominal vascular surgeries highlighted the pivotal role of evaluating vascular morphology to optimize surgical approaches for patients with anatomical anomalies.

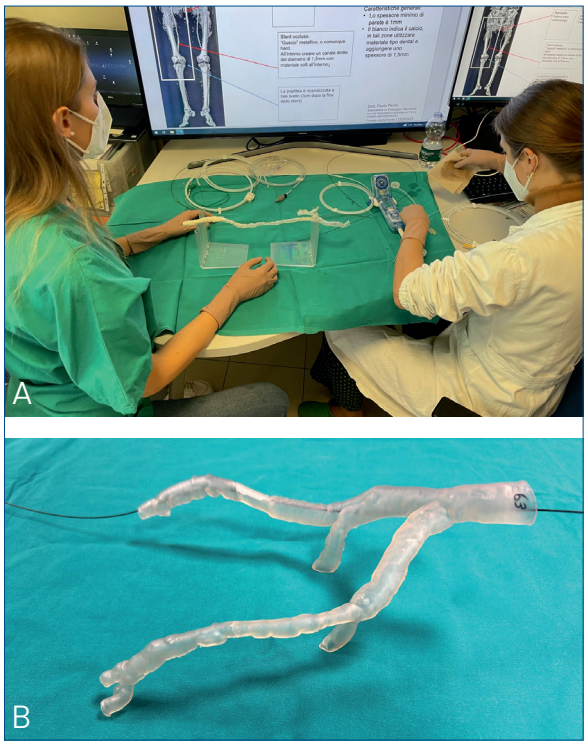


FIGURE 2.3.4 ● A) Vascular surgery residents training on a custom-made patient-specific 3D printed models with guidewires, catheters and angioplasty balloons; B) custom-made patient-specific 3D printed model engaged with a .035" floppy guidewire (Terumo, Shibuya-ku Tokyo, Japan).

FIGURE 2.3.5 ● A) Training with a custom-made patient-specific 3D printed model mimicking the fluoroscopy technique with the use of a light, a camera and a connected screen; B) image visualized at the screen.

Therefore, the ability to create 3D-printed models of specific anatomical conditions for hands-on learning is a key distinction between using 3D printing and traditional anatomical models. 3D printing holds significant appeal for crafting implants tailored to individual patients.[26] The rapid implementation of design improvements is essential for the success of any medical device. With the use of 3D printing models, the rapid feedback also increases confidence in clinical practice and accelerates the process of perfecting the design essential for doctors and also for patients.

3D-printed models revealed to be indispensable assets also for simulation-based training. The training methodology can usually take two forms: either utilizing a custom-designed setup or working exclusively with 3D models (Figure 2.3.4). The setup is constructed by integrating the 3D vascular model with a fluid pump to replicate the circulatory system[3,19,27–30]. Enhancements such as the use of a LED light and a camera linked to a screen are incorporated to emulate the operative room environment and fluoroscopy techniques (Figure 2.3.5).[5, 30, 31]

In the realm of literature, few authors have designed and sketched 3D printed models using CAD rather than deriving the models from patient DICOM data.[31, 32] These simulators are tailored to replicate precise vascular pathologies, as demonstrated by Foresti *et al.*[32] who engineered a 3D model closely resembling the femoral-popliteal segment with stenosis based on measurements extracted from patients' CT images (Figure 2.3.6). The realism of the developed systems and the efficacy of training sessions are assessed through comprehensive evaluations employing questionnaires and rating scales. Simulation-based training has proven effective in enhancing residents' technique and self-confidence enabling them to become familiar with a broad spectrum of materials and techniques in vascular and endovascular surgery.[4, 5, 19, 20, 31] Additionally, the capacity of 3D models to offer precise depths and tactile sensations contributes to a comprehensive understanding of anatomical complexity.[4, 19, 33]

To note, the 3D-printed models we discussed for endovascular planning are considered for all intents and

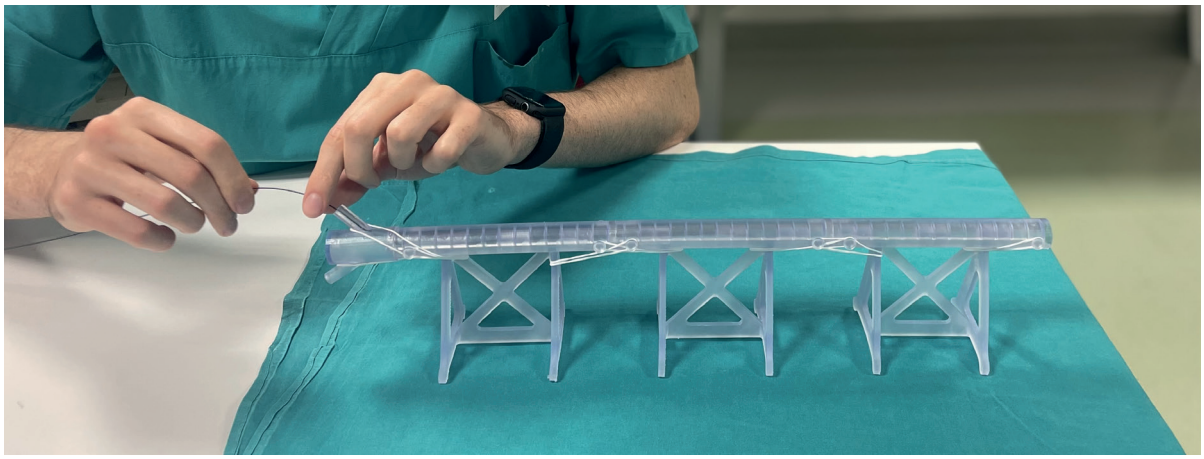


FIGURE 2.3.6 ● Vascular surgery resident training with the Modular System for Endovascular Training (M-SET), the simulator for peripheral artery disease.

purposes as medical devices (patient-specific devices, or custom-made devices, as appropriate). Thus, these 3D-printed models are currently subject to regulatory oversight in accordance with EU Regulation 2017/745 and the Medical Device Coordination Group (MDCG) document 2021-24 "Guidance on classification of medical devices". These regulations establish a framework for the classification and assessment of 3D-printed models used in medical contexts, ensuring compliance with stringent safety and performance standards. Manufacturers in this field are mandated to adhere to these regulations, reflecting the evolving landscape of medical technology and the imperative to uphold patient safety and efficacy in the use of 3D-printed models for vascular surgical applications.[34]

FUTURE PERSPECTIVES

Future perspectives in endovascular surgery are poised to undergo significant advancements through the integration of 3D printed models with innovative materials, technologies, and virtual reality (VR) platforms. One exciting avenue involves the exploration of novel printing materials specifically tailored for vascular simulation, offering enhanced biomechanical properties that mimic vascular tissues more accurately.[35] These advanced materials could provide realistic tactile feedback during simulation, facilitating improved training and procedural rehearsals.

Moreover, the convergence of 3D printing with emerging technologies like augmented reality (AR) and VR holds immense promise. By integrating 3D models into interactive virtual environments, clinicians can immerse themselves in lifelike simulations, visualizing complex anatomies, offering to the patients personalized solutions and augmenting surgical precision in complex cases and practicing interventions in a risk-free setting by offering a trial-and-error approach to residents and fellows. Additionally, the concept of biolibraries—comprehensive repositories of patient-specific anatomical data—can be integrated with 3D printing technologies. This integration could enable rapid prototyping of custom implants and devices, tailored precisely to individual patient anatomy. Together, these advancements signify a transformative future for endovascular surgery, where 3D printing serves as a catalyst for innovation, precision, and personalized patient care.

CONCLUSIONS

3D-printing in endovascular surgery is a developing area with promising future potential, as demonstrated by the wide array of models and reports available in current literature. In the majority of the studies available in literature, researchers have focused on two key aspects: the precision of 3D printed models and the realism of the simulation and planning experience. The capability of conventional 3D printing technologies to produce patient-specific models with high dimensional accuracy was generally confirmed by most of the studies. The capacity of these models to faithfully replicate real-world procedural challenges has been evaluated positively by both trainees and experts, and finally validated. In summary, 3D-printed models used for diagnosis, planning, and finally training and simulation in endovascular surgery are dependable and offer significant clinical value. Future research efforts should be focused on new materials, faster and cheaper technologies, and seamless integration into routine clinical practice and training curriculum for endovascular residents and fellows.

REFERENCES

1. Garg I, Siembida JM, Hedgire S, *et al.* Computed Tomography Angiography for Aortic Diseases. Radiol Clin North Am 2024;62:509–25.
2. Garg I, Grist TM, Nagpal P. MR Angiography for Aortic Diseases. Magn Reson Imaging Clin N Am 2023;31:373–94.

3. Nguyen P, Stanislaus I, McGahon C, *et al.* Quality assurance in 3D-printing: A dimensional accuracy study of patient-specific 3D-printed vascular anatomical models. Front Med Technol 2023;5:1097850.
4. Marone EM, Auricchio F, Marconi S, *et al.* Effectiveness of 3D printed models in the treatment of complex aortic diseases. J Cardiovasc Surg (Torino) 2018;59(5):699–706.
5. Torres I, De Luccia N. A simulator for training in endovascular aneurysm repair: the use of three dimensional printers. Eur J Vasc Endovasc Surg 2017;54:247–53.
6. Coles-Black J, Bolton D, Chuen J. Accessing 3D Printed Vascular Phantoms for Procedural Simulation. Front Surg 2020;7:626212.
7. Nayahangan LJ, Konge L, Schroeder TV, *et al.* A National Needs Assessment to Identify Technical Procedures in Vascular Surgery for Simulation Based Training. Eur J Vasc Endovasc Surg 2017;53:591–9.
8. Goudie C, Kinnin J, Bartellas M, *et al.* The Use of 3D Printed Vasculature for Simulation-based Medical Education Within Interventional Radiology. Cureus. Published online April 3, 2019. doi:10.7759/cureus.4381
9. Salmi M. Additive Manufacturing Processes in Medical Applications. Materials 2021;14:191.
10. Mamo HB, Adamiak M, Kunwar A. 3D printed biomedical devices and their applications: A review on state-of-the-art technologies, existing challenges, and future perspectives. J Mech Behav Biomed Mater 2023;143:105930.
11. Sultan MdT, Lee OJ, Lee JS, *et al.* Three-Dimensional Digital Light-Processing Bioprinting Using Silk Fibroin-Based Bio-Ink: Recent Advancements in Biomedical Applications. Biomedicines 2022;10:3224.
12. Chen EP, Toksoy Z, Davis BA, *et al.* 3D Bioprinting of Vascularized Tissues for in vitro and in vivo Applications. Front Bioeng Biotechnol 2021;9:664188.
13. Bozkurt Y, Karayel E. 3D printing technology; methods, biomedical applications, future opportunities and trends. J Mater Res Technol 2021;14:1430–50.
14. Adugna YW, Akessa AD, Lemu HG. Overview study on challenges of additive manufacturing for a healthcare application. IOP Conf Ser Mater Sci Eng 2021;1201:012041.
15. Gibson I, Rosen D, Stucker B. Sheet Lamination Processes. In: Additive Manufacturing Technologies. Springer New York; 2015:219–44.
16. Grivet-Brancot A, Boffito M, Ciardelli G. Use of Polyesters in Fused Deposition Modeling for Biomedical Applications. Macromol Biosci 2022;22:2200039.
17. Pérez-Davila S, González-Rodríguez L, Lama R, *et al.* 3D-Printed PLA Medical Devices: Physicochemical Changes and Biological Response after Sterilisation Treatments. Polymers 2022;14:4117.
18. Healthcare Additive Manufacturing Market Report. Healthcare Additive Manufacturing Market Size, Share & Trends Analysis Report By Technology (Laser Sintering, Deposition Modeling), By Application, By Material, By Region, And Segment Forecasts, 2023 - 2030. ttps://www.grandviewresearch.com/industry-analysis/healthcare-additive-manufacturing market?utm_source=prnewswire&utm_medium=referral&utm_campaign=hc_03-feb 21&utm_term=healthcare-additive-manufacturing-market&utm_content=rd1, (accessed on September 20, 2021).
19. Magagna P, Xodo A, Menegolo M, *et al.* Applications of Three-Dimensional Printing in the Management of Complex Aortic Diseases. Aorta Stamford Conn 2022;10:242–8.
20. Little CD, Mackle EC, Maneas E, *et al.* A patient-specific multi-modality abdominal aortic aneurysm imaging phantom. Int J Comput Assist Radiol Surg 2022;17:1611–7.
21. Borracci RA, Ferreira LM, Alvarez Gallesio JM, *et al.* Three-dimensional virtual and printed models for planning adult cardiovascular surgery. Acta Cardiol 2021;76:534–43.
22. Marconi S, Negrello E, Mauri V, *et al.* Toward the improvement of 3D-printed vessels' anatomical models for robotic surgery training. Int J Artif Organs 2019;42:558–65.
23. Tam MD, Latham TR, Lewis M, *et al.* A Pilot Study Assessing the Impact of 3-D Printed Models of Aortic Aneurysms on Management Decisions in EVAR Planning. Vasc Endovascular Surg 2016;50:4–9.
24. Taher F, Falkensammer J, McCarte J, *et al.* The influence of prototype testing in three-dimensional aortic models on fenestrated endograft design. J Vasc Surg 2017;65:1591–7.
25. Kliewer ME, Bordet M, Chavent B, *et al.* Assessment of fenestrated Anaconda stent graft design by numerical simulation: Results of a European prospective multicenter study. J Vasc Surg 2022;75:99–108.e2.
26. Javaid M, Haleem A, Singh RP, *et al.* 3D printing applications for healthcare research and development. Glob Health J 2022;6:217–26.
27. O'Reilly MK, Reese S, Herlihy T, *et al.* Fabrication and assessment of 3D printed anatomical models of the lower limb for anatomical teaching and femoral vessel access training in medicine. Anat Sci Educ 2016;9:71–9.
28. Kaschwich M, Sieren M, Matysiak F, *et al.* Feasibility of an endovascular training and research environment with exchangeable patient specific 3D printed vascular anatomy: Simulator with exchangeable patient-specific 3D-printed vascular anatomy for endovascular training and research. Ann Anat Anat Anz Off Organ Anat Ges 2020;231:151519.
29. Kärkkäinen JM, Sandri G, Tenorio ER, *et al.* Simulation of Endovascular Aortic Repair Using 3D Printed Abdominal Aortic Aneurysm Model and Fluid Pump. Cardiovasc Intervent Radiol 2019;42:1627–34.
30. Kaufmann R, Zech CJ, Deutschmann M, *et al.* Endovascular embolization techniques in acute thoracic and abdominal bleedings can be technically reproduced and trained in a standardized simulation setting using SLA 3D printing: a 1-year single-center study. Insights Imaging 2022;13.
31. Matyjas M, Sauerbrey M, Wyschkon S, *et al.* Three-dimensional simulator: training for beginners in endovascular embolization with liquid agents. CVIR Endovasc 2021;4(1).
32. Foresti R, Fornasari A, Bianchini Massoni C, *et al.* Surgical Medical Education via 3D Bioprinting: Modular System for Endovascular Training. Bioengineering 2024;11:197.
33. Göçer H, Durukan AB, Tunç O, *et al.* Evaluation of 3D printing in planning, practicing, and training for endovascular lower extremity arterial interventions. Turk Gogus Kalp Damar Cerrahisi Derg 2021;29:20–6.
34. Medical Device Coordination Group Document. European Union. (2017). Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. Official Journal of the European Union, L 117/1. https://health.ec.europa.eu/system/files/2021-10/mdcg_2021-24_en_0.pdf
35. Foresti R, Rossi S, Pinelli S, *et al.* In-vivo vascular application via ultra-fast bioprinting for future 5D personalised nanomedicine. Sci Rep 2020;10:3205.

3

ENDOVASCULAR EMERGING TECHNOLOGIES AND "SUPER-NOVEL" THERAPEUTICAL STRATEGIES FOR COMPLEX AORTIC DISEASE

3.1 THE ROLE OF NEW ADVANCED TOOLS IN TREATING AORTOILIAC LESIONS: INTRAVASCULAR ULTRASOUND IMAGING AND INTRAVASCULAR LITHOTRIPSY

Franco Grego, Michele Piazza, Sabrina Menara, Elda Chiara Colacchio, Michele Antonello, Francesco Squizzato

INTRODUCTION

The scenario of Aorto-Iliac Occlusive Disease (AIOD) treatment has shifted dramatically in the recent years; endovascular techniques have become the preferred approach, also for more complex disease, if performed by an experienced team and does not compromise the chance for future surgical options.[1] The TASC II classification system is aimed to link the disease severity and extent to specific treatment options;[2] however today, other anatomical characteristics, such as lesion site, occlusion length, calcifications, extension in the common femoral artery or the infrarenal aorta are considered in the decision-making of the type of treatment and endovascular techniques to be used.[1]

In particular, IntraVascular UltraSound (IVUS) and IntraVascular Lithotripsy (IVL) represent important adjuncts that may be used to optimize the results in the treatment of advanced aorto-iliac lesions.

The aim of this chapter is to describe the rationale and results of the use of IVUS and IVL in AIOD.

IVUS

IVUS specifics

IVUS is an endoluminal imaging technique that has developed over the last decades, progressively acquiring greater importance, first in the field of interventional cardiology to then become useful and advantageous also in the treatment of arterial and venous disease.[3, 4] This catheter-based tool uses a piezoelectric transducer tip to generate detailed cross-sectional images of the vessel wall. The transducer emits sound waves and analyzes the returning echoes, creating a precise image of the vessel's internal structure.

The IVUS catheters are currently mainly provided by two companies. The catheter working length ranges from 90 to 150 cm, they require an introducer sheath from 5 to 8.5 French (Fr) and 0.014, 0.018, 0.035-inch guidewires with monorail system. IVUS probes emit ultrasound frequencies between 10 and 30 Hz, and the choice of ultrasound probe frequency is crucial for image quality and penetration depth. Higher frequencies offer superior image resolution, allowing for detailed visualization of the structures: 20 MHz are ideal for examining larger peripheral vessels or occlusive lesions in collateral vessels; 10 MHz have a deeper penetration, making them well-suited for imaging of the aorta.[4]

IVUS generates a two-dimensional image based on the vessel's characteristics. This grayscale image reflects the varying echogenicity of different tissues within the arterial wall.

Color-flow IVUS provides blood flow information thanks to ChromaFlo computer Software available on the Volcano System (Philips Volcano, San Diego, CA, USA). This device identifies blood cells movement by analyzing differences captured between adjacent frames and colors them red. It is useful to identify any anomalies between the vessel wall and the blood flow, but it cannot obtain velocities because Color-flow IVUS does not use the Doppler effect.[5]

It is possible to obtain even a longitudinal reconstruction, created to a sort of "pullback" of the IVUS probe, which can be used in addition to the axial images. Moreover, the Three-Dimensional IVUS technology is developing.[4]

IVUS use in AIOD

1. ***Technical assessment of iliac artery stenting***

   By providing detailed information, IVUS empowers physicians to take corrective actions if needed, ultimately leading to better patency rates and overall success of treatment. Studies have yielded interesting results, IVUS is useful in identification of intraoperative technical defects during endovascular aortic bifurcation repair that would otherwise be missed by Digital Subtraction Angiography (DSA). This capability allows for the prompt implementation of additional endovascular procedures, ultimately improving the outcome of the intervention.[6-8]

   IVUS is a valuable complementary tool to DSA in many arterial applications and this is supported by retrospective studies.[9] This tool provides several precise imaging parameters, these include true vessel diameters, wall thickness and differentiation of layers, length, shape and volume of lesions, plaque composition (fibrous, calcified, mixed), identification and extent of intimal flaps, arterial dissections, plaque ulcerations, thrombus presence, residual stenosis, and stent conformation. Also, in case of reconstruction of the aortic bifurcation by kissing stents or CERAB, IVUS can be used to verify the conformation of the stents and apposition to the aortic wall, that are of mainstay importance to optimize the clinical results.

   Advantages of IVUS for the technical assessment of iliac stents are the possibility to repeatedly re-use the same probe to verify the technical success, and the avoidance of contrast dye and radiation (Figure 3.1.1).

2. ***Selection of proximal and distal landing sites***

   Iliac artery stenting ideally consists in an iliac coverage from healthy to healthy vessel. The healthy proximal

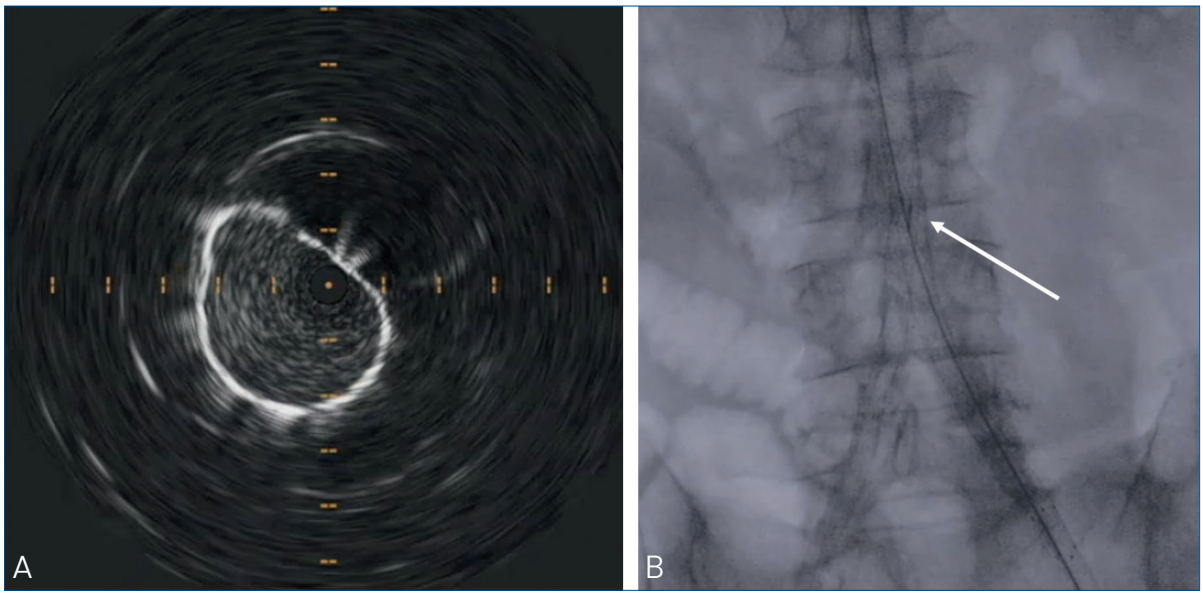


FIGURE 3.1.1 ● IVUS guided intraoperative revision. After kissing stenting of the aortic bifurcation, IVUS technical assessment detected a right stent compression (A). The radiopaque marker of the IVUS probe can be visualized via fluoroscopy (B).

and distal landing site can be determined by IVUS, that can be used to mark the intended proximal and distal stent deployment sites. In case of landing near the origin of important collaterals, such as the inferior mesenteric artery or the hypogastric arteries, these can be precisely visualized and marked by IVUS before stent deployment, in order to avoid their coverage. In case multiple vessels need to be spared, they can be marked under the same C-arm projection, without the need for multiple angiographies, with the result of sparing iodinated radiations and contrast dye exposure.

IVUS is also helpful in the identification of landing sites in cases of heavy calcifications and mural thrombosis. In heavily calcified lesions,[10] landing in a calcified vessel may predispose to rupture or dissection. IVUS can be used to identify a landing site as less calcified as possible, optimizing the outcomes. In case of parietal thrombus, that usually is not visible on DSA, IVUS can identify a thrombus-free region where to land with the stents.

3. ***In situ sizing***

IVUS plays a valuable role in guiding the selection of the balloons and stents to be used during the procedure.[4, 6, 11, 12] IVUS provides precise real-time assessment of the target vessel diameter, while the centimeter-marked catheter allows for a measurement of the lengths.

Rationale for IVUS use

The main rationale for using IVUS in aortoiliac interventions is to overcome the limitations of standard DSA. DSA has been traditionally used as the gold standard imaging modality during endovascular procedures. However, DSA provides a two-dimensional image of the lumen of the vessel and can underestimate the severity of stenosis in diseased arteries, particularly when the lesion is eccentrically located. Moreover, arteriography alone may not be sufficient to determine stent conformation, which is important in aortoiliac reconstructions by kissing stents or CERAB.[2, 11, 12]

The IVUS effectively identifies poorly deployed stents, allowing for immediate corrective measures and preventing the need for future reintervention. IVUS-guided treatment of lower limb endovascular interventions is associated with significantly lower post-procedural complication rates and improved limb salvage rates.

While IVUS offers significant advantages, its routine use for all patients is currently limited by cost considerations. Selecting patients who will benefit most from IVUS is essential. While IVUS adds to the initial cost of procedures, its benefits may outweigh the expense. Studies suggest that IVUS can be cost-effective in the long run. This is because it can lead to more precise and successful procedures, potentially reducing the need for repeated interventions and it may contribute to better patient outcomes, including lower complication rates (morbidity) and mortality. This is especially true for complex cases. Overall, the benefits of IVUS far outweigh the additional procedural costs, making it a cost-effective and valuable tool for improving patient outcomes.[6, 7]

Of equal importance, IVUS plays a crucial role in reducing radiation exposure and contrast agent use. This technique utilizes ultrasound instead of X-rays, significantly lowering radiation risks for both patients and

medical staff. Additionally, IVUS often provides detailed images with minimal iodinated contrast, which is particularly beneficial for patients with chronic kidney disease (CKD) or contrast allergies.[11,13,14]

IVUS shows promise as a valuable tool for AIOD interventions. Retrospective studies suggest high rates of freedom from revascularization when IVUS is used alongside standard DSA. While IVUS demonstrates significant improvement in immediate technical outcomes and short-term results, its widespread adoption requires further research. Developing algorithms that optimize long-term patient outcomes is crucial for broader utilization. Cost-effectiveness analyses suggest that IVUS may ultimately reduce overall costs by reducing complications. However, further studies are needed to definitively demonstrate the cost-effectiveness of routine IVUS use in all endovascular procedures.

Despite the need for more data, IVUS is likely to play an increasingly important role in modern AIOD interventions.[4,11]

IVL

IVL mechanism

Patients with arterial severe calcification are more likely to experience complications like amputation and even have a higher mortality rate. The Global Vascular Guidelines (GVG) reinforce this concern, highlighting that severe calcification is a negative predictor for both technical success of the intervention and a higher risk of amputation. The presence of significant vascular calcification can make aorto-iliac revascularization more challenging, since they may be associated to difficult crossing, subintimal recanalization, risk of rupture, early recoil, and loss of patency during follow-up. Studies have shown a strong correlation between the severity of calcification and the increased risk of in-stent thrombosis and stent fracture, and worse clinical outcomes. Target lesion patency is susceptible to two limitations, insufficient intraoperative balloon dilatation and post-procedure lesion recoil. While covered stents offer a potential benefit of improved patency rates, their placement may still not exert enough radial force to effectively maintain the patency of the vessel.[15,16]

The Shockwave IVL device (Shockwave Medical, Inc, Santa Clara, CA, USA) is a novel endovascular tool for treating severely calcified arterial lesions. This innovative technology utilizes an angioplasty balloon to deliver targeted acoustic waves directly to the vessel wall. These shockwaves create microscopic fractures within the calcified plaque making it less rigid and easier to treat. IVL offers significant advantages for addressing highly calcified blockages: enhanced vessel compliance by breaking down calcifications making it easier to open the artery with balloons or stents during angioplasty procedures; the increased compliance achieved with IVL also lowers the risk of vessel wall rupture during treatment, improving the overall safety; treatment versatility, IVL it is mainly used for vessel preparation before stent placement, but it may be considered also a standalone treatment in selected patients.

IVL specifics

The Shockwave IVL system comprises three essential components: the generator that serves as the central power unit, generating the high-energy acoustic shockwaves, a connector cable, and a catheter. The IVL catheter itself has two key features, a lithotripsy emitter that creates the acoustic shockwaves and an integrated balloon (the balloon's inflation optimizes the apposition of the emitters to the targeted lesion). IVL catheters offer a range of sizes to accommodate varying arterial diameters. These balloon catheters typically measure 30 to 60 mm in length and come in a variety of diameters ranging from 2.5 to 12 millimeters, they require an introducer sheath from 5 to 8 Fr. Following successful passage of a 0.014 guidewire across the calcified lesion, the IVL catheter is carefully advanced through the blockage. Radiopaque marker bands located on the catheter shaft aid in precise positioning within the artery. Once optimally positioned, the Shockwave IVL system delivers targeted acoustic energy to the lesion.[17,18]

Standalone IVL

AIOD represents a considerable barrier impeding a wide spectrum of endovascular procedures: IVL is playing an increasingly important role as a valuable tool for enhancing transfemoral access in minimally invasive procedures requiring large-bore sheaths.[19-21] IVL could potentially eliminate the need for stenting in selected cases, such as to allow for safe passage of large sheaths during transfemoral access. This clinical use has been mostly demonstrated in trans-catheter aortic valve replacement (TAVR),[18] but it is gaining increasing clinical importance also in facilitating the advancement of endovascular aortic devices in thoracic, thoracoabdominal, and abdominal endovascular aortic repair.[22] The advantages of this approach consist in creating a safe passage for the large bore device, without the risk of rupture and avoiding the potential coverage of the hypogastric arteries determined by using covered stents to create an endoconduit. The latter aspect may be particularly important in thoracoabdominal aortic repair, where the maintenance of the hypogastric arteries patency is crucial for the prevention of spinal cord ischemia.

In case of obstructive aorto-iliac disease, standalone IVL may be considered in case there are crucial aortic side vessels arising from a calcified high-grade stenosis, as lumbar arteries, accessory renal arteries, or hypogastric arteries. This approach allows for a safe treatment of the calcified lesion, without the risk of rupture, and avoids covering collateral vessels by covered stents. However, data on the standalone use of intravascular lithotripsy (IVL) remains limited, and this may be considered as a valuable strategy for highly calcified, short segment

stenosis. In case of complete calcified occlusions, considering that the lesion crossing is usually achieved by a subintimal route and there is a consistent risk of early recoiling, we do not consider IVL as a treatment, but only for vessel preparation before stenting.

IVL and stenting

The main use of the Shockwave intravascular lithotripsy (IVL) consists in vessel preparation in case of heavily calcified plaques, to facilitate stent deployment and improved the stent patency over time.[15, 18]

IVL has shown promising potential as an endovascular treatment modality for severely calcified occlusions not only for iliac disease but even for extensive atherosclerotic disease involving the infrarenal aorta: reported cases involving patients with coral-reef occlusion of the infrarenal aorta, and its bifurcation successfully treated with IVL support the feasibility of this approach.[23]

After IVL, the use of both covered and bare metal stents may be considered. Clinical evidence suggests that covered stents offer a significant advantage over bare-metal stents in patients with severe aortoiliac occlusive disease, as they reduce the incidence of restenosis and occlusion. Additionally, they mitigate the risk of rupture, making them the preferred option for treating occlusions, particularly following subintimal recanalization where the risk of early recoil is substantial.[24] In our clinical practice, we avoid the risk of bare metal stent in case of calcified lesion, to avoid the risk of rupture, that may be still present also after IVL. However, bare metal stent after IVL may be indicated to maintain the patency of side vessels, such as the hypogastric arteries. This can be achieved by IVL of the iliac axis, followed by covered stenting of the common and external iliac arteries, and deployment of a short interposition bare metal stent at the level of the origin of the hypogastric artery (Figure 3.1.2).

Further research is necessary to definitively determine IVL's efficacy across different patient profiles, lesion types, and intervention approaches.

CONCLUSIONS

The use of new technologies, such as IVUS and IVL, enhance the endovascular treatment of complex aortoiliac obstructive lesions, expanding its indications and optimizing the outcomes. The combination of these novel endovascular tools allows for an optimization of the outcomes of severely calcified lesions, that have been traditionally treated by open surgery (Figure 3.1.3). Further studies are still necessary to clarify the applications, the clinical outcomes, and the cost-efficacy of these techniques.

REFERENCES

1. Aboyans V, Ricco JB, Bartelink MEL, *et al.* 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:305–68.
2. Norgren L, Hiatt WR, Dormandy JA, *et al.*; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.
3. Arko F, McCollough R, Manning L, *et al.* Use of intravascular ultrasound in the endovascular management of atherosclerotic aortoiliac occlusive disease. Am J Surg 1996;172:546–9; discussion 549-50.
4. Sidawy AN, Perler BA. Rutherford's Vascular Surgery and Endovascular Therapy. 2nd volume Set 9th Edition.
5. Diethrich EB, Irshad K, Reid DB. Virtual histology and color flow intravascular ultrasound in Peripheral Interventions. Semin Vasc Surg 2006;19:155–62.
6. Buckley CJ, Arko FR, Lee S, *et al.* Intravascular ultrasound scanning improves long-term patency of iliac lesions treated with balloon angioplasty and primary stenting. J Vasc Surg 2002;35:316–23.
7. Antonello M, Piazza M, Menara S, *et al.* Role of intravascular

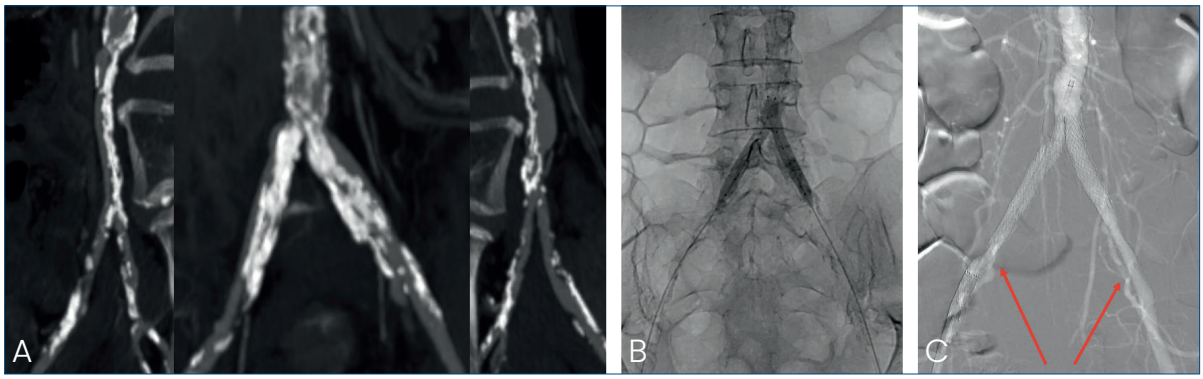


FIGURE 3.1.2 ● A case of AIOD with calcification involving the aortic bifurcation and extending to both the right and left iliac arteries (A). A kissing IVL of the aortic bifurcation was performed, and then extended to both iliac axis (B). IVL was followed by deployment of covered balloon expandable kissing stents on the aortic bifurcation and covered self-expandable stents on the external iliac arteries. On both sides, a bridge bare metal stent was deployed at the level of the common-external iliac artery transition to preserve hypogastric artery patency (C). Despite the extensive calcifications, this could be performed in a safe way thanks to the IVL that allowed the bare metal stent deployment and post dilatation minimizing the risk of rupture.

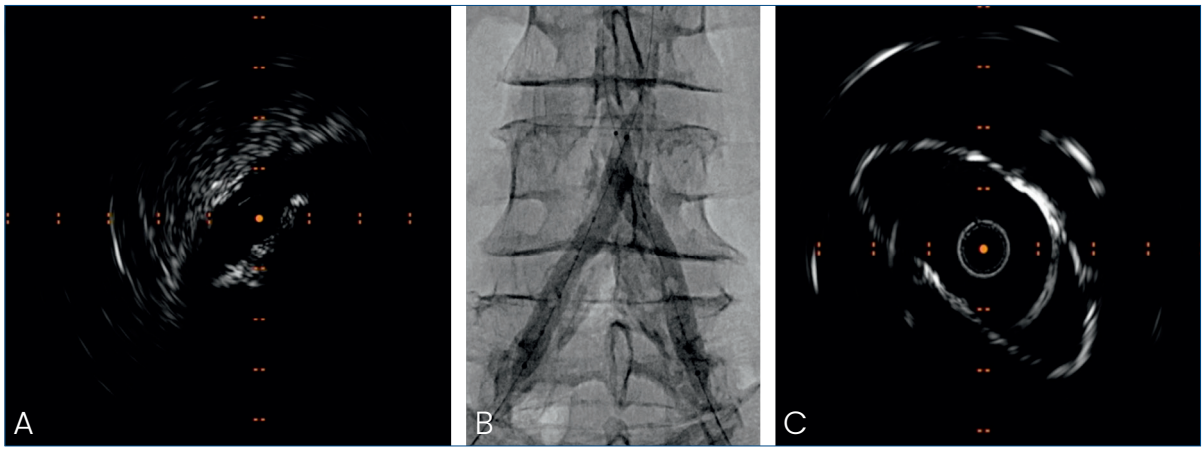


FIGURE 3.1.3 ● Combination of IVUS and IVL in a case of aortoiliac calcific occlusion. Due to the presence of a calcified occlusion, a subintimal lesion crossing was achieved on the left iliac axis. IVUS imaging demonstrates the f subintimal recanalization (A). A kissing IVL ballooning was performed at the level of the aortic bifurcation (B). Technical assessment after IVL and kissing stenting of the aortic bifurcation. IVUS shows a residual stenosis at the level of the distal landing site in the common iliac artery due to early recoil (C).

ultrasound for the technical assessment of endovascular reconstruction of the aortic bifurcation. J Vasc Surg 2024:S0741-5214(24)00432–4.
8. Piazza M, Squizzato F, Saviane G, *et al.* Geometrical Analysis and Preliminary Results for the Endovascular Reconstruction of Aortic Bifurcation Using New-Generation Balloon-Expandable Covered Stents in the Kissing Conformation. Ann Vasc Surg 2020;67:148–57.
9. Makris GC, Chrysafi P, Little M, *et al.* The role of intravascular ultrasound in lower limb revascularization in patients with peripheral arterial disease. Int Angiol 2017;36:505–16.
10. Kawasaki D, Tsujino T, Fujii K, *et al.* Novel use of ultrasound guidance for recanalization of iliac, femoral, and popliteal arteries. Catheter Cardiovasc Interv 2008;71:727–33.
11. Loffroy R, Falvo N, Galland C, *et al.* Intravascular Ultrasound in the Endovascular Treatment of Patients With Peripheral Arterial Disease: Current Role and Future Perspectives. Front Cardiovasc Med 2020;7:551861.
12. Sharafuddin MJ, Hoballah JJ, Kresowik TF, *et al.* Long-term outcome following stent reconstruction of the aortic bifurcation and the role of geometric determinants. Ann Vasc Surg 2008;22:346–57.
13. Secemsky EA, Aronow HD, Kwolek CJ, *et al.* Intravascular Ultrasound Use in Peripheral Arterial and Deep Venous Interventions: Multidisciplinary Expert Opinion From SCAI/AVF/AVLS/SIR/SVM/SVS. J Vasc Interv Radiol 2024;35:335–48.
14. Mariani J Jr, Guedes C, Soares P, *et al.* Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) randomized controlled trial. JACC Cardiovasc Interv 2014;7:1287–93.
15. Wong CP, Chan LP, Au DM, *et al.* Efficacy and Safety of Intravascular Lithotripsy in Lower Extremity Peripheral Artery Disease: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg 2022;63:446–56.
16. Conte MS, Bradbury AW, Kolh P, *et al.*; GVG Writing Group. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg 2019;69(6S):3S-125S.e40.
17. Kereiakes DJ, Virmani R, Hokama JY, *et al.* Principles of intravascular lithotripsy for calcific pla- que modification. JACC Cardiovasc Interv 2021;14:1275–92.
18. Armstrong, Ehrin J. Intravascular lithotripsy for treatment of calcified, stenotic iliac arteries: a cohort analysis from the Disrupt PAD III study. Cardiovascular Revascularization Medicine 2020;21.10:1262–8.
19. Ristalli F, Dini CS, Stolcova M, *et al.* Role of Lithotripsy for Small Calcified Iliacs in the Era of Big Devices. Curr Cardiol Rep 2019;21:143.
20. Rosseel L, De Bacjer O, Sondergaard L, *et al.* Intravascular iliac artery lithotripsy to enable transfemoral thoracic endovascular aortic repair. Catheter Cardiovasc Interv 2020;95:E96-9.
21. Di Mario C. Lithotripsy-assisted transfemoral aortic valve implantation. Eur Heart J 2018;39:2655.
22. Di Mario C, Ristalli F, Ravani M, *et al.* A prospective registry of intravascular lithotripsy enabled vascular access for transfemoral transcath- eter aortic valve replacement. J Am Coll Cardiol Intv 2019;12:502–4.
23. Piazza M, Squizzato F, De Massari C, *et al.* Intravascular lithotripsy angioplasty for treatment of atherosclerotic coral-reef occlusion of the infrarenal aorta and its bifurcation. J Vasc Surg Cases Innov Tech 2023;9:101106.
24. Mwipatayi BP, Thomas S, Wong J, *et al.* Covered Versus Balloon Expandable Stent Trial (COBEST) Co-investigators. A comparison of covered vs bare expandable stents for the treatment of aortoiliac occlusive disease. J Vasc Surg 2011;54:1561–70.

3.2 ROUTINE USE OF CO_2: FORGET IODINATED-CONTRAST INJURIES DURING COMPLEX AORTIC PROCEDURES

Paolo Spath, Enrico Gallitto, Federica Campana, Marcello Lodato, Stefania Caputo, Rodolfo Pini, Chiara Mascoli, Andrea Vacirca, Gianluca Faggioli, Mauro Gargiulo

INTRODUCTION

Endovascular aortic repair (EVAR) represents nowadays the first choice of treatment for aortic pathologies, offering a minimally invasive solutions with reduced morbidity and mortality compared to open surgical techniques.[1, 2] Although the well-known improvements and reduced invasiveness, some issues may arise directly from the nature of EVAR, as radiation exposure to patients and physicians and the impairment of renal function after both standard and complex EVAR repair.[3] Acute kidney injury (AKI) represents one of the most frequent potential postoperative complications in patients treated for abdominal aortic aneurysm (AAA) with EVAR, impacting up to 20% of cases.[4] Specifically, nephrotoxicity secondary to intraprocedural use of iodinated contrast medium (ICM) represents the most frequent cause of postoperative AKI,[5] especially in patients presenting with chronic kidney disease (CKD). This complication has been recently defined in literature as post-contrast acute kidney injury (PC-AKI), affecting 4% to 18% of EVAR cases, and depending on the volume of ICM employed during the procedure and the preoperative hydration protocols used.[4, 6, 7]

In this context, different procedures can be used to reduce the amount of contrast usage, as the use of vertebral bone marks located during pre-operative planning in order to locate vessel origin, intra-operative fusion imaging, and dilution of ICM halved with saline.[8] Carbon dioxide digital subtraction angiography (CO_2-DSA), has emerged as an intriguing option compared traditional ICM angiography, particularly in patients with contraindications such as patients with CKD or with allergy to ICM.

Over the years, CO_2-DSA angiographies have been increasingly adopted in endovascular peripheral[9] and standard and complex aortic repair,[10] alone or with adjunctive iodinated contrast medium, offering a compelling alternative and providing high-quality imaging without the associated above-mentioned risks derived by ICM.

However, since at the present time the use of CO_2 in endovascular aortic procedures lacks of strong evidences yet, CO_2-DSA adopted as an alternative to ICM was still not mentioned in the most recent European Society for Vascular Surgery (ESVS) 2024[3] Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms and Italian Society for Vascular and Endovascular Surgery guidelines on the management of abdominal aortic aneurysm.[11]

This chapter aims to analyze the physical and technical aspects of CO_2-DSA and its evolution over the aortic treatment with an established role for standard EVAR for AAA and focusing specifically as an increasing and advanced solution for fenestrated/branched EVAR (F/B-EVAR) procedures in complex abdominal aneurysm repair, with the ultimate goal in reducing exposure to contrast induced injuries and preserving patient's renal function while obtaining high technical success rates.

CARBON DIOXIDE PHYSICAL CHARACTERISTICS: DIOXIDE ADVANTAGES AND DISADVANTAGES COMPARED TO IODINATED CONTRAST MEDIUM

Iodinated contrast medium (ICM) presents some characteristics that limits its use in specifics situation, where CO_2-DSA might represent an alternative option. Table 3.2.I summarizes the main aspects of CO_2-DSA.

Comparing ICM and CO_2 as contrast agents we need to bear in mind their physical characteristics, advantages, and disadvantages. ICM is known for its high miscibility with blood, providing excellent visualization of all visceral vessels, which is essential in detailed diagnostic aortic procedures. However, its disadvantages are significant, including nephrotoxicity, hepatotoxicity, and allergenic potential. ICM can be administered through both manual and automated injectors.

On the other hand, CO_2 contrast media, characterized by its high buoyancy and low viscosity, eliminates the risks associated with nephrotoxicity, hepatotoxicity, and allergies. Despite these benefits, CO_2 has notable limitations such as the prohibited use above the diaphragm due to risks of air embolism and challenges in visualizing vessels originating from the posterior aortic wall. Additionally, the use of CO_2 may hypothetically increase radiation exposure necessitating longer or more intense imaging sequences.

Due to the low atomic number and density, CO_2 is considered a negative contrast agent, absorbing x-ray to a lesser extent than the surrounding blood and vessel wall, and therefore requiring double subtraction imaging technique.[12] Carbon dioxide pathognomonic physical characteristic is its high buoyancy, meaning its ability of floating on blood since the upwards force pushing up the fluid is significantly greater than the weight of CO_2.[10] This can be highlighted on the cross-table lateral projection of large diameter vessels such as the aorta, and it is responsible of the challenging visualization of visceral vessels originating from the posterior aortic wall such as posterior renal arteries, which might represent a limitation in aortic endovascular repair in specifics anatomies (Figure 3.2.1). Carbon dioxide is about 400 times less viscous than iodinate contrast medium, hence allowing

TABLE 3.2.1 ● Main characteristics and advantages of using CO_2 in endovascular aortic repair (EVAR).

Characteristic	Details and applications
Radiolucency	• *Does not absorb X-rays, enhancing visualization of blood vessels during fluoroscopy.* • *Radiolucency allows for more accurate fluoroscopy navigation and stent deployment during endovascular procedure.*
Solubility	• *Highly soluble in blood, enabling quick absorption and elimination from the body.* • *Solubility reduces the risk of possible embolism, issue that may be common with other contrast agents.*
Low viscosity	• *Lower viscosity 400 times lower than iodinated contrast media.* • *Low viscosity decreases the risk of vascular complications and possibility to be injected by small catheters and introductory with lower pressure.*
Non-allergenic	• *Safe for use in patients who may have allergies to iodinated contrast agents.* • *Its non-allergenic properties eliminate concerns regarding toxicity for renal and liver parenchyma.*
Temporary effects	• *Rapidly absorbed and thus any inadvertent vascular injection is usually temporary.* • *Minimizes the risk of volume exposure.*
Cost-effective	• *Generally less expensive than iodinated contrast agents.* • *The main cost is to be considered for the injection systems.*

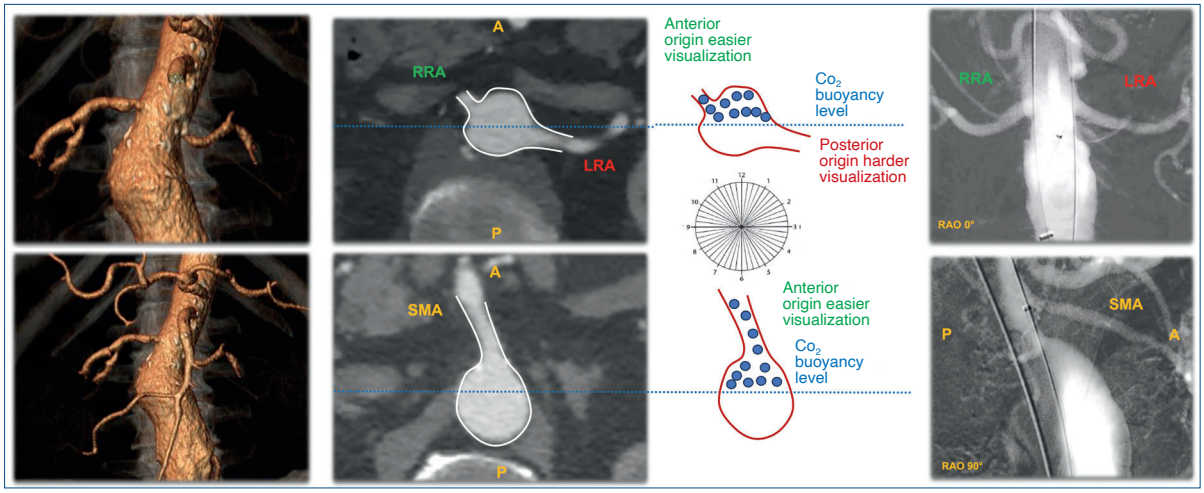


FIGURE 3.2.1 ● Schematic representation of buoyancy of CO_2 in the evaluation of target visceral vessels. Superior line: evaluation of renal arteries at anterior-posterior view, with the Right Renal Artery (RRA) with origin at 10 o'clock and Left Renal Artery (LRA) with origin at 4 o'clock and the favorable filling of CO_2 in the anterior portion of the aorta, allowing in this case a good visualization of both RRA and LRA. Inferior line: evaluation of the superior mesenteric artery (SMA) anterior-posterior view with the origin at 12 o'clock, resulting with easy filling by CO_2 above its buoyancy level and determining complete visualization during 90° projection.

its injection through smaller introducers and small-bore needles.[13] Regarding the ejection process, CO_2-DSA requires a dedicated delivery system to prevent gas compression and air contamination.[14]

Further, CO_2 high solubility admits its injection into the arteries below the diaphragm without any clinically significant gas embolism.[12] On the other hand, in case of inadvertent CO_2 injection above the diaphragm, some issue may arise since the neurotoxic action in disruption of the blood-brain barrier,[15] thus causing seizures and loss of consciousness. On a similar account, due to its buoyance nature, injecting CO_2 into the abdominal aorta in patients in prone position should be avoided, as the gas may enter the spinal and lumbar arteries, resulting in spinal cord ischemia [12]. More frequently, the use of CO_2 in endovascular procedures is associated to self-limited nonserious adverse effects occurring during or shortly after the procedure like abdominal discomfort, nausea, paresthesia or transient focal weakness, and tenesmus.[10, 16]

CO_2 is ejected by the lungs in a single pass, thus allowing consistent volumes of CO_2 to be used. In theory, injections should be separated by 3 to 5 minutes to prevent accumulation and subsequent pulmonary artery vapor lock. Moreover, CO_2-DSA should be cautiously evaluated in patients with patent *foramen ovale* or atrial septal defect.

The main advantages of the use of CO_2 as contrast medium is the lack of anaphylactic response and nephrotoxicity compared to ICM, applicable in patients with CKD and therefore reducing the risk of development of post-contrast acute kidney injury (PC-AKI). Contrast induced nephropathy (CIN) risk classification[12] has been proposed to recognize in patients exposed to ICM those at negligible risk for CIN (eGFR ≥5 mL/min/1.73 m^2), intermediate risk of CIN (eGFR between 30 and 44 mL/min/1.73 m^2), and high risk for CIN (eGFR <30 mL/min/1.73 m^2). In this latter case, it is suggested to avoid contrast-enhanced exams or procedures, whereas in case of intermediate risk or high risk for CIN with unavoidable exposure to ICM it is recommended a prophylactic saline solution hydration and to minimize contrast volume.[17]

CARBON DIOXIDE INJECTION MODALITIES

Carbon dioxide angiographies require a dedicated delivery system to prevent gas compression and air contamination and can be performed through two different injection systems, being manual or automatic. The manual injection is the first line and historical procedure, allowing full injection control and cheaper costs. However, it is characterized by a high radiation exposure, potential risk of air contamination, and the inability to control pressure of the injection.[18]

Literature on procedures performed with manual CO_2-DSA showed high rates of intra- and post-operative adverse events, probably related to air contamination and to high volume and pressure of injection.[19, 20] The automatic injector, with the most widespread in Europe being the Angiodroid injector (Angiodroid S.p.A., San Lazzaro di Savena, Italy), is a mobile, computerized injector with a dedicated remote-control system, that allows for setting specific injection volumes and pressures.[21] The advantages include a reduced operator radiation exposure for operators, the ability to precisely control injection volumes and pressure, and thus potentially reduce associated side effects and eliminate the risk of air contamination.[8, 22, 23] The main disadvantage is represented by the high cost of this system.

Carbon dioxide injection can be performed using diagnostic catheters or introducer. It is suggested to position the tip just above the territory of interest according to bone landmarks and computed tomography preoperative evaluation.[24]

ROLE OF CO_2-DSA IN EVAR

The role of CO_2-DSA in postoperative renal function protection has been well established and investigated in numerous studies in literature[20, 25–33] showing a lower rate of PC-AKI in patients undergoing CO_2-DSA compared to ICM-EVAR (Table 3.2.II). Specifically, Busutti *et al.*[30] recently described a significantly lower incidence of PC-AKI and higher eGFR values in the immediate post-procedure controls, as well as during the follow up period. Further, Criado *et al.*[20] reported a 12.7% greater decrease in postoperative estimated glomerular filtration rate (eGFR) of patients treated with ICM-EVAR compared to group done with CO_2. Moreover, Vacirca *et al.*[29] reported a significantly lower postoperative serum crea-

TABLE 3.2.II ● Principal studies reporting experiences with use of CO_2 in endovascular aortic repair and main role in renal function protection and arteries and endoleak visualization.

Author *et al.*	Year	No. of CO_2 patients	Comparative study	Zero contrast cases, N.	Article focus	PO-RFW in CO_2-EVAR *vs.* ICM-EVAR	Renal arteries visualization with CO_2 -DSA
Chao *et al.*[34]	2007	16	Yes	3	Endoleak detection with CO_2 DSA angiography	-	
AD. Lee *et al.*[25]	2010	17	No	0	Impact of CO_2-DSA in renal function protection and intraoperative arterial visualization	Improved w/o statisitcal significance	Both renal arteries visualized in 53%
Knipp *et al.*[26]	2010	4	Yes	3	Impact of CO_2-DSA in renal function protection in ruptured AAA	Improved w/o statisitcal significance	
Criado *et al.*[20]	2012	114	Yes	72	Comparison in renal function protection between CO_2 and CO_2+ICM angiographies	Improved w/o statisitcal significance	

to be continued

continues

Author *et al.*	Year	No. of CO_2 patients	Comparative study	Zero contrast cases, N.	Article focus	PO-RFW in CO_2-EVAR *vs.* ICM-EVAR	Renal arteries visualization with CO_2 -DSA
Huang *et al.*[35]	2012	76	No	76	Endoleak detection with CO_2 DSA angiography		
Sueyoshi *et al.*[6]	2015	40	No	40	Endoleak detection with CO_2 DSA angiography		
Mendes *et al.*[27]	2017	16	Yes	6	Impact of CO_2-DSA in renal function protection	Improved w/o statisitcal significance	Both renal arteries visualized in 100%
De Angelis *et al.*[28]	2017	17	No	16	Efficacy of CO_2-DSA in arterial visualization and graft deployment		Both renal arteries visualized in 100%
Takeuchi *et al.*[33]	2018	30	Yes	0	Impact of CO_2-DSA in renal function protection	Improved w/o statisitcal significance	
Mascoli *et al.*[16]	2018	31	No	31	Efficacy of CO_2-DSA in arterial visualization and graft deployment		Both renal arteries visualized in 61%
Mascoli *et al.*[37]	2018	21	Yes	16	Type II endoleak detection		
Vacirca *et al.*[29]	2022	72	Yes	16	Impact of CO_2-DSA in renal function protection and arterial detection	Improved with statisitcal significance	Both renal arteries visualized in 69%
Unal *et al.*[32]	2023	34	Yes	0	Impact of CO_2-DSA in renal function protection	Improved with statisitcal significance	
Busutti *et al.*[30]	2023	22	Yes	5	Impact of CO_2-DSA in renal function protection	Improved with statisitcal significance	
Quaglino *et al.*[31]	2023	52	Yes	52	Impact of CO_2-DSA in renal function protection and endoleak detection	Improved w/o statisitcal significance	
Vacirca *et al.*[22]	2023	65	No	19	Compare arterial visualization before, during, and after graft deployment		
Esposito *et al.*[23]	2023	17	No	17	To evaluate feasibility and safety of a "zero contrast" approach in patients with CKD		
TOTAL		644		372			

EVAR: Endovascular Aortic Repair; CO_2; carbon dioxide; ICM: iodinated contrast media; DSA: Digital Subtraction Angiography; PO-RFW: Post-Operative Renal function Worsening; w/o: without.

tinine in CO_2-EVAR population compared to ICM-EVAR group, as well as a lower mean postoperative eGFR decrease.

An important point is to determine the efficiency of arterial visualization with CO_2-DSA to correctly identify proximal and distal landing zone during EVAR (Table 3.2.II). Visualization of both renal arteries to individuate the proximal landing zone before graft deployment ranges between 53% and 100%[16, 22, 25, 27–29] (Figure 3.2.2 A-C) visualization of both hypogastric arteries and correct identification of the distal landing zone was detected in all cases of CO_2-DSA.[16,28,29] For this reason CO_2-DSA

can be an useful tools even for complex aorto-iliac repair such as iliac branch devices (Figure 3.2.2 D-F).

Interestingly, for the rate of visualization of the lowest renal arteries both volume of the aneurysm[16] and the presence of a short aortic proximal neck[29] has been identified as factors inefficient lowest renal artery visualization. Moreover, a multicenter study compared the renal arteries detection between angiography performed through pigtail catheter and femoral introducer, demonstrating a significantly better image quality when using femoral introducer rather than the pigtail and a significantly better image quality when used the femoral introducer rather than the pigtail, probably explainable by the fact that the pigtail catheter, having multiple side holes, might cause higher gas dispersion (Figure 3.2.2B).

Another important topic discussed in literature is the efficiency of endoleak (EL) detection during intraoperative angiographies performed with CO_2.[25, 31, 34–37] Overall, literature shows comparable rate of detection of type I-III endoleaks between CO_2 and ICM.[6, 25] However, when considering type II endoleaks, results are discordant. Some authors[31-37] reported a more accurate type II EL detection with CO_2-DSA compared to ICM-DSA, whereas other report a reduced detection.[35, 36]

ROLE OF CO_2-DSA IN COMPLEX AORTIC ANEURYSMS

Fenestrated and branched endovascular repair (F/B-EVAR) is an established technique used to treat complex abdominal aneurysms, including juxtarenal/pararenal abdominal aortic aneurysms (JPAAA) and thoracoabdominal aortic aneurysms (TAAA).[38–42] One of the most pressing concerns in the postoperative management of patients undergoing F/B-EVAR procedures is the potential deterioration of renal function. This phenomenon represents a common adverse event following the intervention and has been associated with multiple negative outcomes, including prolonged hospitalization, morbidity, together with increased peri-operative and follow-up mortality rates.[39, 43] The precise etiology of post-F/B-EVAR renal function decline is multifaceted, and multiple factors may synergistically to compromise renal perfusion and function. Among them, PC-AKI may play a relevant role and automated CO_2 angiography can be evaluated as an alternative to ICM as it has been widely described for standard endovascular aortic repair.

At the present time, only one experience[8] has been reported in literature describing the use of CO_2 imaging in FEVAR aiming to reduce the amount of ICM and the consequent risk of postoperative renal function failure. Specifically, this monocentric study over 45 patients compared the combined use of CO_2-DSA + fusion imaging and to standard ICM use with fusion imaging.

Overall, results described a successful reduction in the amount of ICM, shorter hospitalization time and better renal function preservation at 30 days in patients treated with CO_2-DSA.

However, technical success, procedure and fluoroscopy time, radiation dose, and 6-month reinterventions were found to be comparable to those of the standard imaging protocol for FEVAR, as well as an equally effective role in endoleaks detection.

It is well known that preoperative planning, together with the accurate indication of vertebral bone marks in order to pre-view the ostia of target visceral vessels, the choice of endograft design and the use of intraoperative fusion imaging, play an important role in reducing contrast media administration. The integration of CO_2-DSA with fusion imaging technologies enhances procedural accuracy and precision. These results can be obtained following a step-by-step procedure that can be implemented in everyday clinical practice during complex endovascular AAA repair and that we have summarized in Table 3.2.III and Figure 3.2.3, for the procedure of a standard custom-made fenestrated endograft with "zero-contrast" procedure, using CO_2-DSA as the unique contrast agent.

After the arterial accesses and placement of guidewire inside the thoracic and abdominal aorta, a 5F or a 6F introducer sheath is introduced and parked in the paravisceral aorta to make the first angiography of the target visceral vessels (TVVs) both in anterior-posterior (to better define the renal arteries) and the lateral views (for celiac trunk and superior mesenteric arteries ostia). In this case the angiography is performed with selected baseline parameters volume of 100 mL and pressure of 600-650 mmHg.

Moreover, angiographies are conducted utilizing a 3-6 frame-per-second (fps) scheme and with selective angiographies, achieving a minimized radiation exposure without compromising image quality or procedural efficacy.

After this first injection of CO_2, fusion imaging is optimized to overlay the aorta and the offspring of TVVs. By overlaying preoperative imaging onto real-time fluoroscopy, fusion imaging provides guidance for device navigation and deployment, ensuring optimal placement and alignment (Figure 3.2.3 B-C).

After Fusion Imaging optimization, the endograft is then released and the opening is guided by fusion imaging overlay, TVVs origin markers and repeated CO_2-DSA to confirm the precise positioning on the custom-made device. These angiographic controls are conducted by the 5F/6F introducer sheath parked in the juxtarenal aorta and left outside the graft.

After the complete graft deployment, and with the aid of the above-mentioned tools, TVVs are catheterized, and bridging stents are deployed. All these passages are performed with CO_2-DSA guidance as mentioned above, without aby visualization issue even with the introducer sheaths inside the target arteries (Figure 3.2.3 D-E).

After bridging stenting of the target vessel, selective angiography is then performed to assess correct positioning, correct flaring, absence of endoleaks and vascularization of the targeted vessel.

For renal arteries these selective angiographies are

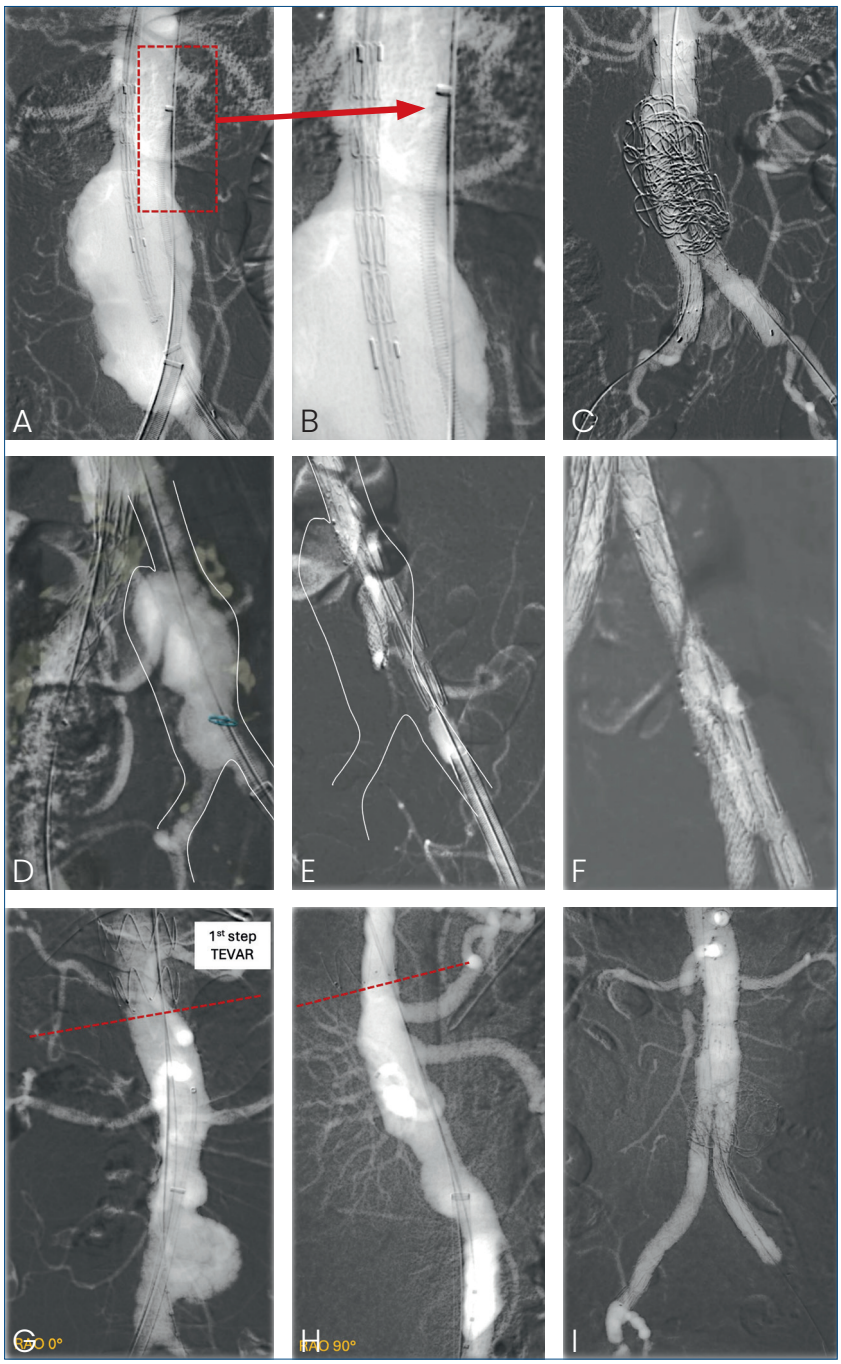


FIGURE 3.2.2 ● Technical aspects in the use of CO_2-DSA both in the standard and complex aortic procedures. A-C) CO_2-DSA used in a zero contrast standard EVAR procedure. A) Evaluation of the proximal neck after main-body delivery with visualization of both renal arteries; B) detail of the CO_2-DSA performed effectively the use of dedicated Flexor 6F introducer sheath; C) final angiography after EVAR and aneurysmal sac coil embolization. D-F) CO_2-DSA used in a zero contrast iliac branch device procedure. D) Evaluation of the internal iliac artery bifurcation by the use of a Flexor 6F introducer sheath; E) selective angiography of the iliac branch device; F) final angiography with patency of the common, internal and external iliac artery and exclusion of the iliac aneurysm. G-I) CO_2-DSA used in a zero contrast repair for a visceral step of a thoraco-abdominal repair. Detail of the previous implanted TEVAR and the angiographies for renal arteries (G) and superior mesenteric artery and celiac trunk (H) always keeping below the previous thoracic graft considered as upper point for injection (red dashed line); I) final angiography with complete aneurysmal exclusion and target visceral vessels patency.

conducted inside the artery, with the dedicated introducer sheaths (generally a 7F 55 cm or a 6F 90 cm). In these specific scenario, in order to reduce potential damages, low pressure (80 mmHg) and low volume (60 mL) are set for the CO_2-DSA (Figure 3.2.3 F, G).

For the superior mesenteric artery and celiac trunk, selective angiography after positioning of bridging stents is carried out differently. Automated CO_2 injection is set at baseline level (650 mmHg pressure and 100 mL volume) using the introducer sheath for stent-graft deployment retrieved from the visceral vessel and left inside the aorta (Figure 3.2.3 H, I).

Eventually, after the completion of the visceral segment, bifurcated endograft is deployed in the infrarenal aorta, followed by iliac limb deployment and final angiography. These last CO_2-DSA are performed using the introducer sheath from femoral artery of both sides. Final angiography is done by advancing the introducer sheath inside the iliac limb, performing both an anterior-posterior and lateral view acquisitions. In all these latter views,

TABLE 3.2.III ● Step-by-step procedure protocol for the optimal use of CO_2-DSA together with fusion imaging in complex endovascular aortic repair.

Step #	Procedural step	Description	Figure 3.2.3 (Panel)
1	Planning, Vertebral Bone Marks and Fusion Imaging set-up	• *After endograft evaluation and leading time period for production, on the pre-operative CTA vertebral bone marks are evaluated for TVVs origin levels and Fusion Imaging is set-up.*	A
2	Patient and access preparation	• *Femoral and arterial accesses are prepared by surgical cut-down or percutaneous eco-guided puncture.* • *Guidewires are inserted into abdominal and thoracic aorta.* • *In case of need for an approach from above, surgical cut-down of the left axillary artery is performed with arterial exposure.*	
3	Diagnostic CO_2 Angiographies	• *Performed in anteroposterior and lateral projections using a 5F/6F flexor introducer sheath positioned and then left in position at the level of the juxtarenal aorta.* • *Automated CO_2 injector set at 650 mmHg pressure and 100 mL volume.*	B-C
4	Fusion Imaging Optimization	• *CO_2 angiography images acquired in the first angiographies are used to optimize fusion imaging with the origins of TVVs.*	B-C
5	Endograft Deployment and TVVs catheterization	• *Angiographies are repeated step-by-step as necessary, with adjustments based on fusion images to ensure optimal positioning of the endograft.* • *The angiographies are conducted by the 5F/6F 55 cm introducer sheath parked in the juxtarenal aorta outside the graft, allowing correct visualization of the TVVs during graft positioning, vessel catetherization and bridging stenting.*	D-E
6	Selective CO_2 Angiographies of Renal Arteries after bridging stenting	• *Performed to assess deployment of bridging stent grafts and presence of endoleak and renal artery and parenchymal perfusion.* • *Automated CO_2 injection set at 80 mmHg pressure and 60 mL volume using the introducer sheath for stent-graft deployment inside the targeted artery.*	F-G
7	CO_2 Angiographies for SMA and CT after bridging stenting	• *Performed to assess deployment of bridging stent grafts and presence of endoleak and vessel correct vascularization.* • *Automated CO_2 injection set at baseline level (650 mmHg pressure and 100 mL volume) using the introducer sheath for stent-graft deployment left inside the aorta and not in the target artery.* • *In case of TVV catheterization from above an 8F introducer via left axillary access should be required.*	H-I
8	Bifurcated Graft and iliac limbs Deployment	• *Angiographic assessment for aortic bifurcation, contralateral and ipsilateral iliac bifurcations, facilitated by automated CO_2 injection through femoral sheaths of both the main body and contralateral limb.* • *Automated CO_2 injection set at baseline level (650 mmHg pressure and 100 mL volume)*	L
9	Completion Angiography	• *Final angiography performed by the introducer sheath from femoral artery, positioned proximally inside iliac limb, capturing both anteroposterior and lateral views.* • *CO_2 injection set at baseline level (650 mmHg pressure and 100 mL volume)*	M

CO_2: carbon-dioxide; F: French; CTA: Computed Tomography Angiography; TVVs: Target Visceral Vessels; FI: Fusion Imaging; mmHg: millimeters of mercury; mL: milliliters; SMA: superior mesenteric artery; CT: celiac trunk.

automated angiography is set with aortic baseline volume and pressure values (Figure 3.2.3 L-M).

Several experiences have already demonstrated that both hybrid room and fusion imaging technologies are effective in reducing radiation exposure and the amount of ICM in standard and advanced endovascular aortic procedures.[44, 45] Thus, combining these advantages with CO_2-DSA might lead to a "zero contrast" approach even for F/B-EVAR procedures.

Renal artery visualization remains a critical issue, particularly when the artery has a posterior origin in large-volume aneurysms due to CO_2 physical tendency to

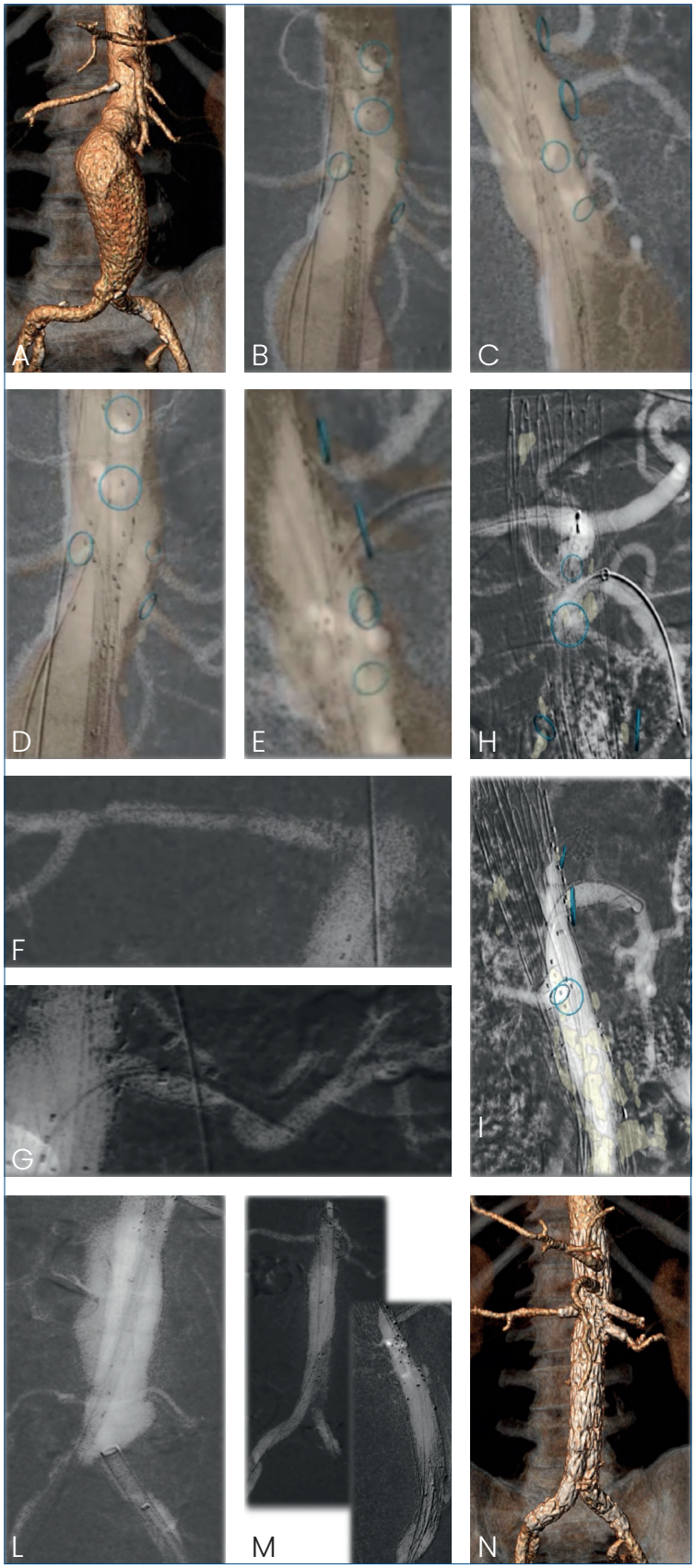


FIGURE 3.2.3 ● Technical aspects of the implantation of a 5-fenestration custom-made endograft (FEVAR) using synergic application of fusion imaging and CO_2-DSA. A) Pre-operative computed tomography evaluation in three-dimension volume rendering of the juxtarenal aneurysm; B) anterior posterior CO_2-DSA and adjustment of the fusion imaging for renal arteries (RA); C) lateral view CO_2-DSA and adjustment of the fusion imaging for superior mesenteric artery (SMA) and celiac trunk (CT); D, E) deployment, opening of the endograft following step by step fusion imaging guidance and CO_2-DSA and cannulation of the target vessels with diagnostic introducer outside the main body endograft; F) selective CO_2-DSA of right RA after stenting with diagnostic introducer inside the target artery; G) selective CO_2-DSA of lower left RA after stenting with diagnostic introducer inside the target artery; H) selective CO_2-DSA of CT after stenting with diagnostic introducer inside the main body endograft; I) selective CO_2-DSA of SMA after stenting with diagnostic introducer inside the main body endograft; L) CO_2-DSA of the abdominal aorta and positioning of distal bifurcated universal body and iliac limbs; M) final CO_2-DSA in both anterior-posterior and lateral views with diagnostic introducer inside the iliac limb artery; N) postoperative CTA with 3-D volume rendering reconstruction.

replaces the blood floating in the anterior aortic portion.

The combination of fusion imaging and CO_2-DSA allows to bring together the information provided by both techniques, being sufficient to visualize at least two target visceral vessels to modify the position of the fusion imaging mask. Hence, the superior mesenteric artery and the celiac trunk mostly originate from the anterior portion of the aorta, and they can be easily detected by CO_2-DSA, therefore being sufficient to optimize the fusion imagining position and to have reasonable guidance for target vessels cannulation (Figure 3.2.1).

With the application of these protocol, CO_2-DSA can be used to treat all complex abdominal aortic aneurysm (juxta-renal and para-renal pathologies) and thoraco-abdominal aortic aneurysm (TAAA). Since the use of CO_2 above the diaphragm has been correlated to air embolism and potential brain damages,[23] CO_2 can be only used for evaluating the paravisceral aortic segment. This can be satisfactory for juxtarenal and pararenal AAAs, where the proximal injection is delivered below the level of diaphragm. However, in case of Crawford extent I-II-III-IV TAAA, it could be combined with a small amount of iodinated contrast media for the visualization of the proximal landing zone at the level of the thoracic aorta, whereas CO_2-DSA can be used in the following paravisceral and abdominal steps, using the pre-implanted TEVAR as reference for the proximal overlap of the fenestrated/branched device (Figure 3.2.2 G–I).

Eventually, since the presence of air in the bowel is associated with diagnostic artifacts that could disturb CO_2-DSA diagnostics. Preoperative administration of active carbon pills and avoidance of fruit and vegetable intake for 2 or 3 days before the procedure may limit this problem.[22, 29]

No further experiences on the use of CO_2-DSA in complex aortic repair are yet published in Literature. Published results are still preliminary, and ICM remains necessary for specific cases of target visceral vessels selective angiography after bridging stenting and for completion angiography, especially for extended TAAA repairs. After increased experience and technical knowledge, ICM angiography could be totally replaced by CO2 injection, retaining ICM exclusively for doubtful cases or in specific anatomies where CO_2-DSA will be insufficient.

CONCLUSIONS

The use of carbon dioxide in endovascular aortic repair represents a significant advancement in this field, offering a promising alternative to iodinated contrast media. It is beneficial for patients, as extensively reported in current literature, combining the reduction of renal injuries with the provision of stable, high-quality images and positive technical outcomes. Specific aspects such as the visualization of renal arteries and guidance during standard EVAR deployment have now reached a stable, satisfactory level, allowing "zero contrast" procedures to become routine clinical practice. However, some issues, such as endoleak visualization, remain topics of debate. The lack of comprehensive bibliographic studies on large experiences, together with the need for long-term results and randomized controlled trials, are still required to provide this technique with a strong evidence base for recommendation.

The evolution of these techniques has made it possible to apply this diagnostic procedure even in the more challenging scenarios of advanced endovascular aortic procedures, such as during fenestrated and branched endografting procedures for thoraco-abdominal and complex abdominal aneurysms. This application is now gaining ground, although some aspects, such as the assessment of the thoracic aortic segment, are not feasible due to the physical limitations of CO_2. In this complex field, the synergistic application of CO_2-DSA, together with fusion imaging techniques and hybrid room facilities, plays an active role in preserving patient renal function and reducing the amount of radiation, while maintaining both technical success and procedural time comparable to the standard of care. Multicenter studies and larger experiences are now required to establish this technique as routine use even in complex aortic procedural protocols.

REFERENCES

1. Powell JT, Sweeting MJ, Ulug P, *et al.* Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg 2017;104:166–78.
2. Greenhalgh RM, Brown LC, Kwong GPS, *et al.* EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet 2004;364:843–8.
3. Wanhainen A, Van Herzeele I, Bastos Goncalves F, *et al.* European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. European Journal of Vascular and Endovascular Surgery. 2024 Jan;S1078588423008894.
4. Saratzis A, Melas N, Mahmood A, *et al.* Incidence of Acute Kidney Injury (AKI) after Endovascular Abdominal Aortic Aneurysm Repair (EVAR) and Impact on Outcome. Eur J Vasc Endovasc Surg 2015;49:534–40.
5. Liu Y, Liang X, Xin S, *et al.* Risk factors for contrast-induced acute kidney injury (CI-AKI): protocol for systematic review and meta-analysis. BMJ Open 2019;9:e030048.
6. Mun JH, Kwon S kyung, *et al.* Renal function-adjusted contrast medium volume is a major risk factor in the occurrence of acute kidney injury after endovascular aneurysm repair. Medicine 2021;100:e25381.
7. Cheng EL, Hong Q, Yong E, *et al.* Validating the use of contrast-induced nephropathy prediction models in endovascular aneurysm repairs. J Vasc Surg 2020;71:1546–53.
8. Gallitto E, Faggioli G, Vacirca A, *et al.* The benefit of combined carbon dioxide automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting. J Vasc Surg 2020;72:1906–16.
9. Palena LM, Diaz-Sandoval LJ, Candeo A, *et al.* Automated Carbon Dioxide Angiography for the Evaluation and Endovascular Treatment of Diabetic Patients With Critical Limb Ischemia. J Endovasc Ther 2016;23:40–8.
10. Sharafuddin MJ, Marjan AE. Current status of carbon dioxide angiography. J Vasc Surg 2017;66:618–37.

11. on behalf of the Italian Guidelines for Vascular Surgery Collaborators - AAA Group, Pratesi C, Esposito D, Apostolou D, Attisani L, Bellosta R, *et al.* Guidelines on the management of abdominal aortic aneurysms: updates from the Italian Society of Vascular and Endovascular Surgery (SICVE). J Cardiovasc Surg [Internet]. 2022 Jun [cited 2024 May 22];63(3). Available from: https://www.minervamedica.it/index2.php?show=R37Y2022N03A0328
12. Cho KJ. Carbon Dioxide Angiography: Scientific Principles and Practice. VSI 2015;31:67–80.
13. Corazza I, Rossi PL, Feliciani G, *et al.* Mechanical aspects of CO2 angiography. Physica Medica 2013;29:33–8.
14. Hawkins IF, Mladinich CRJ, Storm B, *et al.* Short-term Effects of Selective Renal Arterial Carbon Dioxide Administration on the Dog Kidney. J Vasc Interv Radiol 1994;5:149–54.
15. Rudnick MR, Leonberg-Yoo AK, Litt HI, *et al.* The Controversy of Contrast-Induced Nephropathy With Intravenous Contrast: What Is the Risk? Am J Kidney Dis 2020;75:105–13.
16. Mascoli C, Faggioli G, Gallitto E, *et al.* Standardization of a Carbon Dioxide Automated System for Endovascular Aortic Aneurysm Repair. Ann Vasc Surg 2018;51:160–9.
17. Mueller C. Prevention of contrast-induced nephropathy with volume supplementation. Kidney Int 2006;69:S16–9.
18. Jakobi T, Meyborg M, Freisinger E, *et al.* Feasibility and impact of carbon dioxide angiography on acute kidney injury following endovascular interventions in patients with peripheral artery disease and renal impairment. J Nephrol 2021;34:811–20.
19. Fujihara M, Kawasaki D, Shintani Y, *et al.* Endovascular therapy by CO2 angiography to prevent contrast-induced nephropathy in patients with chronic kidney disease: a prospective multicenter trial of CO2 angiography registry. Catheter Cardiovasc Interv 2015;85:870–7.
20. Criado E, Upchurch GR, Young K, *et al.* Endovascular aortic aneurysm repair with carbon dioxide-guided angiography in patients with renal insufficiency. J Vasc Surg 2012;55:1570–5.
21. Corazza I, Sapignoli S, Cercenelli L, *et al.* Automated CO2 angiography: Injection pressure and volume settings. Medical Engineering & Physics 2020;80:65–71.
22. Vacirca A, Faggioli G, Vaccarino R, *et al.* The optimal operative protocol to accomplish CO2-EVAR resulting from a prospective interventional multicenter study. J Vasc Surg 2023;77:1405-1412.e1.
23. Esposito D, Fargion AT, Dorigo W, *et al.* Total Iodine Contrast-free Strategy for the Endovascular Management of Abdominal Aortic Aneurysms in Chronic Kidney Disease Patients: A Pilot Study. Ann Vasc Surg 2023;93:92–102.
24. Gallitto E, Faggioli G, Gargiulo M, *et al.* Planning, Execution, and Follow-up for Endovascular Aortic Aneurysm Repair Using a Highly Restrictive Iodinated Contrast Protocol in Patients with Severe Renal Disease. Ann Vasc Surg 2018;47:205–11.
25. Lee AD, Hall RG. An Evaluation of the Use of Carbon Dioxide Angiography in Endovascular Aortic Aneurysm Repair. Vasc Endovascular Surg 2010;44:341–4.
26. Knipp BS, Escobar GA, English S, *et al.* Endovascular Repair of Ruptured Aortic Aneurysms Using Carbon Dioxide Contrast Angiography. Ann Vasc Surg 2010;24:845–50.
27. De Almeida Mendes C, De Arruda Martins A, Teivelis MP, *et al.* Carbon Dioxide as Contrast Medium to Guide Endovascular Aortic Aneurysm Repair. Ann Vasc Surg 2017;39:67–73.
28. De Angelis C, Sardanelli F, Perego M, *et al.* Carbon dioxide (CO2) angiography as an option for endovascular abdominal aortic aneurysm repair (EVAR) in patients with chronic kidney disease (CKD). Int J Cardiovasc Imaging 2017;33:1655–62.
29. Vacirca A, Faggioli G, Mascoli C, *et al.* CO2 Automated Angiography in Endovascular Aortic Repair Preserves Renal Function to a Greater Extent Compared with Iodinated Contrast Medium. Analysis of Technical and Anatomical Details. Ann Vasc Surg 2022;81:79–88.
30. Busutti M, Sensoni A, Vacirca A, *et al.* Renal Benefits of CO2 as a Contrast Media for EVAR Procedures: New Perspectives on 1 Year Outcomes. J Endovasc Ther 2023;152660282311622.
31. Quaglino S, Ferrero E, Ferri M, *et al.* Safety, Effectiveness and Pitfalls of Carbon Dioxide Routine Use as a Contrast Agent for Endovascular Abdominal Aortic Repair. Ann Vasc Surg 2024 Apr;101:120–6.
32. Unal EU, Iscan HZ, Erol ME, *et al.* Carbon Dioxide Guided Endovascular Aortic Aneurysm Repair in Impaired Renal Function: Propensity Score Matched Study. Eur J Vasc Endovasc Surg 2023;66:521–9.
33. Takeuchi Y, Morikage N, Matsuno Y, *et al.* Midterm Outcomes of Endovascular Aortic Aneurysm Repair with Carbon Dioxide–Guided Angiography. Ann Vasc Surg 2018;51:170–6.
34. Chao A, Major K, Kumar SR, *et al.* Carbon dioxide digital subtraction angiography–assisted endovascular aortic aneurysm repair in the azotemic patient. J Vasc Surg 2007;45:451–60.
35. Huang SG, Woo K, Moos JM, *et al.* A Prospective Study of Carbon Dioxide Digital Subtraction versus Standard Contrast Arteriography in the Detection of Endoleaks in Endovascular Abdominal Aortic Aneurysm Repairs. Ann Vasc Surg 2013;27:38–44.
36. Sueyoshi E, Nagayama H, Sakamoto I, *et al.* Carbon dioxide digital subtraction angiography as an option for detection of endoleaks in endovascular abdominal aortic aneurysm repair procedure. J Vasc Surg 2015;61:298–303.
37. Mascoli C, Faggioli G, Gallitto E, *et al.* The Assessment of Carbon Dioxide Automated Angiography in Type II Endoleaks Detection: Comparison with Contrast-Enhanced Ultrasound. Contrast Media & Molecular Imaging 2018;2018:1–7.
38. Abdelhalim MA, Tenorio ER, Oderich GS, *et al.* Multicenter trans-Atlantic experience with fenestrated-branched endovascular aortic repair of chronic post-dissection thoracoabdominal aortic aneurysms. J Vasc Surg 2023;S0741521423013095.
39. Gallitto E, Faggioli G, Melissano G, *et al.* Preoperative and postoperative predictors of clinical outcome of fenestrated and branched endovascular repair for complex abdominal and thoracoabdominal aortic aneurysms in an Italian multicenter registry. J Vasc Surg 2021;74:1795–1806.e6.
40. Oderich GS, Forbes TL, Chaer R, *et al.* Reporting standards for endovascular aortic repair of aneurysms involving the renal-mesenteric arteries. J Vasc Surg 2021;73:4S–52S.
41. Dias-Neto M, Vacirca A, Huang Y, *et al.* Outcomes of Elective and Non-elective Fenestrated-branched Endovascular Aortic Repair for Treatment of Thoracoabdominal Aortic Aneurysms. Ann Surg 2023;278:568–77.
42. Spath P, Tsilimparis N, Gallitto E, *et al.* Endovascular Repair of One-hundred Urgent and Emergent free or Contained Thoraco-abdominal Aortic Aneurysms Ruptures. An International Multi-Center Trans-Atlantic experience. Annals of Surgery [Internet]. 2024 Feb 7 [cited 2024 Apr 7]; Available from: https://journals.lww.com/10.1097/SLA.0000000000006231
43. Gallitto E, Sobocinski J, Mascoli C, *et al.* Fenestrated and Branched Thoraco-abdominal Endografting after Previous Open Abdominal Aortic Repair. Eur J Vasc Endovasc Surg 2020;60:843–52.
44. Dias NV, Billberg H, Sonesson B, *et al.* The effects of combining fusion imaging, low-frequency pulsed fluoroscopy, and low-concentration contrast agent during endovascular aneurysm repair. J Vasc Surg 2016;63:1147–55.
45. Ahmad W, Hasselmann HC, Galas N, *et al.* Image fusion using the two-dimensional-three-dimensional registration method helps reduce contrast medium volume, fluoroscopy time, and procedure time in hybrid thoracic endovascular aortic repairs. J Vasc Surg 2019;69:1003–10.

3.3 EXTREME OFF-LABEL TECHNIQUES TO TREAT TAAA: PHYSICIAN-MODIFIED ENDOGRAFTS, IN-SITU FENESTRATIONS, AND ELECTRIFIED WIRE-BASED MANEUVERS

Davide Esposito, Martina Bastianon, Caterina Melani, Gaddiel Mozzetta, Jessica Lanza, Giuseppe Baldino, Fabio Grimaldi, Enrica Bosisio, Giovanni Pratesi

With the implementation of techniques and materials, and in light of excellent long-term results, the treatment of thoraco-abdominal aortic pathology is increasingly shifting towards a minimally invasive endovascular approach.[1, 2] The possibility of endovascular exclusion of aneurysmal, dissecting, or traumatic pathologies of the thoraco-abdominal aorta using endoprosthetic grafts has significantly reduced the surgical impact associated with open surgery, limiting its use to fit patients, or when endovascular approaches are not advisable, or in cases in which a hybrid approach combining the endovascular and open solutions would be recommended.[3] Additionally, in recent years we have witnessed the development of a number of new stent-grafts designed to treat the visceral aorta, by means of fenestrated and/or branched devices (F/BEVAR) which can be available as off-the-shelf solutions or customized.

On the other hand, there are cases where off-the-shelf endoprostheses may not adequately adapt to the patient's anatomy, and other cases where the applicability of custom-made endoprostheses is limited by the need to wait for production times. These latter circumstances could be addressed by manually customizing standard endoprostheses before the procedure, or during the procedure itself through in-situ fenestrations of the graft, to guarantee treatment opportunities even in urgent and emergent scenarios, although representing extreme solutions to isolated cases.

PHYSICIAN-MODIFIED ENDOGRAFTS

A physician-modified endograft (PMEG) means modifying a standard, readily available endograft on the operating table, where the surgeon creates holes for fenestrations or directional branches to achieve supra-renal or supra-visceral aortic sealing. This technique enables immediate endovascular treatment of aneurysms that would otherwise not be manageable with standard EVAR repair. It is particularly valuable for symptomatic aneurysms or in cases where patients are at risk of impending rupture. Surgeons have the opportunity to fabricate the endograft while the patient is being prepared for surgery and before they enter the operating room, thereby optimizing the timing and efficiency of the procedure.

A recent meta-analysis reported on the early outcomes of 909 PMEGs for the treatment of thoraco-abdominal and complex abdominal aortic aneurysms from twenty observational studies, separately analyzing urgent and elective repairs, and thoraco-abdominal and complex abdominal aortic aneurysms. Authors showed an overall technical success of 97.2% (98.0% for extent I e III thoraco-abdominal aortic aneurysms and 99.4% for complex abdominal and extent IV thoraco-abdominal aortic aneurysms) and a major adverse events rate of 15.5% (higher in the urgent compared with the elective setting, 24.6% *versus* 11.6%), while the 30-day mortality and overall mortality at follow up were 4.4% and 12.8% respectively.[4] These results confirmed the applicability and safety of the technique, but longer-term follow-up data are still needed for further validations. It must be remembered indeed that this approach is still not considered in the standards of practice of International Guidelines, and for this reason it is essential to provide the patient with an exhaustive preoperative informed consent with an explanation of the off-label nature of the intervention.[3, 5]

Technically, the graft modification occurs within a surgical environment under sterile conditions, prior to administering anesthesia to the patient. Extensive planning on preoperative computed tomography angiography (CTA) is crucial. Operators should have substantial elective experience in complex aortic repair and grasp the implications of oversizing on the clock position of fenestrations. One or more holes can be strategically planned, and diameter-reducing ties can be incorporated into the graft to facilitate easier cannulation of the fenestrations within a narrow segment of the aorta. The graft is partially or totally unfolded on the operating table, and the process of measuring and marking fenestrations is carried out based on the plan. Cautery is employed to create the holes at the pre-marked positions; following this, in order to guarantee adequate visibility and strength, the fenestrations are reinforced using a snare or a guide wire extremity and secured in place using a continuous locking suture. In cases where diameter-reducing ties are required, sutures are utilized to form loops around the graft, anchoring them with a release wire extracted from the delivery system using a scalpel, and then reinserted once the suture loops are in position. The device is re-sheathed using silk tapes and tourniquets to envelop and compress the graft.[6-8] A step-by-step modification process example of a standard endograft to a PMEG is illustrated in Figure 3.3.1.

Although this procedure proves beneficial in intricate scenarios, it does possess certain limitations. Standardizing the manufacturing procedure is crucial since the learning curve inevitably impacts the immediate and long-term success of the procedure. Inaccurate measurements may impede the catheterization of intended target vessels, potentially leading to stent compression and increased occlusion risk during follow-up. These factors are likely to contribute to the observed variations in target vessel

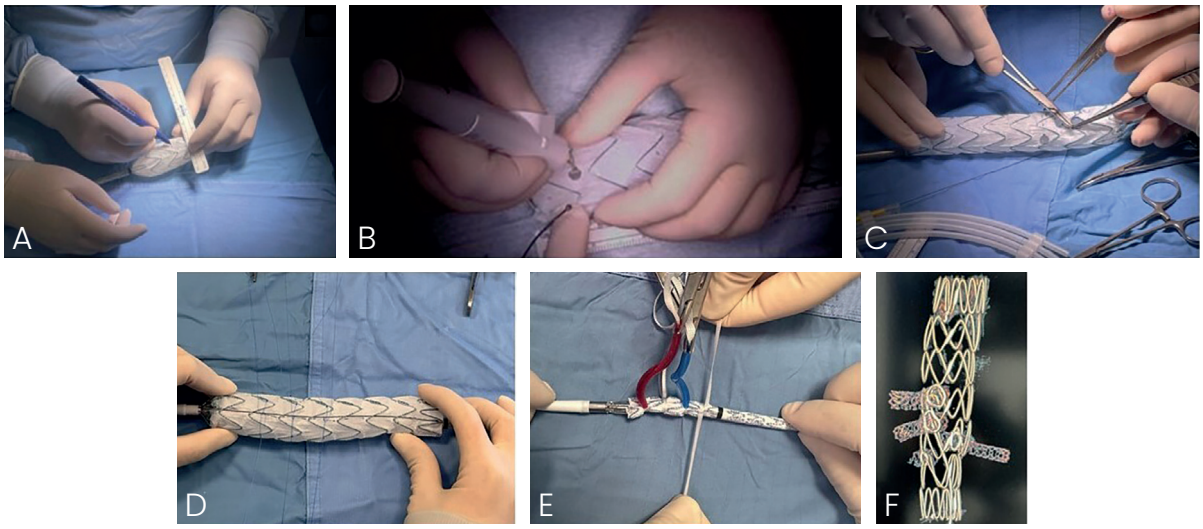


FIGURE 3.3.1 ● Step-by-step modification process of a standard endograft to a PMEG. The precise fenestration points are marked on the graft (A). A cautery is utilized to create the holes (B), subsequently fortified with sutured guide wire extremities (C). Diameter-reducing ties are fashioned to aid in graft positioning (D). The graft is closed using tapes and tourniquets to ease re-sheathing (E). The cone-beam computed tomography illustrates the favorable outcomes of the procedure (F).

primary patency between fenestrations and branches[4]. Unlike custom-made devices, where branches tend to occlude more frequently than fenestrations probably due to longer bridging stents and tortuous courses, PMEGs showed better patency results for branches (99.6%, 95% CI 94.7 to 100) compared to fenestrations (95.2%, 95% CI 82.0 to 100), probably due to the fact that branches may tolerate imperfections better than fenestrations, as misalignment is easier to correct.[4]

Finally, there remains a requirement for longer-term and precise data to validate the procedure. However, it is worth noting that in the United States the number of physician-sponsored investigational device exemption trials for PMEGs has increased from one in 2012 to eight currently enrolling, indicating that reliable data will soon be available.[9]

IN-SITU FENESTRATIONS

Similarly to what was mentioned for PMEG, laser-generated or needle-assisted *in-situ* fenestrations of standard stent grafts represent another off-label treatment solution in cases of complex aneurysms for whom the waiting time for manufacturing a custom-made device is too long, or when a suitable off-the-shelf graft is not available.[3] This approach finds its ideal place in the case of urgent and emergent ruptured aneurysms requiring the coverage of the pararenal or paravisceral aorta, particularly in situations where there would be insufficient time even for crafting a PMEG, such as unstable patients.

While satisfactory results regarding the successful creation and integrity of the fenestration itself have been reported through bench-testing, particularly demonstrated for Dacron stent grafts, as well as experimental findings revealed no discernible distinction between needle and laser fenestrations during fatigue testing, there is only limited clinical data available.[10, 11]

Despite still limited in numbers, retrospective and single-center based, studies report promising clinical results in the early application of in-situ fenestration for the treatment of complex aortic aneurysms.[12-14] Le Houérou *et al.*, evaluating a cohort of 44 consecutive non-deferrable treatments for complex aortic aneurysms with endovascular endografting and 108 antegrade in situ laser fenestrations, reported a median ischemia duration time of 7, 48, 48, and 45 minutes for the superior mesenteric artery, celiac trunk, right and left renal arteries respectively, with a technical success rate of 97%, and a 30-day mortality of 4.5%. Median follow up was 24.7 months, and Kaplan-Meier 2-year estimates for overall survival, aortic related re-intervention free survival, and stent related re-intervention free survival were 73%, 70%, and 90.6% respectively.[14]

Documented techniques for graft perforation involve utilizing existing endovascular tools beyond their typical applications. These techniques can be broadly categorized as mechanical, employing tools like wires and hollow needles, and physical, which include methods such as laser, electrified-wire and radiofrequency perforation. The first documented in-situ fenestration case was conducted by utilizing the rear end of a 0.018-inch guide wire within a TX1 endograft (Cook Inc, Bloomington, IN, USA) to maintain the integrity of the left subclavian artery.[15] The primary challenge with needle punctures lies in their inability to remain stable within a large vessel when attempting to penetrate the fabric. Various stabilization methods have been proposed, including the use of steerable sheaths and inflated endovascular balloons

in an attempt to give additional support while reducing movements. In addition to mechanical puncture, physical methods can also puncture the fabric, resulting in a precise fenestration while preserving the overall integrity of the endograft. Murphy *et al.* initially described a retrograde laser fenestration of the left subclavian artery using a Turbo Elite laser ablation catheter (Spectranetics, Colorado Springs, CO, USA) in a case involving aortic rupture.[16]

Furthermore, in order to enhance the precision of locating the optimal fenestration site, an additional approach involves the pre-stenting of the target vessel. By implementing this technique, not only is the visibility of the vessel's origin improved, but it also facilitates a more accurate determination of the ideal point for fenestration execution.

Electrified wires present another potentially valuable tool for performing in-situ fenestrations. An Astato wire (Asahi Intecc USA, Santa Ana, CA, USA) is a viable option for addressing this challenge. To prepare it for use, the coating at the backend of the guidewire is carefully removed using a scalpel until the metal is exposed. The guidewire is then positioned at the desired fenestration point with the assistance of a guiding sheath and a supportive catheter. To prevent blood coagulation during the cauterization process, the catheter must be flushed with 5% dextrose.[17] Once the insulation of the guidewire is ensured, its backend is connected to the cautery, and a 40 Watts power energy is applied to facilitate the fenestration of the graft and allow target vessel cannulation.

Besides fabric perforation, another significant challenge arises when attempting to cross the hole to enlarge it and facilitate the release of the bridging stent. This critical step is currently achieved by maneuvering a balloon over the wire to further inflate the fenestration, but it can pose challenges.

In a laboratory study conducted by Riga *et al.*, the variability of fenestrations created in various graft types was examined. The study revealed that the puncture angle and the selection of an angioplasty balloon for subsequent hole dilatation were critical factors in creating fenestrations without margin tears. Fenestrations in PTFE exhibited more tears and elliptical shapes compared to Dacron. Additionally, the use of cutting balloons led to significantly more fabric tears than conventional angioplasty balloons.[18]

After enlarging the fabric hole, the procedure typically involves deploying a balloon-expandable covered stent to bridge the fabric hole towards the target artery, potentially with the use of an additional stent to reinforce the fenestration within the bridging stent. Figure 3.3.2 details the various endovascular phases involved in the *in situ* fenestration procedure of a standard endograft.

Despite its usefulness and potential for use in extremely complex management cases, this procedure has several drawbacks that need to be considered. Firstly, the need to cover the visceral aorta for a duration determined by the speed of fenestration of each target vessel may pose a risk of renal and/or mesenteric insufficiency due to temporary ischemia. In critical scenarios involving the paravisceral aorta, one potential strategy is to incorporate a two-hole PMEG for the celiac trunk and the superior mesenteric artery, coupled with in-situ fenestration of renal arteries. This approach aims to diminish the likelihood of complications arising from ischemia time, offering a more comprehensive solution compared to relying solely on in-situ fenestration.

Secondly, the long-term potential for target vessel branch instability resulting from the absence of fenestration reinforcement, has yet to be evaluated. Lastly, as mentioned already for PMEG procedures, this intervention should not be used in settings different from emergency situations, unless performed for investigational studies approved by local Ethics Committees.[3] In such cases, each center is obliged at the time of signing the surgical consent to present to the patient all possible therapeutic alternatives, explaining in detail the decision-making process that led to the choice of such method.

ELECTRIFIED WIRE-BASED MANEUVERS

In addition to their potential use for in situ fenestrations, electrified-wires have proven to be an extremely effective tool for the treatment of post-dissection thoracic and thoraco-abdominal aortic aneurysms where graft positio-

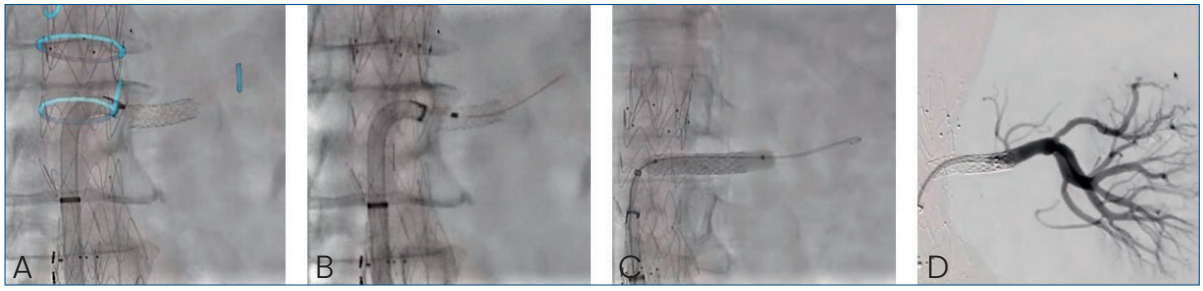


FIGURE 3.3.2 ● Endovascular maneuvers performed for the in situ-fenestration procedure of a standard endograft. The target vessel is pre-stented in order to enhance the fenestration (A); a steerable sheath is employed to facilitate in-situ fenestration of the endograft (B); upon successful fenestration, the target vessel is bridged with a balloon-expandable stent (C); a completion angiography is conducted to assess visceral vascularization (D).

ning and adequate wall apposition are compromised by aortic characteristics at the proximal and/or distal landing zones. The use of electrified-wires is indeed effective for performing aortic septotomy aimed at restoring a single aortic lumen at the site of dissection, ensuring better sealing zones of the endoprosthesis and promoting a positive aortic remodeling process following endoprosthesis placement, which has been shown to reduce reinterventions and improve survival following treatment of this condition.[19] Indeed, achieving complete occlusion of the false lumen during post-dissection thoraco-abdominal aortic aneurysm follow-up proves challenging, with less than 72% of patients treated via endovascular repair attaining this outcome.[20] In response to this issue, adjunctive endovascular strategies, such as the false lumen occluder, have emerged as potential solutions aimed at mitigating false lumen reperfusion. However, despite these advancements, these adjunctive options continue to exhibit a success rate of less than 80%.[21]

Fukuhara *et al.* described their approach of laser aortic septotomy to optimize the landing zone in patients with chronic type B aortic dissection undergoing thoracic endovascular exclusion (TEVAR), and subsequently compared this technique performed on 31 patients with 57 patients which underwent stand-alone TEVAR. The overall technical success rate of aortic septotomy was of 97%, and during the follow-up period there were no deaths in the septotomy group whereas 21% sudden deaths and 30% combined aorta-related and sudden deaths in the group without aortic septotomy (P<0.001). Moreover, patients who did not undergo aortic septotomy required aortic reinterventions more frequently compared to those who underwent aortic septotomy (30% *vs*. 7%; P=0.014), and positive aortic remodeling was significantly less observed (37% *vs*. 90%; P<0.001).[22, 23] Hence, aortic septotomy could serve as a supplementary technique to broaden the range of applicability of endovascular solutions, as for extensive dissections affecting the paravisceral segment of the aorta, particularly in cases with an extremely narrow true lumen and where visceral vessels originate from both the true and false lumens. Perhaps, more precise indications for aortic septotomy may encompass several objectives: firstly, to establish proximal and/or distal landing zones within aortic segments affected by dissection but without significant enlargement, thereby restricting the extent of aortic coverage; secondly, to relieve compression of the true lumen, facilitating stent graft expansion and catheter manipulation; and finally, to create communication between the true and false lumens, aiding in the incorporation of target vessels during F/BEVAR, particularly when the vessels originate from separate luminal sources.[24]

The initial phase of performing the septotomy involves cannulating the true and false lumens, and obtaining a fenestration of the lamella, unless a natural fenestration is already available. Adequate positioning may be confirmed using intravascular ultrasound (IVUS). If a natural fenestration is absent or inaccessible, various techniques can be employed to create one, including the use of the back end of a guidewire, needles, laser, reentry device, and an electrified wire, possibly with the aid of a steerable sheath to align perpendicularly to the lamella. Afterwards, a guidewire is snared across the fenestration from the contralateral access or from the same femoral access in case the dissection involves the iliaco-femoral region, and then exchanged for an Astato XS 20 0.014-inch 300 cm wire (Asahi Intecc USA, Santa Ana, CA, USA). This guidewire is previously kinked in the middle, and in this portion the coating is removed using a scalpel until the metal is exposed. The distal uncovered portion of the wire is then connected to the cautery, after having positioned the kinked portion across the septum, having positioned a 5 Fr 55mm Flexor sheath (Cook Medical, Bloomington, IN, USA) on both sides of the wire and having flushed them with 5% dextrose to prevent blood coagulation, and after having ensured full isolation of the wire [17, 25]. While applying a 40 Watts power energy through the wire, the latter is gently pulled downward to enhance the septotomy of the targeted aortic segment. An IVUS examination is then conducted to confirm the completion of the septotomy. Additionally, a diagnostic angiography is conducted to rule out aortic injuries and septal bulging, which could potentially lead to occlusion of aortic or visceral vessel ostia.[26, 27] The above mentioned technique and the postprocedural results are illustrated in Figures 3.3.3 and Figure 3.3.4.

However, the procedure described is one of several methods for performing aortic septotomy; indeed, other techniques have been described in the literature, with acceptable results.[26, 28, 29] These methods are commonly classified into Balloon-based and Wire-pull methods. Balloon-based fenestration involves a sequential expansion process, initially employing a small balloon (4-10 mm), followed by dilation to the desired diameter using a large-vessel balloon (20-25 mm). Alternatively, a large compliant balloon can be utilized, with caution exercised to prevent over-dilation. Multiple adjacent or coalescent point fenestrations may also be considered for expansion if large-diameter dilation poses risks, albeit necessitating additional adjacent septal fenestrations. Wire-pull fenestration, commonly known as "cheese cutter" fenestration, is executed by capturing a trans-septal guidewire and maneuvering both ends in a see-saw motion to achieve a slicing effect. While generally effective, this method presents challenges in terms of control and carries a risk of aortic wall injury, particularly in diseased or calcified aortas and tortuous anatomy. Wire-pull fenestration should be avoided in acute dissections due to the heightened risk of complications such as intimal sloughing and bunching, potentially resulting in occlusive filling defects. An evolved modification, termed "Squeegee" wire fenestration, integrates elements of both wire-pull and balloon fenestration techniques. This approach offers enhanced control and safety while maximizing the resulting fenestration diameter.

Electrocautery septotomy emerges as a promising al-

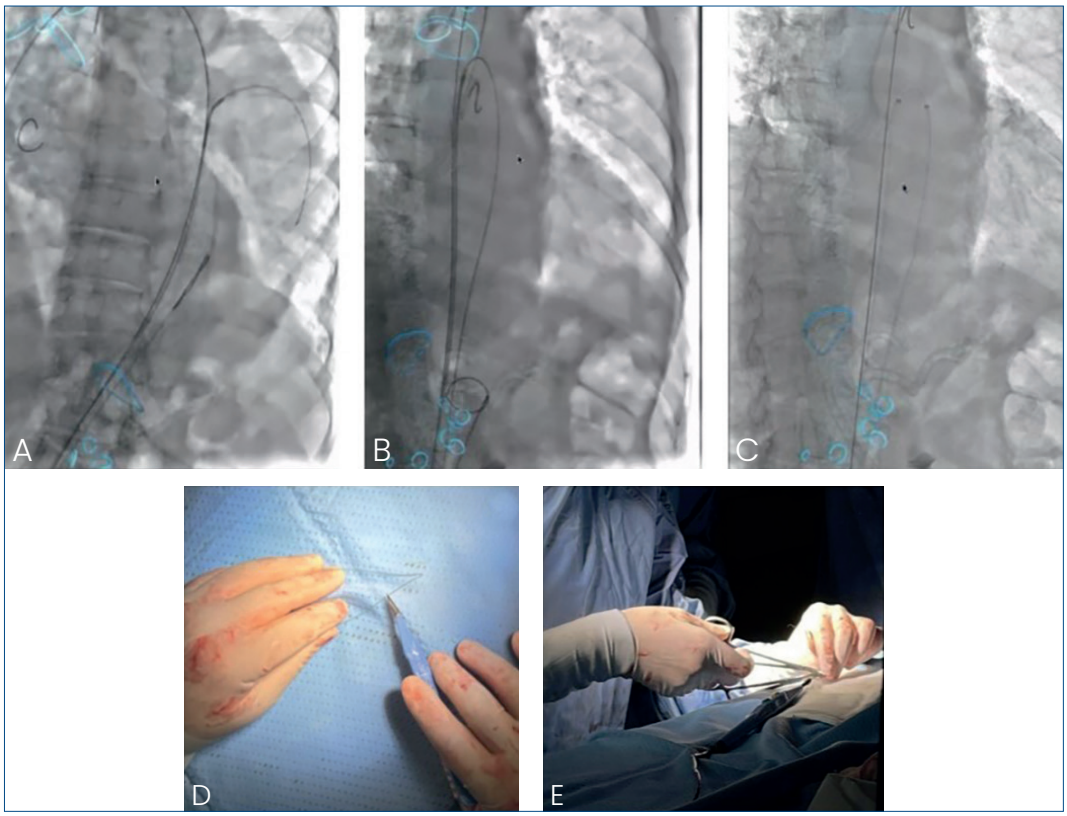


FIGURE 3.3.3 ● Setup for electrified wire-assisted aortic septotomy. Both the true and false lumens are cannulated (A). Subsequently, a guidewire is snared across the fenestration from the contralateral access (B), followed by its exchange for an Astato wire (Asahi Intecc USA, Santa Ana, CA, USA) using a Flexor sheath (Cook Medical, Bloomington, Indiana, USA) on both sides of the wire (C). Prior to this, the guidewire is kinked at the midpoint, where the coating is removed with a scalpel until the metal is exposed (D). The distal uncovered portion of the wire is then connected to the cautery (E), making it ready for the septotomy procedure.

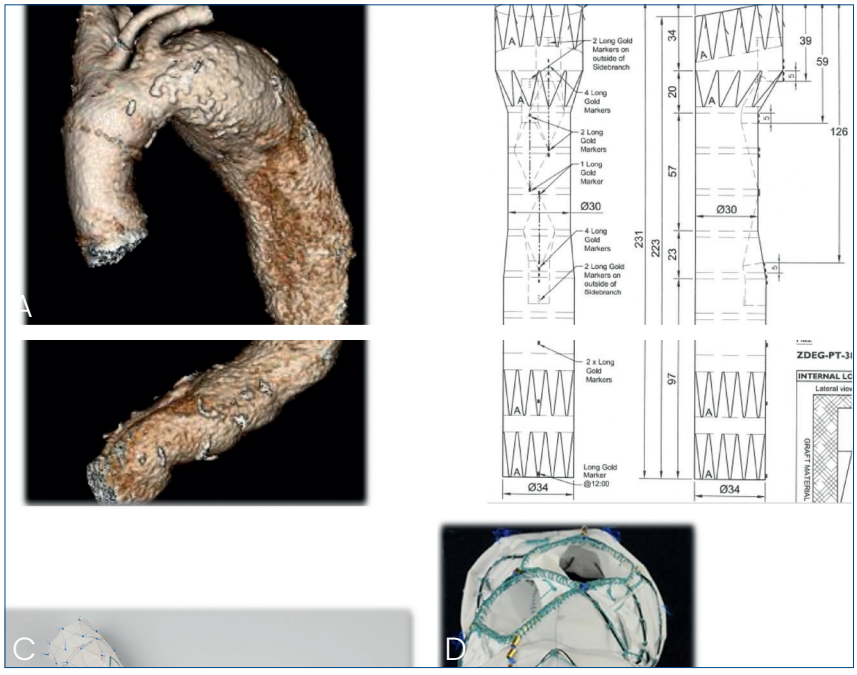


FIGURE 3.3.4 ● Remodeling of the paravisceral aortic segment. In the preoperative CTA (A), a dissected aortic lumen at the level of the pararenal aorta is evident. Subsequent to aortic septotomy, as depicted in the postoperative CTA (B), significant remodeling occurs. IVUS evaluations are conducted both before (C) and after (D) aortic septotomy to assess the efficacy of the procedure.

ternative, offering several advantages over the aforementioned techniques, although it is still not recommended in acute dissection for its potential intimal bunching effect. Notably, it enhances control during septum tearing and reduces the requisite pulling force on the guidewire, thereby mitigating the risks associated with aortic injuries and septal bunching.

Besides their utility for aortic septotomy, electrified wires could serve as a valuable tool for performing bailout procedures. A case in point would be instances where cannulating a fenestration or branch of a F/BEVAR is rendered difficult due to imprecise positioning. In such scenarios, electrified wires could be employed to carry out in-situ fenestrations when other options prove unsuccessful. Another example could indeed be represented by the in-situ fenestration of a bailout renal stent to safeguard an early renal branch of the same artery, and subsequently stenting it. Nonetheless, regarding the long-term efficacy of this approach, it is important to note that definitive data are still lacking. Therefore, this option should be exercised with caution and reserved for exceptional cases.

REFERENCES

1. Guéroult AM, Bashir A, Azhar B, *et al.* Long Term Outcomes and Durability of Fenestrated Endovascular Aneurysm Repair: A Meta-analysis of Time to Event Data. Eur J Vasc Endovasc Surg 2024;67:119–29.
2. Antoniou GA, Juszczak MT, Antoniou SA, *et al.* Fenestrated or Branched Endovascular versus Open Repair for Complex Aortic Aneurysms: Meta-Analysis of Time to Event Propensity Score Matched Data. Eur J Vasc Endovasc Surg 2021;61:228–37.
3. Wanhainen A, Van Herzeele I, Bastos Goncalves F, *et al.* Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2024;67:192–331.
4. Gouveia E Melo R, Fernández Prendes C, Caldeira D, *et al.* Systematic Review and Meta-analysis of Physician Modified Endografts for Treatment of Thoraco-Abdominal and Complex Abdominal Aortic Aneurysms. Eur J Vasc Endovasc Surg 2022;64:188–99.
5. Pratesi C, Esposito D, Apostolou D, *et al.* Guidelines on the management of abdominal aortic aneurysms: updates from the Italian Society of Vascular and Endovascular Surgery (SICVE). J Cardiovasc Surg (Torino) 2022;63:328–52.
6. Singh A, Mafeld S, Williams R, McCaslin J. Physician-Modified Fenestrated Endografts for Managing the Ruptured or Symptomatic Aortic Aneurysm: Technique Overview and Clinical Outcomes. Vasc Endovascular Surg 2018;52:607–12.
7. Oderich GS. Technique of adding a diameter-reducing wire to the modified TX2 fenestrated stent graft. Vascular 2010;18:350–5.
8. Piazza M, Squizzato F, James Bilato M, *et al.* Physician-Modified Single-Fenestrated EndoSuture Aneurysm Repair (FESAR) for Urgent Juxtarenal AAA Repair. J Endovasc Ther 2023 Nov 22:15266028231212131.
9. O'Donnell TF, Dansey KD, Schermerhorn M, *et al.* National Trends in Utilization of Surgeon Modified Grafts for Complex and Thoracoabdominal Aortic Aneurysms. J Vasc Surg 2024:S0741-5214(24)00285–4.
10. Grima MJ, Wanhainen A, Lindström D. In Situ Laser Fenestration Technique: Bench-Testing of Aortic Endograft to Guide Clinical Practice. J Endovasc Ther 2024;31:126–31.
11. He Y, Wang Y, Zhou X, *et al.* Effects of Long Term Fatigue Cycling on In Situ Fenestrations of Polyethylene Terephthalate and Expanded Polytetrafluorethylene Thoracic Aortic Stent grafts: An Experimental Study. Eur J Vasc Endovasc Surg 2023 Aug 26:S1078-5884(23)00726–8.
12. Glorion M, Coscas R, McWilliams RG, *et al.* A Comprehensive Review of In Situ Fenestration of Aortic Endografts. Eur J Vasc Endovasc Surg 2016;52:787–800.
13. Le Houérou T, Fabre D, Alonso CG, *et al.* In Situ Antegrade Laser Fenestrations During Endovascular Aortic Repair. Eur J Vasc Endovasc Surg 2018;56:356–62.
14. Le Houérou T, Álvarez-Marcos F, Gaudin A, *et al.* Midterm Outcomes of Antegrade In Situ Laser Fenestration of Polyester Endografts for Urgent Treatment of Aortic Pathologies Involving the Visceral and Renal Arteries. Eur J Vasc Endovasc Surg 2023;65:720–7.
15. McWilliams RG, Murphy M, Hartley D, *et al.* In situ stent-graft fenestration to preserve the left subclavian artery. J Endovasc Ther 2004;11:170–4.
16. Murphy EH, Dimaio JM, Dean W, *et al.* Endovascular repair of acute traumatic thoracic aortic transection with laser-assisted in-situ fenestration of a stent-graft covering the left subclavian artery. J Endovasc Ther 2009;16:457–63.
17. Khan JM, Rogers T, Greenbaum AB, *et al.* Transcatheter Electrosurgery: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1455–70.
18. Riga CV, Bicknell CD, Basra M, *et al.* In vitro fenestration of aortic stent-grafts: implications of puncture methods for in situ fenestration durability. J Endovasc Ther 2013;20:536-43.
19. Lombardi JV, Hughes GC, Appoo JJ, *et al.* Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections. J Vasc Surg 2020;71:723–47.
20. Tenorio ER, Oderich GS, Farber MA, *et al.* Outcomes of endovascular repair of chronic postdissection compared with degenerative thoracoabdominal aortic aneurysms using fenestrated-branched stent grafts. J Vasc Surg 2020;72:822–36.e9.
21. Palmier M, Mougin J, Bendavid J, *et al.* Evaluation of false lumen occluders implanted in the abdominal aorta false lumen. J Vasc Surg 2023;78:1146–52.
22. Fukuhara S, Tchouta L, Pampati R, *et al.* Laser aortic septotomy during thoracic endovascular aortic repair for chronic type B aortic dissection. J Thorac Cardiovasc Surg 2022;164:450–9.e2.
23. Fukuhara S, Khaja MS, Williams DM, *et al.* Aortic septotomy to optimize landing zones during thoracic endovascular aortic repair for chronic type B aortic dissection. J Thorac Cardiovasc Surg 2023;165:1776–86.e5.
24. Baghbani-Oskouei A, Savadi S, Mesnard T, *et al.* Transcatheter electrosurgical septotomy technique for chronic post-dissection aortic aneurysms. J Vasc Surg Cases Innov Tech 2023;10:101402.
25. Kabbani L, Eng M, Onofrey K, *et al.* Novel technique to fenestrate an aortic dissection flap using electrocautery. J Vasc Surg Cases Innov Tech 2023;9:101108.
26. Sharafuddin MJ, Bhama JK, Bashir M, *et al.* Distal landing zone optimization before endovascular repair of aortic dissection. J Thorac Cardiovasc Surg 2019;157:88–98.
27. Bastianon M, Di Gregorio S, Melani C, *et al.* Visceral Aorta Electrocautery Septotomy to Allow Branched Endovascular Aortic Repair in Ruptured Chronic Post-Dissection Thoraco-Abdominal Aneurysm. J Endovasc Ther 2024 Mar 27:15266028241240900.
28. Stern JR, Pham XD, Lee JT. Reverse Cheese-Wire Septotomy to Create a Distal Landing Zone for Thoracic Endovascular Aortic Repair. J Endovasc Ther 2023;30:38–44.
29. Bozzani A, Farè C, Arici V, *et al.* Aortic septotomy with scissor-technique. JTCVS Tech 2022;16:14–5.

3.4 PUSHING THE LIMITS PROXIMALLY 1: ENDOVASCULAR TREATMENT OF AORTIC ARCH DISEASE WITH BRANCHED CUSTOM-MADE DEVICES

Paolo Spath, Jan Stana, Nikolaos Tsilimparis

INTRODUCTION: ADVANCES AND OPTIONS IN AORTIC ARCH DISEASE MANAGEMENT

Recent advancements and choices in managing diseases affecting the arch have become increasingly diverse. These conditions include arch aneurysms, penetrating aortic ulcers (PAU) and acute or chronic aortic dissections (AD). They often are associated with thoracic and thoracoabdominal aortic aneurysms (TAAA) where thoracic aortic repair (TEVAR) might involve the aortic arch to establish a secure sealing zone categorized into zones 0 1 or 2 based on the Ishimaru's classification.[1, 2]

Traditionally open surgical repair has been the treatment of choice for young and healthy patients. However this approach carries risks such as postoperative mortality rates ranging from 2% to 20% and stroke rates between 10% to 15%.[3] It involves invasive technical aspects like clamping of the aorta, inducing mild to deep hypothermia and the use of extracorporeal circulation and cardiopulmonary bypass. Despite being well established procedures, these inherent operative and perioperative risks, especially for fragile and ederly patients.[4–6]

In the recent decades, changes in clinical recommendations have propelled endovascular treatment as a less invasive option that is particularly suitable for patients who are not eligible for open surgery due, to age or underlying health conditions.The European Society of Vascular Surgery[1] and the European Association of Cardio Thoracic Surgery[2] now support methods emphasizing their safety and effectiveness for patients with suitable anatomy and reasonable life expectancies. These procedures, such as using fenestrated and branched endografts (F/B EVAR) help avoid the surgical trauma linked to open repair thereby lowering the occurrence of severe adverse postoperative events.[7]

A simpler procedure, when the selected anatomy is feasible, combines a simple tube TEVAR with proximal surgical transposition or bypass debranching of the supra aortic trunks (SAT).[8–10] This approach combines the advantages of repair with essential surgical interventions to ensure optimal results, although these procedures carry a relevant 10% risk of complications due to access and surgical exposure.[10, 11]

Recent reviews have highlighted the effectiveness and potential benefits of fenestrated and branched thoracic endovascular aortic repair of the arch using CMDs, with technical success up to 96% and potential benefits in terms of clinical outcomes.[6, 12]

Parallel grafts, physician modified or in situ fenestrated TEVAR offer alternative options to F/B EVAR, but should be reserved for urgent cases.[13–15]

As we delve deeper into the field of repair this chapter seeks to thoroughly examine the newest advancements and results related to both tailored and off-the-shelf devices for complete and partial endovascular repair of the aortic arch.

Especially the focus will be on TEVAR using branched custom-made devices (CMD), aiming to point-out the effectiveness of treatment and patient well being aligning with current clinical recommendations and research.[1, 2]

ANATOMICAL CONSIDERATIONS AND INDICATIONS FOR INTERVENTION IN AORTIC ARCH PATHOLOGIES

According to guidelines[1,2] surgical treatment should be considered when isolated aortic arch aneurysms reach 55 mm in diameter (class IIa, level B) symptoms, like pain, or the presence for signs of rupture are factors that call for immediate action irrespective for diameter (Class I Level C).

The aortic arch can be impacted by conditions that could affect the ascending and descending parts of the thoracic aorta and therefore carefull planning should consider helthy landing zone, the location of the pathology and the supra-aortic vessel that would be directly involved in the repair.

To facilitate treatment the aortic arch is categorized into three Ishimaru's zones for intervention planning:

- Zone 0 (Z0); Spans, from the sinotubular junction to the brachio cephalic trunnk (BCT);
- Zone 1 (Z1); Extends from the end of the BCT to the left common carotid artery (LCCA);
- Zone 2 (Z2); From the end of the LCCA to the left subclavian artery (LSA).

CHALLENGES AND KEY FACTORS FOR SUCCESSFUL COMPLEX TEVAR

Endovascular repair despite being minimally invasive poses several challenges.

The first is the accurate selection of Landing Zone, that is crucial, for ensuring immediate and long-term repair outcomes.[7, 16]

To prevent future issues such as endograft migration or endoleaks, it's important that the selected landing zone is at least 25 mm long, without calcification, thrombus, sharp bends of more than 60 degrees with an ideal diameter under 38 mm.[17]

When deploying the endograft it's crucial to plan an accurate deployment despite movements of the aortic arch during heartbeats and breathing cycles. For managing these situations, cardiac output reduction techniques should be considered, such as cardiac rapid pacing (organ), either rapid ventricular pacing, balloon occlusion of the inferior vena cava, Munich Valsalva maneuver (MUVIT).[18]

Another important issue is correct aligment of the graft at the outer curvature, due to many tortuosity during the navigation from the iliac accesses up to the arch and to reduce as much as possibile movements that may produce cerebral embolism and stroke.

Using pre-curved grafts with self-aligning systems can help reduce manipulation risks.[19]

In the past the presence of a mehanical valve might have being considered a exclusion criterion: new endovascular tools with more flexible and shortend tips have been designed to navigate past the aortic valve without causing harm thus lowering the chances of sudden valve failure.[20]

In addressing conditions modern techniques involve using fenestrated and branched CMD.[6, 21–24]

These advanced technologies have been specifically designed to tackle the challenges presented by the structure of the arch even in unusual pathologies as aberrant right sublavioan artery.[25, 26] They offer options that help lower the risks, for patients particularly those considered high risk for traditional open surgery. The field is constantly progressing with enhancements in graft design and deployment techniques, fueled by advancements in technology and growing clinical expertise.[27–29]

TYPES OF ENDOGRAFTS USED IN AORTIC ARCH REPAIR

Choosing the right endograft for repairing the aortic arch is crucial, depending on the specific arch anatomy and the type of condition being treated. This section explores different types of endografts available.

1. ***Fenestrated and Branched Endografts***
   These endografts are mainly custom-made endografts and are designed with custom-made fenestrations or branches that align with the supra-aortic vessels to maintain blood flow. These grafts are ideal for treating issues in zones 0 and 1 of the aortic arch and partial and total repair.[1, 6, 22, 30, 31] However, they require 6-12 weeks for planning and production.[30, 32]
2. ***Parallel Graft Technique***s
   They are used when anatomical conditions do not permit fenestrated or branched grafts, especially in urgent and bailout situations. However, there is a higher risk of leaks along gutters with this approach compared to using custom made grafts.[2, 33, 34]
3. ***Physician Modified Endografts***
   Different modification designs have been suggested for the arch, including scallops, small fenestrations, large fenestrations of the outer curvature or even physician modified inner branches. The main challenge of physician modified endografts is the lack of the ability to orientate the graft in the arch to align the fenestrations/branches to the target vessels. This can only occur by retracting the graft in the mid-thoracic aorta and positioning it in a way anticipated to align in the arch.
4. ***In-situ fenestrated endografts***
   These endografts undergo modifications on site by surgeons to incorporate fenestrations or branches that align with the aortic arch vessels, either a laser fenestration made by the retrograde cannulation of the vessel, subsequent ballooning and stenting.[35–37] They are used in situations where patient specific custom grafts are not available, especially in urgent cases. This approach offers adaptability and allows for personalized adjustments during the procedure.[15, 38] A specific procedure might be the use of a laser fenestrations like what is done in the thoraco-abdominal aorta,[39] but innovative technique such as the use of an adjustable needle to perform a correct perpendicular puncture with a dedicated device, often as on option to revascularize LSA and to permit a landing zone in zone 2.[40, 41]
   On a similar account, growing experience with dedicated semi customized devices with dedicated single retrograde branch for LSA are now available, aiming to treat distal arch pathologies, and extending proximal landing zone in descending aorta diseases.[42–44]
   Advancements in endograft technologies, coupled with growing clinical evidence, are making these endografts safer and more efficient, offering personalized solutions that improve patient outcomes.[6, 21, 28] Especially, TEVAR using branched CMD (b-TEVAR) seem to show a higher adatability,[26–29, 45] reducing endoleaks issues and permitting a easier application in zone-0 landing zone, reducing the issues of retrograde type-A dissection rates due to a more stable proximal landing zone coverage.[6, 46, 47]

DETAILED PROCEDURE FOR A CUSTOM MADE BRANCHED ENDOGRAFT DEPLOYMENT IN THE AORTIC ARCH[19, 26, 48, 49] (Table 3.4.I)

Device overview and initial setup (Figure 3.4.1)

Multibranched endografts are designed to treat complex aortic arch diseases requiring a proximal seal in Zone 0. These custom-made devices feature configurations that accommodate various anatomical challenges, including the strategic placement of branches to ensure vital blood flow is maintained to the supra-aortic vessels.

Often, these devices include a specific design, optimizing sealing within the ascending aorta and descending thoracic aorta, but also allowing flow to the supra-aortic vessels. This is possible due to the narrow design of multibranched arch devices at the mid-portion.

This devices employ a hydrophilic introducer with a pre-curved, flexible nose that facilitates navigation through the aortic valve into the left ventricle.

Pre-operative preparation

The procedure is performed in a hybrid operating room, fully equipped for both open surgery and endovascular interventions. General anesthesia is administered, and intravenous access is established for heparin (to maintain an ACT target >250 seconds) and antibiotic

TABLE 3.4.I ● Step-by-step endovascular procedure for a custom-made b-TEVAR device with triple inner branch.

Step	Description	Details/tools used
1. Pre-operative Preparation	Preparation in a hybrid operating room with general anesthesia, vascular access, and reducing cardiac output setup.	General anesthesia, intravenous heparin, antibiotic prophylaxis, vascular access through the common femoral artery,carotid arteriers or axillary arteries.
2. Guidewire and sheath placement	Placement of a floppy hydrophilic guidewire advanced through the femoral artery into the left ventricle, exchanged for a stiff Lunderquist guidewire.	Hydrophilic guidewire, Lunderquist guidewire (300 cm, extra-stiff), real-time imaging.
3. Endograft advancement	Advancement of the arch branched endograft through the femoral artery into the aortic arch, aligning with supra-aortic trunks under imaging guidance.	Custom made arch branched endograft.
4. Deploying BCT branch	Cannulation and deployment of a custom-modified limb into the BCT via RCCA/right axillary access, followed by angioplasty.	Dedicated custom-made limb, high-pressure balloon.
5. Deploying LCCA branch	Similar to BCT branch, using either a self-expanding or balloon-expandable stent graft deployed into the LCCA.	LCCA access, appropriate stent graft (self-expanding or balloon-expandable).
6. Deploying LSA branch (if applicable)	Retrograde cannulation and deployment of a stent graft in the LSA via a pre-cannulated pathway from a femoral approach.	Femoral access, pre-cannulated pathways, stent graft for LSA.
7. Completion of procedure	Conducting a final angiography to ensure no endoleaks, correct graft alignment, and proper blood flow through all branches. Withdrawal of the delivery system and guidewires.	Angiography, Closure devices.
8. Post-operative monitoring	Continuous monitoring of cardiac, neurological, and vascular functions post-procedure and scheduling follow-up imaging studies.	Monitoring equipment, follow-up imaging.

prophylaxis. The patient is positioned supinely, and main vascular access is performed through the common femoral artery percutaneously. Upper extremity access through the right axillary artery or RCCA, and eventually the LCCA are obtained generally through a small cervical cutdown.

New techniques as the "branch-to-branch-to-branch" technique described by Prendes *et al.*[27] require only the exposure of the right axillary artery, without exposure of the carotid arteries (Figure 3.4.2). Alternatively total percutaneous techniques have also been described by Mougin *et al.*[29]

Guidewire and sheath placement (Figure 3.4.3)

A floppy hydrophilic guidewire is advanced through the femoral access, navigating through the aortic valve into the left ventricle. This guidewire is then replaced with a 300 cm extra-stiff Lunderquist guidewire, which is carefully positioned in the apex of the ventricle. Accurate positioning is crucial to avoid cardiac perforation and is continuously monitored throughout the procedure.

Endograft advancement and deployment

With the guidewire in place, the arch branched endograft is introduced via the femoral artery. The device's advancement is meticulously monitored using fluorosocpy imaging technology to ensure precise alignment with the aortic arch and supra-aortic trunks. Upon reaching the correct position, the endograft is opened while cardiac output reduction is initiated to reduce heart ejection fraction and stabilize the aortic arch, while reducing movement that could displace the endograft form its precise position.

Deploying each branch

1. ***Brachio-cephalic-trunk (BCT) branch***
   In the standard technique the BCT branch is accessed via the RCCA cut down with a 7F introducer sheat either from the right axillary/brachial access. A dedicated catheter is advanced over a guidewire into the BCT branch opening. Once access is secured, a custom-made dedicated limb, due to the larger diameter of this vessel, is deployed into the BCT, ensuring robust sealing and fixation. In this specific situation, in c ase of smaller diameter or shorter origin of the RCCA or an aberrant right subclavian artery, a standard balloon-exapandale stent-graft might be used.
2. ***Left Common Carotid Artery (LCCA) branch***
   Similar steps are followed for the LCCA branch using the left carotid access. Depending on the vessel's size and orientation, either a self-expanding or balloon-expandable stent graft is selected and deployed. In case of alternative techniques (percutanous, branch-to-branch) the LCCA might be cannulated retrogradely, avoiding exposure of the carotuide artery.

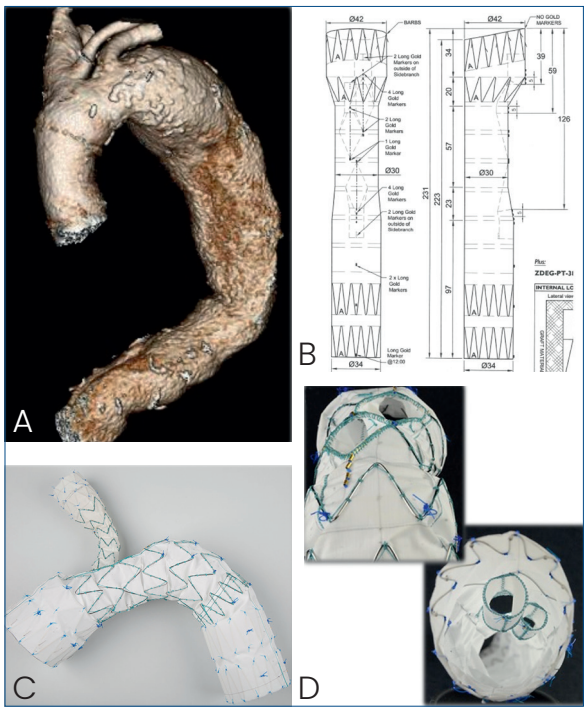


FIGURE 3.4.1 ● Arch aneurysm and arch-endograft details. A) Arch aneurysm of zone 2-3 requiring a proximal landing zone in zone 0. B) Details of a triple inner branch custom-made endograft (Cook Medical) reported in front view (left) and lateral view (right) with the depicted gold markers, with proximal diameter 42 mm; distal diameter 34 mm and narrowed part of the graft at the level of the inner branches of 30 mm. C) Details of the open graft with the dedicated custom-made limb for the brachio-cefalic trunk. D) Details of the inner branched from outside (upper) and inside (lower) view.

3. *Left Subclavian Artery (LSA) branch*

First generation graft did not have a third inner branch and therefore the LSA would have been revascularized through a LCCA carotid- LSA subclavian surgical bypass, generally using a 8mm dacron or PTFE graft.[6, 7, 50]

For endografts equipped with a third branch for the LSA, the procedure involves retrograde cannulation from the femoral approach though a precanulated route in a reversed down-ward facing inner branch. This pre-cannulated pathways allows for straightforward access to the LSA without the need for branchial access and speeding up the procedure. A ballon-expandable either slef-expandabel stent-graft is then deployed within the LSA to connect the dedicated inner branch. Often, an additional stenting may be required to ensure optimal flow and reiforce the angulation of the retrograde branch.

Completion of procedure

Following the successful deployment and fixation of all branches, a comprehensive angiographic final assessment is performed to confirm the absence of endoleaks, proper alignment of the grafts, and blood flow through all treated vessels. The delivery system and guidewires are then carefully withdrawn, and access are sealed in standard fashion.

Post-operative monitoring

After the procedure, the patient remains under close observation, with continuous monitoring of cardiac, neurological, and vessel accesses complications. Follow-up imaging studies are always scheduled to assess the position of the graft and the overall success of the revascularization.

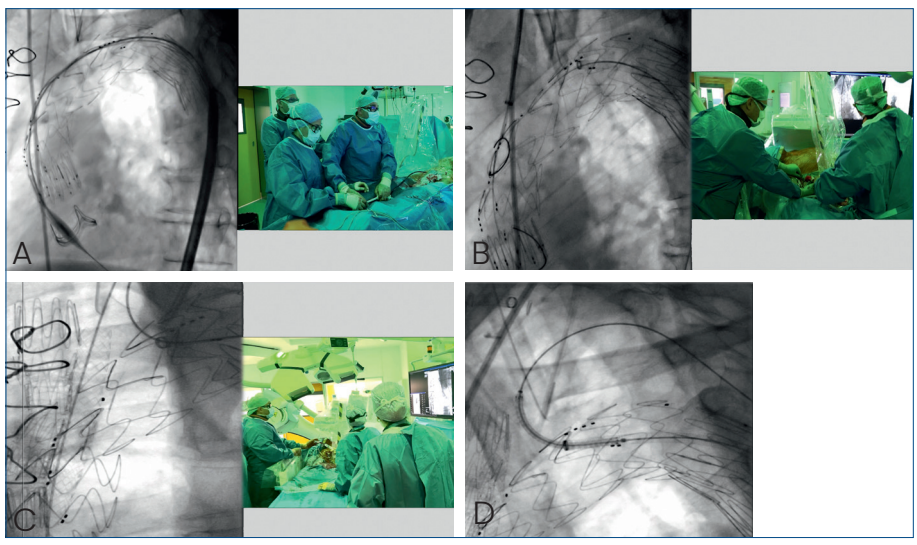


FIGURE 3.4.2 ● Operating hybrid room set-up and main steps for the branch-to-branch-to-branch technique[27] for the deployment of a triple inner branch custom made device (Cook Medical). A) Deployment of the main endograft from percutanous right femoral access, this procedure is performed with the aid of fusion imaging and with reduction of cardiac output with the MuVIT valsalva technique;[18] B) positionin from the right axillary cut-down access for the cannulation and deployment of the brachio-cephalic dedicated limb; C) deployment of the left common carotid artery stent-graft from the right axillary access usign the through-and-through technique; D) deployment of stent-graft for the left sublclavian artery in the retrograde inner-branch with precannulated guidewire from the femoral percutanous right access.

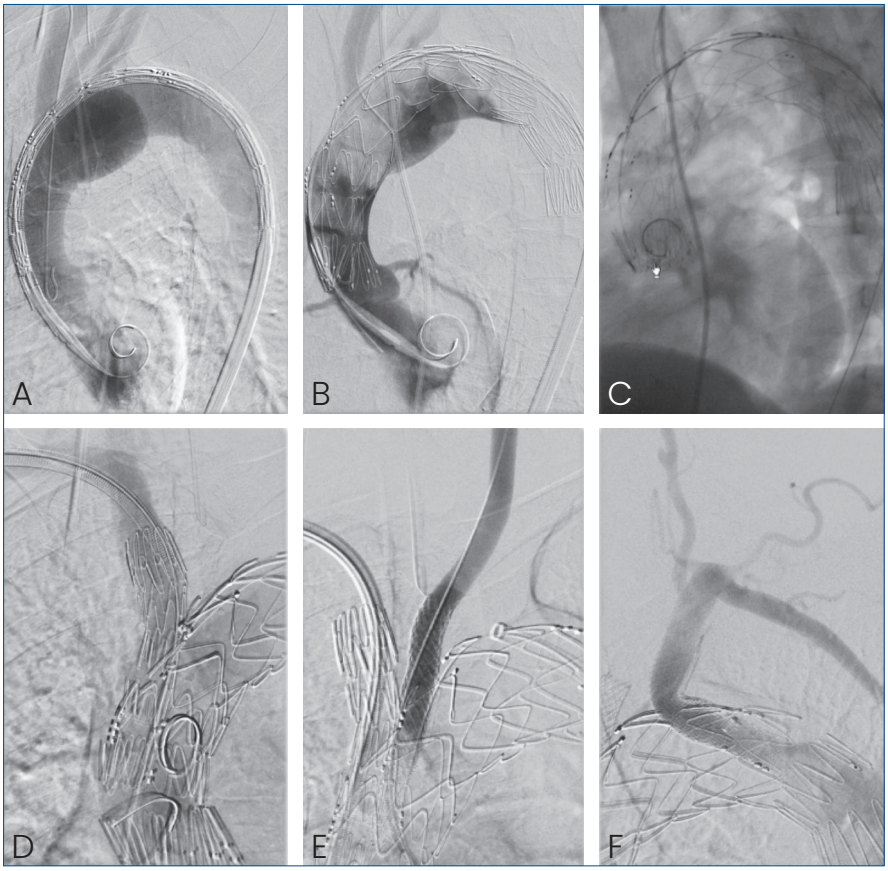


FIGURE 3.4.3 ● Step-by-step procedure for the implantation of a triple inner branch custom made device (Cook Medical) for a penetrating aortic ulcer of the arch. A) Advancement of the custom-made device into the aortic arch and aligment of the markers for the inner branches to the intended supra-aortic vessels; B) deployment of the endograft together with cardiac output reduction and above the origin of both coronary arteries; C) delivery system retrieval and full deployment of the main endograft; D) cannulation of the brachio-cephalic inner branch and deployment of the dedicated custom-made limb; E) cannulation (retrogradely from left carotid access or like in this case in antegrade fashion trhough the branch for the innominate artery with the branch-to-branch-to branch guidewire technique) of the left carotide artery and dedicated inner branch and deplyment of balloon expandable stent-graft; F) canulation from the femoral access of the pre-loaded retrograde inner branch for the left subclavian artery and deployment of balloon expandable stent graft with patency of the left vertebral artery. Disclosure: Nikolaos Tsilimparis is proctor for Cook Medical for fenestrated/branched endovascular aneurysm repair. The other authors declare that they have no competing interests.

NARRATIVE REVIEW OF RECENT OUTCOMES OR BRANCHED ENDOVASCULAR REPAIR OF THE AORTIC ARCH WITH CUSTOM-MADE B-TEVAR DEVICES

Several review and multicenter studies have focused the attention on the whole expericence in the aorttic arch repair, merging in the same results the off-the-shelf and custom-made endografts, as well as debranching tecnhiques and parallel graft solutions.[12, 51, 52]

On the same account, many of these experiences covered the entire learning curve of dedicated centers with arch devices and procedures,[7, 16, 23, 53] that along the years have deeply evolved and adapted from clincal and intra-operative feedback and improvements in materials both for the main endografts and bridingins stents.

Recently a systematic review and meta-analysis[6] was published by a collaborative reasearch group between an Italian and a German Vascular Surgery departments, focusing the attention exclusively on manufactured off-the-shelf and custom made fenestrated and branched TEVAR and collectig data from 2018 to 2021.

The results were based on 91% of off-the-shelf devices, showing a promising 96% pooled rate techinical success rate and 30-day morttality pooled rate of 6.7%. Specifically b-TEVAR was used in a larger choort of patients (54.3%) and showed a favourable trend in the use for zone 0 repair (89% of cases) and decreasing the amount of type I-III endoleak when compared to f-TEVAR, possibly for a more durable and stable configuration to face 4-directional arch movements durgin cardiac and respiratory cycles.[7, 54]

At the same time b-TEVAR has been recently used for alternative specific procedures and innovative techniques, as reported by coherent series of the Aortic Center in Munich, Germany.[27, 28]

Recently, the largest single center study on the f/b-TEVAR repair has been published by the German Aortic center group[21] over 209 patients in a 10-year experience. Therefore we performed a narrative review extrapolating data solely on the indications, applications and outcomes of custom-made b-TEVAR devices in these last reported experiences. We conducted a comprehensive review of branched endovascular aortic repair (b-TEVAR) across 10 research studies conducted between 2018 and 2024,

in a range of global centers. Collectively, these studies analyzed the outcomes of 364 patients treated with b-TEVAR. The interventions spanned from 2011 to 2023, reflecting advancements in technique and variations in practice over more than a decade (Table 3.4.II).

The size of the patient cohorts in individual studies ranged from 5 to 116, with a significant study conducted by Rohlffs *et al.*[21] in 2024 contributing the largest sample. Follow-up periods across these studies varied significantly, with the shortest mean follow-up being 3.2 months (range 1-14 months) reported by Tenorio *et al.*[16] in 2021, and the longest mean follow-up extending to 48 months by Kudo *et al.*[55] in 2020. Notably, two studies, Law *et al.*[56] and Rohlffs *et al.*,[21] did not specify follow-up durations, which suggests variability in the data completeness and follow-up capabilities.

Among these patients, degenerative aneurysms were observed with highest incidence in Kudo *et al.*'s study[55] (78.6% of patients). Chronic dissections were more prevalent, with Verscheure *et al.* reporting chronic dissections in all their studied cases (100%). Penetrating aortic ulcers (PAU) were less common, found in 15 patients, with Ferrer *et al.* reporting the highest number (37.5% of their patients)[57]. Pseudo-aneurysms were solely reported in Becker *et al.*'s study, all treated with an inner branch device. Urgent cases were noted in 17 instances, with Tsilimparis *et al.*[23] showing the highest number of urgent interventions (20.4% of their patients).

The types of devices utilized across all studies were exclusively custom-made, with Cook Medical being the predominant manufacturer, followed by Terumo Aortic/Bolton Medical (Table 3.4.III). The proximal landing zone for all devices was consistently Zone 0 (LZ0), underscoring a uniform surgical approach to aortic arch repair. Adjunctive cervical bypass techniques varied, with the majority involving the left common carotid to subclavian artery (LCCA-LSA). Notably, complex bypass configurations such as RCCA-RSA or LSA transpositions were also reported, particularly in studies with a higher number of patients.[21, 58]

The reported mean follow-up periods varied, with some studies providing specific ranges, while some other studies reported exclusively 30-day results (Table 3.4.II).

Mortality rates across these studies varied, with the highest observed rate being 20% in both Becker *et al.*[28] and Law *et al.*[56] even if they were directly linked to urgent perfomred repair in small chort of patients. The lowest rate reported as 0% in several studies including

Table 3.4.II ● Outcomes and complications related to branched endovascular aortic repair (b-TEVAR).

Author *et al.*	Year	N. patients	Mortality (%)	CV-events (%)	SCI (%)	Endoleaks (%)	Renal function worsening (%)	Cardiac events (%)	Retrograde type A dissection (%)	Reinterventions (%)	Mean follow-up (range/SD)
Rohlffs *et al.*	2024	116	12 (10.3)	20 (17.2)	5 (4.3)	39 (33.6)	15 (12.9)	11 (9.6)	2 (1.7)	35 (30.2)	-
Becker *et al.*	2023	10	2 (20)	1 (10)	0	2 (20)	0	1 (10)	0	3 (30)	6 (1-11)
Prendes *et al.*	2023	7	0	0	0	2 (28.5)	0	0	0	2 (28.5)	20 (55)
Verscheure *et al.*	2021	70	2 (2.9)	2 (2.9)	0	2 (2.9)	2 (2.9)	3 (4.3)	0	12 (17.1)	3.2 (1-14)
Tenorio *et al.*	2021	39	2 (5)	2 (5)	0	2 (5)	2 (5)	2 (5)	0	7 (18)	10 (5-21)
Kudo *et al.*	2020	28	0	4 (14.3)	0	0	0	0	0	0	48 (24)
Van der Weijde *et al.*	2020	11	2 (18.2)	4 (36.4)	1 (9)	0	1 (9)	0	0	0	17 (3-42)
Ferrer *et al.*	2019	24	4 (16.7)	6 (25)	0	2 (8.3)	1 (4.2)	0	2 (8.3)	4 (16.7)	8 (1-50)
Tsilimparis *et al.*	2019	54	3 (6)	6 (11.1)	3 (5.5)	1 (1.8)	4 (7.4)	9 (16.7)	0	12 (22.2)	12 (9)
Law *et al.*	2018	5	1 (20)	1 (20)	0	0	0	0	0	0	-
Total/Range		364									Range: 1-55

CV-events: cerebrovascular events (minor and major strokes); SCI: spinal cord ischemia.

Kudo *et al.*[56] Cardiovascular event rates ranged from 0% to 36.4%. Spinal cord ischemia was noted in a limited number of studies, not exceeding 9% in any study. Endoleaks were another significant concern, appearing in up to 33.6% of patients in the study by Rohllffs *et al.*,[21] which also documented the highest rates of reinterventions (30.2%). The vast majority of these procedures were access related reinterventions. The incidence of renal function worsening and cardiac events was comparably low across most studies, rarely exceeding 10%. Retrograde type A dissection was rare.

DISCUSSION: BRANCHED ENDOGRAFTS FOR AORTIC ARCH REPAIR

This review presents a wide cohort of patients treated consistenlty with custom-made b-TEVAR devices and with proximal landing zone in zone 0 in all cases. Therefore all procedure were accomplished as a total arch repair as described by recent guidelines.[1, 2] The collected data from these studies provide valuable insights into the evolving practices and outcomes associated with b-TEVAR across different global centers and focus the attention on the second half of the global learning curve, with advenced techniques, experices and the evolution of devices in dedicated centers.[7, 16, 17, 21] As reported by Rohffls *et al.*,[21] the technical success from the initial chohort and the earliest expriences raised significanlty from an initial 93.9% up to 99.2%.

Among these aspects, the clinical game changer has been represented by the introduction of a tripler inner branched configuration[46] that enabled the possibilty to revacularize all the supra-aortic vessels by endovascular means and providing therefore possiblity to mininvasive

Table 3.4.III ● Summary of Branched Endovascular Aortic Repair (b-TEVAR) studies and detailed of detailed overview of b-TEVAR repair.

Authors *et al.*	Year	Study design	Years of intervention	N. of patients	Model	Manufacturer	Proximal landing zone	Adjunctive cervical bypass
Rohlffs *et al.*[21]	2024	Retrospective	2011-2022	116	91 2-inner branches for BCT and LCCA, 25 3-inner branched	Cook Medical All CM Devices	116 LZ0	84 LCCA-LSA; 5 LSA transposition; 2 RCCA-LCCA; 8 RCCA-RSA
Prendes *et al.*[27]	2023	Retrospective	2022-2023	7	2 2-inner branches for BCT and LCCA, 8 3-inner branched	Cook Medical All CM Devices	10 LZ0	2 LCCA-LSA
Becker *et al.*[28]	2023	Retrospective	2018-2022	10	7 3-inner-branch (Custom Made)	Cook Medical All CM Devices	7 LZ0	0
Tenorio *et al.*[16]	2021	Retrospective, Multicenter	2016-2019	39	39 3-inner branches	Cook Medical All CM Devices	39 LZ0	7 RCCA-RSA
Verscheure *et al.*[58]	2021	Retrospective, Multicenter	2011-2018	70	63 2-inner branches for BCT and LCCA, 7 3-inner branched	Cook Medical All CM Devices	70 LZ0	63 LCCA-LSA or transposition, 7 RCCA-RSA or transposition
Kudo *et al.*[55]	2020	Retrospective	2012-2018	28	4 1-inner-branch, 24 2-inner-branch	Bolton Medical All CM Devices	28 LZ0	1 LCCA-LSA, 24 RAA-LSA, 3 RAA-LCCA-LSA
Van der Weijde *et al.*[60]	2020	Retrospective, Multicenter	2014-2018	11	11 2-inner-branch (Customized Relay NBS Plus)	Terumo Aortic All CM Devices	11 LZ0	5 LCCA-LSA, 3 LSA transpositions
Ferrer *et al.*[57]	2019	Retrospective, Multicenter	2012-2018	24	24 2-inner-branch (RelayBranch)	Terumo Aortic All CM Devices	24 LZ0	21 LCCA-LSA, 2 LSA transpositions
Tsilimparis *et al.*[23]	2019	Retrospective	2012-2017	54	54 2-inner-branch	Cook Medical All CM Devices	54 LZ0	54 LCCA-LSA
Law *et al.*[56]	2018	Retrospective	-	5	5 2-inner-branch (custom-made Zenith Ascend)	Cook Medical All CM Devices	5 LZ0	5 LCCA-LSA
Total/Range	-	-	-	364				

CM: Custom-Made; OTS:Off-The-Shelf; LZ0, LZ1, LZ2 represent landing zones 0, 1, and 2, respectively; LCCA: left common carotid artery; LSA: left sublcavian artery; RCCA: right common carotide artery; RSA: right sublcavian artery.

procedure like one unique upper extremity access either a total percutaneous repair.[27, 29]

Mortality rates varied notably across studies, with some reporting no deaths while others noted rates as high as 20%, even is this data need to be considered in lit of a high prevalnce of urgent repair while instead in other studies only elective cases were reported. At the same time, as reported by the largest cohort in this review,[21] 30-day death rate was assocated with stroke rates, pericadial effusion post-operatively and respiratory faiulure. This last aspect convey the importance of post-opertaive mangement of these patients and has been similarly advocated in other complex endovascular repair experiences as main factor for patient survival.[59]

Endoleaks presented as a prevalent issue, even if as reported, in vast majority they tabnd to solve spontaneiusly in the peri-operative period.[21] As well, type I-III endoleak seem to be protected by the b-TEVAR configurations due to a higher adaptability and movement resistence compared to fenstrated devices,[6] howevere these aspect should be futrher investigated since the different materials involved with overlap zones that need to be carefully analyzied over a consistent imagin follow-up.

Interestingly, the incidence of retrograde type A dissection was low across the board, suggesting that when b-TEVAR it is a relatively safe procedure probably for its specific long coverage of the ascending aorta which stabilize the repair even in post-dissection conditions.[6, 58] The low rates of spinal cord ischemia and other severe complications further support the effectiveness of modern protective strategies and technological advancements in the field.

Limitations

The diversity in patient numbers, the retrospective nature of the reported study, the difference oin graft design and especially the absence of detailed follow-up data in some studies could impact the understanding of long-term outcomes, stressing the importance of consistent, data collection and the need for standardized protocols to enhance comparability and generalizability of outcomes in future research.

CONCLUSIONS

Branched endovascular aortic arch repair (b-TEVAR) show significant advancements in the challenging treatment of complex aortic arch pathologies. The data herein presented technical success rates improving over time, attributed largely to advancements in device technology and growing surgical expertise.

Mortality rates varied but remained within expected ranges for high-risk patient population, as well as cerebrovascular events and spinal cord ischemia even if acceptable, still remain devastating complications underscoring the need for careful patient selection and preoperative planning.

Reinterventions were relatively common, indicating that while b-TEVAR offers a promising alternative to open surgery, it is not without long-term challenges, especially related to access complications.

The importance of centralized care in specialized centers, offering a combination of advanced technology and specialized expertise is of pramount importance to reach satisfactory technical and clinical outcomes.

REFERENCES

1. Czerny M, Schmidli J, Adler S, *et al.* Current Options and Recommendations for the Treatment of Thoracic Aortic Pathologies Involving the Aortic Arch: An Expert Consensus Document of the European Association for Cardio-Thoracic Surgery (EACTS) & the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2019;57:165–98.
2. Czerny M, Grabenwöger M, Berger T, *et al.* EACTS/STS Guidelines for Diagnosing and Treating Acute and Chronic Syndromes of the Aortic Organ. Ann Thorac Surg 2024;S0003497524000778.
3. Preventza O, Coselli JS, Price MD, *et al.* Elective primary aortic root replacement with and without hemiarch repair in patients with no previous cardiac surgery. J Thorac Cardiovasc Surg 2017;153:1402–8.
4. Donas KP, Rancic Z, Lachat M, *et al.* Novel sutureless telescoping anastomosis revascularization technique of supra-aortic vessels to simplify combined open endovascular procedures in the treatment of aortic arch pathologies. J Vasc Surg 2010;51:836–41.
5. Lioupis C, Abraham CZ. Results and Challenges for the Endovascular Repair of Aortic Arch Aneurysms. Perspect Vasc Surg Endovasc Ther 2011;23:202–13.
6. Spath P, Campana F, Tsilimparis N, *et al.* Outcomes of Fenestrated and Branched Endografts for Partial and Total Endovascular Repair of the Aortic Arch – A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg 2023;S1078588423006147.
7. Haulon S, Greenberg RK, Spear R, *et al.* Global experience with an inner branched arch endograft. J Thorac Cardiovasc Surg 2014;148:1709–16.
8. Bellamkonda KS, Yousef S, Nassiri N, *et al.* Trends and outcomes of thoracic endovascular aortic repair with open concomitant cervical debranching. J Vasc Surg 2021;73:1205-1212.e3.
9. Dieleman IM, Zuidema R, De Beaufort HW, *et al.* Determination of the gained proximal sealing zone length after debranching of the left subclavian artery in thoracic endovascular aortic repair. J Cardiovasc Surg [Internet]. 2023 Mar [cited 2023 Aug 10];64(2). Available from: https://www.minervamedica.it/index2.php?show=R37Y2023N02A0134
10. Konstantinou N, Kölbel T, Debus ES, *et al.* Fenestrated versus debranching thoracic endovascular aortic repair for endovascular treatment of distal aortic arch and descending aortic lesions. J Vasc Surg 2021;73:1915–24.
11. Konstantinou N, Debus ES, Vermeulen CFW, *et al.* Cervical Debranching in the Endovascular Era: A Single Centre Experience. Eur J Vasc Endovasc Surg 2019;58:34–40.
12. Nana P, Spanos K, Dakis K, *et al.* Systematic Review on Customized and Non-customized Device Techniques for the Endovascular Repair of the Aortic Arch. J Endovasc Ther 2022 Nov 8;152660282211337.
13. Atkins MD, Lumsden AB. Parallel grafts and physician modified endografts for endovascular repair of the aortic arch. Ann Cardiothorac Surg 2022;11:16–25.
14. Guo B, Guo D, Chen B, *et al.* Endovascular Outcomes in Aortic Arch Repair with Double and Triple Parallel Stent Grafts. J Vasc Intervent Radiol 2020;31:1984-1992.e1.

15. Spath P, Stana J, Marazzi G, *et al.* Emergent physician modified carotid fenestrated TEVAR for the treatment of a complicated acute type nonA-nonB aortic dissection with undetected multiorgan malperfusion. J Cardiovasc Surg [Internet]. 2023 Jul [cited 2024 Apr 27];64(4). Available from: https://www.minervamedica.it/index2.php?show=R37Y2023N04A0450
16. Tenorio ER, Oderich GS, Kölbel T, *et al.* Multicenter global early feasibility study to evaluate total endovascular arch repair using three-vessel inner branch stent-grafts for aneurysms and dissections. J Vasc Surg 2021;74:1055-1065.e4.
17. Tsilimparis N, Debus ES, Von Kodolitsch Y, *et al.* Branched versus fenestrated endografts for endovascular repair of aortic arch lesions. J Vasc Surg 2016;64:592–9.
18. Stana J, Prendes CF, Melo RG, *et al.* First Experience with the Munich Valsalva Implantation Technique (MuVIT) for Cardiac Output Reduction During Standard and Complex Thoracic Endovascular Aortic Repair. Eur J Vasc Endovasc Surg 2022;63:817–26.
19. Spanos K, Panuccio G, Rohlffs F, *et al.* Technical Aspects of Branched Thoracic Arch Graft Implantation for Aortic Arch Pathologies. J Endovasc Ther 2020;27:792–800.
20. Konstantinou N, Peterss S, Stana J, *et al.* Passing a Mechanical Aortic Valve With a Short Tip Dilator to Facilitate Aortic Arch Endovascular Branched Repair. J Endovasc Ther 2021;28:388–92.
21. Rohlffs F, Nana P, Panuccio G, *et al.* A Retrospective Analysis of 10-year Experience on Branched and Fenestrated Endovascular Aortic Arch Repair. Annals of Surgery [Internet]. 2024 Mar 19 [cited 2024 May 5]; Available from: https://journals.lww.com/10.1097/SLA.0000000000006271
22. Tsilimparis N, Prendes CF, Rouhani G, *et al.* Pre-Loaded Fenestrated Thoracic Endografts for Distal Aortic Arch Pathologies: Multicentre Retrospective Analysis of Short and Mid Term Outcomes. Eur J Vasc Endovasc Surg 2021;62:887–95.
23. Tsilimparis N, Detter C, Law Y, *et al.* Single-center experience with an inner branched arch endograft. J Vasc Surg 2019;69:977-985.e1.
24. Clough RE, Spear R, Van Calster K, *et al.* Case series of aortic arch disease treated with branched stent-grafts. Br J Surg 2018;105:358–65.
25. Bath J, D'Oria M, Rogers RT, *et al.* Contemporary outcomes after treatment of aberrant subclavian artery and Kommerell's diverticulum. J Vasc Surg 2023;77:1339-1348.e6.
26. Spath P, Marazzi G, Stana J, *et al.* Endovascular Repair With Triple Inner-Branch Endograft for Aberrant Subclavian Artery Aneurysm: A Case Report. J Endovasc Ther 2022 Aug 8;152660282211167.
27. Prendes CF, Spath P, Stana J, *et al.* Transaxillary Branch-to-Branch-to-Branch Carotid Catheterization Technique for Triple-Branch Arch Repair. J Endovasc Ther 2023 May 24;152660282311691.
28. Becker D, Stana J, Prendes CF, *et al.* Endovascular arch repair of anastomotic aneurysm and pseudoaneurysm in patients after open repair of the ascending aorta and aortic arch: a case series. Eur J Cardiothorac Surg 2023;64:ezad345.
29. Mougin J, Azogui R, Guihaire J, *et al.* "First in Man" Total Percutaneous Aortic Arch Repair With 3-Inner-branch Endografts: A Report of Two Cases. Ann Surg 2021;274:e652–7.
30. Gouveia E Melo R, Fernández Prendes C, Khanafer A, *et al.* Common Designs of Custom-Made Fenestrated Arch Devices and Applicability of an Off-the-Shelf Design. J Endovasc Ther 2023 Jun 9;152660282311795.
31. Bosse C, Kölbel T, Mougin J, *et al.* Off-the-shelf multibranched endograft for total endovascular repair of the aortic arch. J Vasc Surg 2020;72:805–11.
32. Gallitto E, Faggioli G, Spath P, *et al.* The risk of aneurysm rupture and target visceral vessel occlusion during the lead period of custom-made fenestrated/branched endograft. J Vasc Surg 2020;72:16–24.
33. Ullery BW, Tran K, Itoga NK, *et al.* Natural history of gutter-related type Ia endoleaks after snorkel/chimney endovascular aneurysm repair. J Vasc Surg 2017;65:981–90.
34. Bosiers MJ, Donas KP, Mangialardi N, *et al.* European Multicenter Registry for the Performance of the Chimney/Snorkel Technique in the Treatment of Aortic Arch Pathologic Conditions. Ann Thorac Surg 2016;101:2224–30.
35. Qin J, Zhao Z, Wang R, *et al.* In Situ Laser Fenestration Is a Feasible Method for Revascularization of Aortic Arch During Thoracic Endovascular Aortic Repair. JAHA 2017;6:e004542.
36. Tish S, Chase JA, Scoville C, *et al.* A Systematic Review of Contemporary Outcomes from Aortic Arch In Situ Laser Fenestration During Thoracic Endovascular Aortic Repair. Ann Vasc Surg 2023;91:266–74.
37. Shang T, Tian L, Li D lin, *et al.* Favourable Outcomes of Endovascular Total Aortic Arch Repair Via Needle Based In Situ Fenestration at a Mean Follow-Up of 5.4 Months. Eur J Vasc Endovasc Surg 2018;55:369–76.
38. Gouveia E Melo R, Fernández Prendes C, Caldeira D, *et al.* Systematic Review and Meta-analysis of Physician Modified Endografts for Treatment of Thoraco-Abdominal and Complex Abdominal Aortic Aneurysms. J Vasc Surg 2022;76:1424.
39. Le Houérou T, Álvarez-Marcos F, Gaudin A, *et al.* Midterm Outcomes of Antegrade In Situ Laser Fenestration of Polyester Endografts for Urgent Treatment of Aortic Pathologies Involving the Visceral and Renal Arteries. Eur J Vasc Endovasc Surg 2023;65:720–7.
40. Yu Z, Hu S, Wang D, *et al.* Early and midterm outcomes of in situ fenestration via adjustable puncture needle for Ankura aortic stent graft: A single-center experience. Vascular 2023 Jul 26;17085381231192376.
41. Piffaretti G, Franchin M, Gnesutta A, *et al.* Anatomic Feasibility of In-Situ Fenestration for Isolate Left Subclavian Artery Preservation during Thoracic Endovascular Aortic Repair Using an Adjustable Needle Puncturing System. JCM 2023;13:162.
42. Mougin J, Sobocinski J, Kratzberg J, *et al.* Applicability of a standardized thoracic endograft with a single branch for the left subclavian artery to treat aortic disease involving the distal arch. J Vasc Surg 2020;72:1516–23.
43. Leone N, Andreoli F, Bartolotti LAM, *et al.* Anatomical feasibility of a 'semi-custom' unibody single-branch endograft in previous zone 2 thoracic endovascular aortic repair. Eur J Cardiothorac Surg 2023;64:ezad290.
44. Vacirca A, Tenorio ER, Mesnard T, *et al.* Technical tips and clinical experience with the Gore Thoracic Branch Endoprosthesis®. J Cardiovasc Surg [Internet]. 2023 Feb [cited 2024 May 31];64(1). Available from: https://www.minervamedica.it/index2.php?show=R37Y2023N01A0018
45. Stana J, Fernandes Prendes C, Banafsche R, *et al.* Emergent Triple-Branched TEVAR and Redistribution of the Branches to the Supra-Aortic Target Vessels for Treatment of a Contained Ruptured Descending Aortic Aneurysm Associated With a Chronic Type A Aortic Dissection. J Endovasc Ther 2021;28:309–14.
46. Spear R, Haulon S, Ohki T, *et al.* Subsequent Results for Arch Aneurysm Repair with Inner Branched Endografts. Eur J Vasc Endovasc Surg 2016;51:380–5.
47. Spear R, Hertault A, Van Calster K, *et al.* Complex endovascular repair of postdissection arch and thoracoabdominal aneurysms. J Vasc Surg 2018;67:685–93.
48. Tsilimparis N, Spath P, Stana J, *et al.* Endovascular Management of Aortic Arch Disease. In: Geroulakos G, Avgerinos E, Becquemin JP, Makris GC, Froio A, editors. Mastering Endovascular Techniques [Internet]. Cham: Springer International Publishing; 2024 [cited 2024 May 1]. p. 621–31. Available from: https://link.springer.com/10.1007/978-3-031-42735-0_60
49. Gallitto E, Faggioli G, Spath P, *et al.* Trattamento endovascolare di un aneurisma dell'arco aortico mediante endoprotesi custom-made con tre branch interni. Giornale Italiano di Cardi-

ologia [Internet]. 2021 Mar 1 [cited 2024 Apr 27];(2021Marzo). Available from: https://doi.org/10.1714/3578.35635
50. Chait J, Tenorio ER, Kawajiri H, *et al.* Mid-Term Outcomes of "Complete Aortic Repair": Surgical or Endovascular Total Arch Replacement With Thoracoabdominal Fenestrated-Branched Endovascular Aortic Repair. J Endovasc Ther 2023 Jun 14;15266028231181211.
51. Spanos K, Tsilimparis N, Rohlffs F, *et al.* Total endovascular arch repair is the procedure of the future. J Cardiovasc Surg [Internet]. 2018 Jun [cited 2022 Oct 10];59(4). Available from: https://www.minervamedica.it/index2.php?show=R37Y2018N04A0559
52. Blanco Amil CL, Mestres Alomar G, Guarnaccia G, *et al.* The Initial Experience on Branched and Fenestrated Endografts in the Aortic Arch. A Systematic Review. Ann Vasc Surg 2021;75:29–44.
53. Negmadjanov U, Motta JC, Lee WA. Total endovascular aortic arch repair using the Terumo Aortic triple-branch arch endograft. Ann Vasc Surg 2021;77:351.e7-351.e14.
54. Lu Q, Feng J, Zhou J, *et al.* Endovascular repair by customized branched stent-graft: A promising treatment for chronic aortic dissection involving the arch branches. J Thorac Cardiovasc Surg 2015;150:1631-1638.e5.
55. Kudo T, Kuratani T, Shimamura K, *et al.* Early and midterm results of thoracic endovascular aortic repair using a branched endograft for aortic arch pathologies: A retrospective single-center study. JTCVS Techniques 2020;4:17–25.
56. Law Y, Tsilimparis N, Rohlffs F, *et al.* Combined Ascending Aortic Stent-Graft and Inner Branched Arch Device for Type A Aortic Dissection. J Endovasc Ther 2018;25:561–5.
57. Ferrer C, Cao P, Coscarella C, *et al.* iTalian RegIstry of doUble inner branch stent graft for arch PatHology (the TRIUmPH Registry). J Vasc Surg 2019;70:672-682.e1.
58. Verscheure D, Haulon S, Tsilimparis N, *et al.* Endovascular Treatment of Post Type A Chronic Aortic Arch Dissection With a Branched Endograft: Early Results From a Retrospective International Multicenter Study. Ann Surg 2021;273:997–1003.
59. Spath P, Tsilimparis N, Gallitto E, *et al.* Endovascular Repair of One-hundred Urgent and Emergent free or Contained Thoraco-abdominal Aortic Aneurysms Ruptures. An International Multi-Center Trans-Atlantic experience. Annals of Surgery [Internet]. 2024 Feb 7 [cited 2024 Apr 7]; Available from: https://journals.lww.com/10.1097/SLA.0000000000006231
60. van der Weijde E, Heijmen RH, van Schaik PM, *et al.* Total Endovascular Repair of the Aortic Arch: Initial Experience in the Netherlands. Ann Thorac Surg 2020;109:1858–63.

3.5 PUSHING THE LIMITS PROXIMALLY 2: ENDOVASCULAR TREATMENT OF AORTIC ARCH DISEASE WITH PHYSICIAN-MODIFIED DEVICES

Ludovic Canaud, Thomas Gandet

INTRODUCTION

Our experience with modifying thoracic endoprostheses began in 2014. Initially, the modification was very simple. It involved creating a large window to preserve the left subclavian artery for acute pathologies of the aortic arch in zone 2.[1]

The markers for the window were attached to the outer face of the launcher with tape. Some of these markers were lost after deployment. Building on these initial successes, we progressed to single-window modifications in zone 2,[2] and then to combined single windows in zones 0 and 1.[3] To move towards completely endovascular practice in zones 0 and 1, we developed the concept of the double fenestrated stent-graft adapted to the patient's anatomy in 2017.[4]

We have a large proximal fenestration called the island, which is not reinforced, that will accommodate the brachiocephalic trunk (BT) and the left common carotid artery (LCCA), and a distal reinforced fenestration for the left subclavian artery (LSA).

This design has evolved over time to achieve a 'standard' design and the introduction of a preloaded guide to facilitate deployment.

INDICATION FOR A DOUBLE FENESTRATED STENT-GRAFT

Indications

Zone 1 aortic arch lesions

Patients with zone 1 aortic arch lesions are appropriate for this approach if the lengths of the proximal and distal neck (length from distal end of aneurysm to celiac artery) are of at least 20 mm and if the proximal and distal neck diameters are between 20 mm and 40 mm.

Zone 0 aortic arch lesions

Zone 0 aortic arch lesions suitable for a double fenestrated stent-graft:

- saccular aneurysms on the lesser curvature of the arch (Figure 3.5.1);
- acute Type B dissections with an entry tear requiring zone 0 landing;
- residual dissection after type A aortic dissection if the maximum diameter of the aorta at the level of the BT and LCCA is not more than 40 mm (Figure 3.5.2).

Contraindications

- Degenerative aneurysm of the outer curvature of the aortic arch: were deemed unsuitable because the size of the proximal fenestration was proximally and laterally larger than that of the BT and LCCA orifice, increasing the risk of endoleak.
- Thrombus in the aortic arch: risk of stroke.
- Ascending aorta diameter over 40 mm: risk of retrograde type A aortic dissection. In some cases a replacement of the ascending aorta or a wrapping of the ascending aorta can be performed to allow placement of a double fenestrated stent-graft.

PREOPERATIVE SIZING

Preoperative sizing is crucial when using a workstation. The crucial information for preoperative sizing will be reported.

Aortic diameters

To decide on the appropriate size for the stent-graft, the aortic diameter is measured at various levels: at the level of the ascending aorta, just before the brachiocephalic trunk, at the level of the left common carotid artery (LCCA), left subclavian artery (LSA), and at the distal neck.

Aortic lengths: using outer curvature lengths

- The distance for the island (proximal fenestration) is measured from the beginning of the brachiocephalic trunk (BT) to the distal part of the left common carotid artery (LCCA).
- The distance between the fenestrations is measured from the distal part of the LCCA to the proximal part of the LSA.
- The diameter of the LSA is measured.

Orientation of the supra-aortic trunks

The position of the supra-aortic trunks is determined using clock positions with the left subclavian artery (LSA) as the reference point.

Orientation of the C-Arm to be perpendicular to the LSA

We determine the orientation of the C-arm for stent-graft deployment by ensuring it is perpendicular to the LSA.

The length for aortic coverage

We determine the length for aortic coverage required by using the centerline.

PREPARATION OF A DOUBLE FENESTRATED STENT-GRAFT

A full video of the stent-graft modification is available on Vascupedia (https://vascupedia.com/presentation/

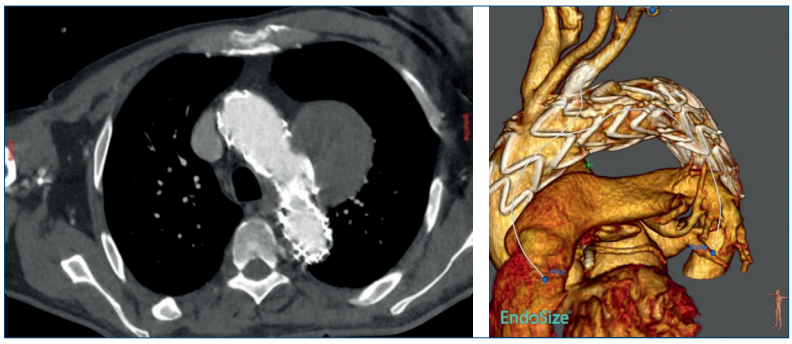


FIGURE 3.5.1 ● Endovascular repair using a double fenestrated TEVAR for a saccular aneurysms on the lesser curvature of the arch.

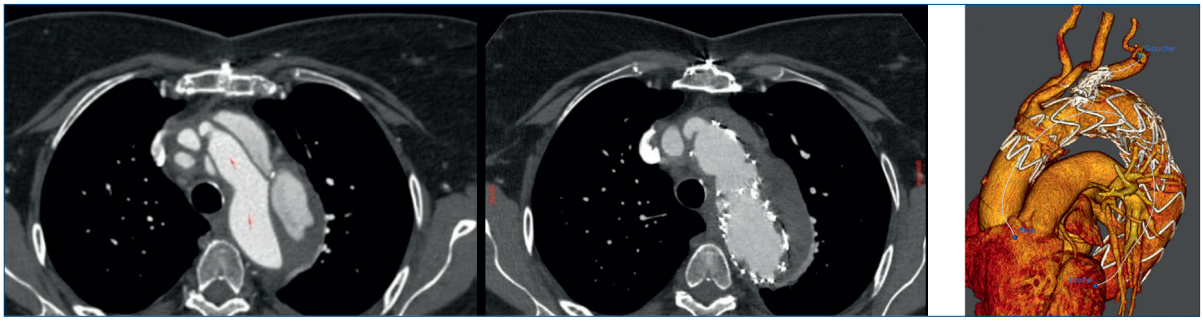


FIGURE 3.5.2 ● Endovascular repair using a double fenestrated TEVAR for a residual dissection after Type A aortic repair.

double-homemade-fenestrated-stent-graft-for-total-endovascular-aortic-arch-repair/).

On a back table, the stent-graft is fully unsheathed, except for the proximal bare stent that remains attached to the tip capture.

Our preferred length of stent-graft for modification is 150 mm. In fact, in the case of a 1000 mm stent-graft, the overlapping may not be sufficient if an additional distal stent-graft is required. With a 2000 mm stent-graft, it increases the length of stent-graft that will need to be reloaded, thus increasing preparation time.

Creation of the windows

For the proximal large fenestration, in order to avoid damage to the fabric the fenestration was created using a size 11 blade. At least 5 mm of fabric seems to be required between the proximal fenestration and the proximal edge of the stent graft to not compromise the integrity and stability of the graft. A cautery device is utilized to fashion the LSA fenestration. The floppy part of the Lunderquist (Cook Bloomington, IN, USA) is sutured around the fenestration both to reinforce seal (dilation of a covered stent against the nitinol ring) and to mark the position.

We did not utilize wire reinforcement of the large fenestration. We are not concerned about durability as we are using the same design as the Zenith Fenestrated stent graft system (Cook Medical, Bloomington, IN, USA) where large fenestrations are not reinforced by a nitinol ring.[5]

We do not feel that the absence of a radiologic marker for the BT/LCCA is dangerous. Procedure and device preparation planning using a dedicated three dimensional vascular imaging workstation is crucial. Furthermore, to decrease the risk of inadvertent coverage of the supra aortic trunk, the proximal fenestration is 2 mm larger laterally than that of the BT and LCCA orifices.

Preloading of the LSA fenestration

The sheath of the stent-graft launcher is punctured at the reinforced end with a metal needle. This needle allows the introduction of a 260 cm long Terumo stiff guide .0035. This guide then passes through the window to the subclavian artery.

Resheathing of the stent-graft

Afterwards, the stent-graft can be resheathed. Tissue loops with a tourniquet are used for this purpose. Each stent of the endoprosthesis is collapsed with a tissue loop. We start with the first 2 proximal stents (including the bare stent). This prevents the tip capture from being lost when we begin to re-sheath the prosthesis. Then, we start with the before one. The last one is always a bit more complicated to collapse, which is why collapsing the before last one helps collapse the last one.

When we reach the stent at the reinforced window, we ensure to keep the window outside. Otherwise, when collapsing the stent at the subclavian window, it tends to invaginate, making it less visible and precise during the deployment of the endoprosthesis in the aortic arch.

When we reach the proximal stents, including the bare stent, we pay attention not to catch the preloaded

guide with the tissue loops to avoid trapping them in the prosthesis.

When all the stents are collapsed using the tissue loops, we can begin to re-sheath. An assistant rolls the wheel while the operator pushes on the sheath to re-sheath the prosthesis.

When we reach the part of the endoprosthesis with the preloaded guide that has exited the subclavian window, we keep this guide in a straight line along the axis of the subclavian window.

When the prosthesis is fully resheathed, we flush it with a heparinized solution to prevent air presence. The prosthesis must be held upwards, and the puncture site should be sealed with a finger to allow entry of the preloaded guide.

STANDARD DESIGN FOR THE DOUBLE FENESTRATED STENT-GRAFT[6]

Aortic Arch Anatomy Pattern in Patients Treated Using Double Homemade Fenestrated Stent-Grafts for Total Endovascular Aortic Arch Repair

Study design

A retrospective analysis was conducted of the CTA data on aortic arch morphology and aortic length from 33 consecutives patients treated between January 2017 and March 2019 using PMEGs with double fenestrations for TEVAR landing in zone 0. Image analysis was completed according to a standardized measurement technique and was assessed by 2 vascular surgeons with experience of commercially available fenestrated stent-grafts to ensure interobserver agreement. The CTA data were transferred to the EndoSize 3D vascular workstation (version 3.1.25; Therenva, Rennes, France) with center lumen line reconstruction for all measurements.

Results (Figure 3.5.3)

The center of the supra-aortic trunk origins in all patients were contained within a proximal 30×30-mm square area (IA and LCCA) and a second distal circular area of 8 mm diameter (LSA). The square and circular common areas are separated by 5 mm. When the diameter, longitudinal distance between the edges, and the clock-face orientation of each supra-aortic branch vessel is considered, 32 patients (97%) fit completely within these areas.

Use of the standard double fenestrated stent graft

At the beginning of our practice, fenestration creation was tailored to each patient's anatomy. However, we found that the fenestration cuts were very similar from one patient to another. Following this anatomical study, we have adopted a standard design using a diamond-shaped cut for the large fenestration, measuring at least 38 mm in length (this measurement increases with the diameter of the endoprosthesis). Additionally, an 8 mm fenestration for the left subclavian artery (LSA) is created distally 5 mm from the large fenestrations in patients, after verifying concordance on the perioperative scan (Figure 3.5.4).

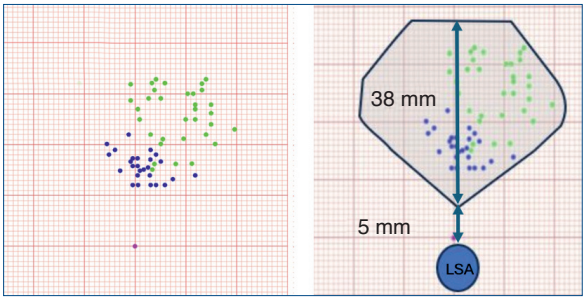


FIGURE 3.5.3 ● The blue dots [center of the left common carotid artery (LCCA)] and green dots [center of the innominate artery (IA)] indicate the location of the artery in relation to a fixed point (purple dot) based on the center of the left subclavian artery (LSA). IA (green dots) and LCCA (blue dots) arise from a common 30×30-mm area (gray square) in all patients. A second circular 8-mm-diameter area (gray) represents the center of the LSA (purple dot) in all patients. The background has 10 squares per centimeter.

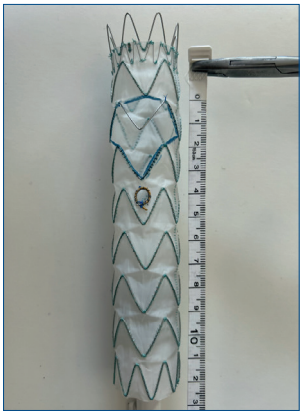


FIGURE 3.5.4 ● Standard double fenestrated stent graft with proximal fenestration in a diamond shape.

Creating the diamond-shaped fenestration while leaving a first covered stent is particularly useful in cases of previous replacement of the ascending aorta (especially after type A aortic repair) or in lesions of the inner curve of the aorta starting very proximally at the level of the brachiocephalic trunk.

DEPLOYMENT OF A DOUBLE FENESTRATED STENT-GRAFT

The procedure can be performed under general anesthesia or under local anesthesia and sedation.

A careful monitoring of the patient is essential. Monitoring the right radial artery enables checking the patency of the brachiocephalic trunk and detecting any iliac

rupture during the placement or removal of the stent-graft. Near-infrared spectroscopy (NIRSE) brain saturation is also an excellent tool for monitoring brain perfusion. The patient is always draped to allow iliac access and any cervical debranching if necessary.

Access

We perform percutaneous access on the left femoral and humeral arteries. We can choose either to use a femoral introducer of suitable size for the endoprosthesis or a smaller-sized introducer if we plan to insert the endoprosthesis without an introducer. For the humeral access, we use a 45 cm in length 6Fr introducer which is advanced just distally to the off spring of the LSA. A Lundquist double-curved guidewire is inserted via the femoral route and positioned against the aortic valve.

Establishing a humero-femoral through and through

In parallel with the Lundquist, a lasso is inserted and advanced into the descending thoracic aorta. A 260 cm Terumo guide .0035 is inserted via the left humeral route. This guide is captured by the femoral lasso and establishes a humero-femoral through and through. A catheter or a 130 cm carrier balloon is then inserted via the humeral route onto this guide. This catheter exits through the femoral route. The Terumo guide can then be removed, allowing the insertion of the preloaded guide of the endoprosthesis, which exits through the left humeral route. At this point, the catheter can be removed.

Stent-graft insertion

The stent-graft can be inserted over the Lundquist. If we have decided to proceed without an introducer, the 'temporary' femoral introducer can be inserted.

Entanglement of the preloaded wire around the Lunderquist

We can't anticipate if the preloaded guide is not wrapped around the endoprosthesis. Indeed, when we capture the humeral guide with the lasso, we are not sure if we are not wrapped around the Lundquist.

The best way to check includes the following steps:

- Tilt the C-arm to the left anterior oblique to unfurl the aortic arch (typically 30°).
- Align the subclavian window with the outer curvature of the descending thoracic aorta.
- Advance the endoprosthesis into the aortic arch to observe if the preloaded guide forms a V-angle when reaching the level of the left subclavian artery.

To address the issue of guide wrapping, several procedures are possible:

- remove the Lundquist guide from the endoprosthesis launcher and then advance it again. This procedure is not recommended in cases of difficulty catheterizing the aortic arch or aortic arch dissection. However, it is still necessary to verify that there is no persistent wrapping by rechecking the previously described verification process.
- A clockwise or counterclockwise rotation of 360° must be performed, focusing on the position of the subclavian window, which should always return against the outer curvature of the descending thoracic aorta. It may be necessary to perform multiple rotations until there is no longer any wrapping of the guide. It is essential to always verify this by advancing the prosthesis into the aortic arch afterward.

Positioning of the stent-graft in the aortic arch

The position of the C-arm was determined preoperatively to be perpendicular to the left subclavian artery. We advance the endoprosthesis while keeping the subclavian window aligned with the outer curvature of the descending thoracic aorta and then the aortic arch. During the progression of the endoprosthesis, the surgical assistant pulls on the preloaded guide until the nose of the endoprosthesis reaches the level of the aortic arch. At this point, the assistant stops pulling on the guide, allowing the rest of the endoprosthesis to progress.

If the marker of the left subclavian window loses its alignment with the outer curvature of the aortic arch due to the twists of the aorta at the end of the aortic arch, we must then try to determine if the rotation of the window is clockwise or counterclockwise by tilting the C-arm.

We then retract the endoprosthesis into the descending thoracic aorta, correct the marker of the subclavian window (most often in a clockwise direction). The window will no longer be aligned with the outer curvature of the descending thoracic aorta. We advance the endoprosthesis back into the aortic arch and then verify the achievement of a perfect alignment of the subclavian window marker in the aortic arch.

This maneuver can be performed multiple times, gradually increasing the correction of the window in the descending thoracic aorta each time to anticipate the rotation of the stent-graft when arriving in the aortic arch.

In cases of severe and multiple angulation of the aortic arch and descending thoracic aorta, maneuvers can facilitate the alignment of the windows:

- placement of the Lundquist into the left ventricle to provide more support;
- use of a 65 cm long large femoral introducer to navigate through iliac tortuosity and the descending thoracic aorta.

Deployment of the stent-graft in the aortic arch

Dropping the pressure or rapid pacing are not required. The stent graft is stabilized by the femoro-humeral through and through. Furthermore, when starting to deploy the stent graft, the first part of the stent graft that will open will be the large fenestration, allowing all the blood flow to the brain and thus avoiding distal migration of the stent graft.

Placement of the LSA fenestration a few centimeters proximal to the left subclavian artery (LSA) before deployment

We need to do that for 2 reasons:

- during deployment, the second surgeon will pull on the preloaded wire to prevent it from being trapped between the stent-graft and the aortic wall, thereby pulling distally the stent-graft;
- for the alignment of the fenestration, it is easy when the stent-graft is halfway deployed to pull it back, but almost impossible to push it forward.

Deployment: pulling the preloaded wire

After achieving perfect alignment and being proximal to the LSA target, we can perform the first angiography through the humeral introducer to check the position of the LSA.

The stent-graft is deployed, and the second surgeon pulls on the preloaded wire consistently and significantly. Pulling on the preloaded wire aims to prevent it from becoming trapped around one of the nitinol stents.

It is better to focus on the progressive liberation of the preloaded wire during deployment rather than solely on the position of the fenestration. Pulling on the preloaded wire will also perfectly position the fenestration at its intended location and place the stent-graft against the outer curve of the aortic arch. When the preloaded wire comes out perfectly in the LSA and the stent-graft is deployed up to the LSA fenestration, the second surgeon can stop pulling on the preloaded wire, and the stent-graft is fully deployed.

Blockage of the preloaded wire

The guidewire can become blocked during deployment. That's why it's important during deployment to focus on liberating the preloaded wire to ensure its freedom before the stent-graft is fully deployed.

- The best way to avoid the blockage is that the second surgeon pulls on the preloaded wire consistently and significantly.
- In case of blockage:
  - We can attempt to push the preloaded wire proximally from the humeral access and then restart pulling it back.
  - The small flick of the wrist. A small but firm flick of the wrist when pulling the preloaded wire, if blocked, can remove the blockage. It is important to keep in mind, and it is one of the very important aspects of creating its own fenestration, that the wire can only be blocked due to a strut of the stent-graft. Even if a stent of the stent-graft is damaged during the unblocking process, it can be restored by ballooning off the stent-graft.
  - The last possibility is to abandon the procedure. The stent-graft, half deployed, is pulled back into the descending thoracic aorta, and then fully deployed.

Stent-graft launcher removal

After being recaptured, the stent-graft launcher is removed from the patient. Once outside the patient, the launcher is then redeployed to retrieve the guide from the subclavian window.

If the procedure has been performed without a femoral introducer, a 4 French femoral introducer, smaller than the recommended size for the stent-graft introducer, is used and inserted over the Terumo wire to achieve femoral sealing.

Bridging of the LSA fenestration

An 80 cm long 9 or 10 Fr introducer is then advanced over the preloaded wire from the femoral access. Crossing the fenestration is highly facilitated by pulling on both sides of the femoral-brachial loop. A covered stent of 10 up to 12 mm is then inserted and expanded, with at least 10 mm inside the aortic arch. The covered stent is subsequently flared using a larger balloon.

Ballooning of the stent-graft and/or placement of a distal stent-graft

In order to balloon the stent-graft or add a distal stent-graft, it's important to protect the LSA fenestration by placing a 10 mm balloon from the humeral access and inflating it. In fact, when inserting an extra-stent graft, the advancement of the new graft in the aortic arch may push the fenestrated stent-graft proximally, inducing the risk of covering the supra-aortic trunks.

Another tip is that the placement of an additional distal stent-graft will require loosening the 'through and through' wire to advance the new stent-graft through the femoral access.

Final angiography is performed to assess the outcome, followed by the removal of the introducer.

RATIONALE FOR THE DOUBLE FENESTRATED STENT-GRAFT - DECREASING STROKE RATE DURING TOTAL ENDOVASCULAR REPAIR OF THE AORTIC ARCH

Outcomes of branch devices for total endovascular repair of the aortic arch: the stroke rate is the Achilles' heel of the technique

Custom-made branched devices are currently available. The world experience with 38 branched arch devices was first reported as a multicenter experience in 2014 by Haulon *et al.*[7] They reported a 13% mortality rate, a 16% stroke rate, a technical failure rate of 15.8% and a secondary procedure rate of 19.6%. Factors such as the planning and manufacturing delays, both anatomical and technical restrictions as well as expense limit the widespread uptake of this technology particularly for emergent cases. In particular, the technical challenges of branch catheterization results in an intrinsically high risk of cerebral embolism. The results of inner branched en-

dograft repair of the aortic arch in contemporary series demonstrates an improvement in patient outcome when compared with the early experience of the approach published in 2014.[7, 8]

But when we look at results from high-volume expert centers, the outcomes are less encouraging. Italian[9] and Dutch[10] registries report stroke rates of 26% and 36%, and mortality rates of 16.7% and 19.8% respectively. The only prospective study conducted in the USA reported a stroke rate of 50% and a mortality rate of 25%.[11]

Another concern is the applicability of this approach. A recent systematic review[12] found only 273 reported cases over the last 17 years, averaging fewer than 30 cases per year worldwide. They reported an all-cause mortality rate of 16%, a stroke rate of 14%, and an endoleak rate of 13%, confirming the previously reported outcomes.

Factors contributing to the risk of stroke in this type of procedure

The reasons for this high stroke rate seem to be multifactorial.

- Firstly, this procedure requires carotid manipulation/ cannulation increases the risk of dislodging plaque or causing emboli to travel to the brain especially in patients with atheromatous lesions of the aortic arch.
- Secondly, more complex endovascular procedures, such as those involving branched may entail longer procedure times and increased manipulation in the aortic arch, thereby raising the risk of stroke.

Understanding and addressing these factors are crucial for minimizing the risk of stroke during such procedures.

The rationale behind employing double fenestrated TEVAR to decrease the stroke rate lies in several factors

We have recently published[13] our ongoing experience with the double fenestrated stent-graft. Out of the first 100 patients treated, technical success rate was 97%. The 30-day mortality was 2% (N.=2). Four patients (4%) had minor stroke with full recovery.

Compared to other endovascular techniques, the double homemade fenestrated stent graft led to fewer neurological complications. This can be explained by several factors.

Firstly, with careful pre-operative planning, the simple handling of the device during operation decreases manipulations in the aortic arch. Namely the proximal fenestration is appropriately directed to the orifices of the BT and LCCA automatically when the LSA fenestration is catheterized.

Secondly, no manipulation, clamping, catheterization or stenting of the BT and LCCA are required.

The long-term risk of stroke is heightened by the absence of endovascular grafts in the carotid arteries

Intra-prosthetic thrombus is very common after stent-graft implantation. In a recently published series, the rate was 39% in iliac stent grafts.[14] Therefore, we can easily anticipate the risk of stroke if such thrombus appears in the carotid bridging grafts. Long-term outcomes of branch devices in the arch have never been published, assessing the risk of thrombus formation in carotid branches. In many cases, the outer portion of the aortic arch, where the supra-aortic trunks arise to supply blood to the head, neck, and upper extremities, remains relatively unaffected by aortic diseases such as aneurysms or dissections. This spared region provides a suitable landing zone for surgical interventions aiming to repair or reinforce the aorta. Traditionally, the island technique has been widely regarded as the gold standard approach for addressing aortic pathologies involving the arch[15]. In this technique, a segment of the healthy aorta is isolated and used as a stable platform to anchor surgical grafts or stent grafts. This method has demonstrated excellent outcomes in terms of durability and effectiveness in restoring normal blood flow through the aortic arch.

The natural angulation of the aortic arch refers to the characteristic curvature or bend present in the aorta as it extends from the ascending aorta to the descending aorta. This curvature typically occurs at the level of the aortic arch, where the vessel bends posteriorly before continuing inferiorly.

When utilizing fenestrated TEVAR in the aorta, this natural curvature becomes particularly useful. By positioning these fenestrations against the outer curvature of the aorta, we maximize the stability and efficiency of the prosthesis.

Furthermore, reinforcing this position can be achieved by placing stents and flaring the stent of the LSA. This provides additional adherence of the aortic prosthesis to the aortic wall, thus minimizing the risk of migration or leakage.

In summary, by using the natural curvature of the aorta to our advantage during the implantation of fenestrated TEVAR, we can enhance the stability and efficiency of the prosthesis while reducing the risk of endoleak associated with the procedure.

REPRODUCIBILITY OF OUR OUTCOMES

Helping to develop the double fenestrated TEVAR in other centers

We have thus far assisted other physicians in modifying and implanting double fenestrated stent-grafts in over 80 patients across Europe (mainly France and Italy), Canada, South America (Chile, Mexico), and Asia (Japan, Thailand).

The EVERGREEN Trial

The EVERGREEN trial (Evaluation of the Valiant Captivia physician fEnestRated stent GRaft system in the aortic arch and dEscendiNg thoracic aorta pathologies) is an investigator initiated trial.

The goal of this prospective trial is to evaluate the feasibility and outcomes (stroke, mortality, endoleak, etc.) of using a double homemade fenestrated TEVAR for aortic

lesions. A core lab will review all the pre- and postoperative CT scans. Patients will undergo follow-up assessments at 1 month, 6 months, and annually thereafter for 3 years.

Ten centers in France and Italy will be recruiting participants. Enrollment commenced in December 2023, and thus far, 17 patients have been included.

DURABILITY OF THE HOMEMADE DOUBLE FENESTRATED TEVAR

Fatigue testing of double fenestrated physician-modified endovascular stent-graft for aortic arch treatment (Figure 3.5.5)

We have assessed the fatigue behavior of the physician-modified double fenestrated endovascular graft (PMEG) using the Valiant Captivia (Medtronic, Minneapolis, MN, USA) prosthesis. Endograft fatigue testing was performed using an electroforce testing unit (TA Instruments, Eden Prairie, MN, USA), the stent was flexed over an angle of 90° to the graft main axis, in an alternative way, at a frequency of 5 Hz. These testing conditions were considered as extreme. Cycling was conducted over 500,000 cycles. Tensile strength tests were performed on the endografts before and after fatigue testing to identify potential degradation of the textile material.

A total of 6 endografts were tested. No macroscopic or microscopic degradation was detected after cycling. Extension tensile testing showed no significant modification of the cycled fenestrated samples, and no difference in fenestration measurements.

This research is currently under review.

Total aortic arch repair with double-fenestrated physician-modified endografts, at least 3-year follow-up

This study[16] aimed to report the efficacy and safety of double-fenestrated physician-modified endovascular grafts (PMEGs) for total aortic arch repair with at least 3 years of follow-up.

74 patients were treated for pathological arch conditions with a double-fenestrated PMEG.

During long-term follow-up (mean time 40.7 months), one type 1 endoleak appeared and was successfully treated; no type 2 or type 3 endoleak requiring intervention occurred. No stent fractures or migrations were reported. Four percent of patients required reintervention, but no surgical conversion to open surgical repair was needed on the aortic arch. No patient died from a cause related to the main procedure.

POTENTIALLY AN OFF-THE-SHELF SOLUTION

The anatomical findings have helped us develop a standard pattern for the double fenestrated TEVAR that could allow for the development of an off-the-shelf solution for more than 90% of patients with aortic arch lesions.

CONCLUSIONS

The global experience with total endovascular aortic arch repair is expanding. Thus far, devices have been manufactured by companies to suit the anatomy of the arch and supra-aortic vessels. Significant progress has been

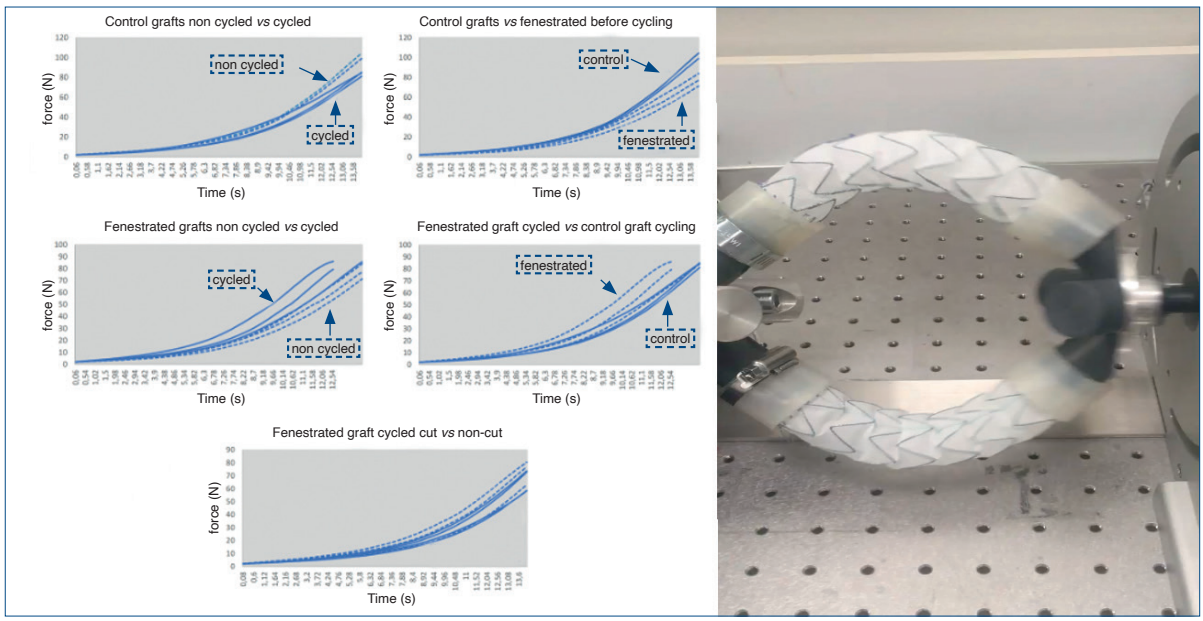


FIGURE 3.5.5 ● Comparison of graft's response after tensile strength testing. Grafts are inserted in a mock artery at both extremities in order to replicate the clinical anchoring. The fenestrated zone is positioned on the outer curvature to induce local exaggerated stress.

made, particularly in terms of bridge stents and deployment techniques. However, this technique presents numerous pitfalls. The time delay to obtain the grafts prevents its use in emergent cases. Privileged relationships between companies and highly selected surgeons and institutions limit its widespread adoption, which is detrimental for ordinary patients.

Complex procedures are associated with prolonged operation durations and complications, while the complex grafts also incur high costs.

Simplicity is a key to progress. Physician-modified endograft is a relatively simple and rapid procedure that overcomes many pitfalls associated with the custom-made stent grafts mentioned earlier. Surgeons engaged in large-scale activities are asserting their knowledge and expertise, leading to a shift towards acknowledging their input and insights. Through this technique, vascular surgeons will autonomously refine their strategies, optimize intervention timing, and decrease healthcare expenditure. Most importantly, there is no doubt that patients will benefit from a simplified and expedited procedure.

REFERENCES

1 Canaud L, Gandet T, Khantalin I, et al. Homemade proximal scalloped stent graft for thoracic endovascular aortic repair of zone 2 acute aortic syndrome. J Thorac Cardiovasc Surg 2016;152:1301–6.

2 Canaud L, Morishita K, Gandet T, et al. Homemade fenestrated stent-graft for thoracic endovascular aortic repair of zone 2 aortic lesions. J Thorac Cardiovasc Surg 2018;155:488–93.

3 Canaud L, Baba T, Gandet T, et al. Physician-Modified Thoracic Stent-Grafts for the Treatment of Aortic Arch Lesions. J Endovasc Ther 2017;24:542–8.

4 Canaud L, Ozdemir BA, Chassin-Trubert L, et al. Double homemade fenestrated stent graft for total endovascular aortic arch repair. J Vasc Surg 2019;70:1031–8.

5 e Almeida Sandri G, Ribeiro MS, Macedo TA, et al. Planning endovascular aortic repair with standard and fenestrated-branched endografts. J Cardiovasc Surg (Torino) 2017;58:204–17.

6 Chassin-Trubert L, Gandet T, Ozdemir BA, et al. Aortic Arch Anatomy Pattern in Patients Treated Using Double Homemade Fenestrated Stent-Grafts for Total Endovascular Aortic Arch Repair. J Endovasc Ther 2020;27:785–91.

7 Spear R, Hertault A, Van Calster K, et al. Complex endovascular repair of postdissection arch and thoracoabdominal aneurysms. J Vasc Surg 2018;67:685–93.

8 Pear R, Haulon S, Ohki T, et al. Editor's choice - subsequent results for arch aneurysm repair with inner branched endografts. Eur J Vasc Endovasc Surg 2016;51:380–5.

9 Ferrer C, Cao P, Coscarella C, et al. TRIUmPH Registry Investigators. iTalian RegIstry of doUble inner branch stent graft for arch PatHology (the TRIUmPH Registry). J Vasc Surg 2019;70:672–82.

10 van der Weijde E, Heijmen RH, van Schaik PM, et al. Total Endovascular Repair of the Aortic Arch: Initial Experience in the Netherlands. Ann Thorac Surg 2020;109:1858–63.

11 Roselli A. Total endovascular Aortic Arch repairs with the Realy 2 branched stent-graft. Veith Symposium. 2019.

12 Basha AM, Moore RD, Rommens KL, et al. Herget EJ, McClure RS. A Systematic Review of Total Endovascular Aortic Arch Repair: A Promising Technology. Can J Cardiol 2023;39:49–56.

13 Canaud L, Chassin-Trubert L, Abouliatim I, et al. Hireche K, Bacri C, Alric P, Gandet T. Total Arch Thoracic Endovascular Aortic Repair Using Double Fenestrated Physician-Modified Stent-Grafts: 100 Patients. J Endovasc Ther 2024;31:89–97.

14 Ulsaker H, Lam M, Herje ML, et al. A Retrospective Evaluation of Intra-Prosthetic Thrombus Formation After Endovascular Aortic Repair in Cook Zenith Alpha and Medtronic Endurant II Patients. Eur J Vasc Endovasc Surg 2023;66:644–51.

15 Smith T, Heijmen RH. Is a four-branched prosthesis advantageous over a straight prosthesis in Frozen elephant trunk surgery? Cardiovasc Diagn Ther. 2023;13:61–6.

16 Bacri C, Hireche K, Alric P, et al. Total aortic arch repair with double-fenestrated physician-modified endografts, at least 3-year follow-up. J Vasc Surg 2024 Mar 27:S0741-5214(24)00516–0. doi: 10.1016/j.jvs.2024.03.029.

3.6 PUSHING THE LIMITS PROXIMALLY 3: NOVEL SOLUTIONS TO TREAT THE ASCENDING AORTA, AND THE CHALLENGE OF ENDO-BENTALL PROCEDURES

Mario Lescan, Martin Czerny

INTRODUCTION

The development and technical improvement of thoracic endografts in recent decades has led to the advancement of thoracic endovascular aneurysm repair (TEVAR) towards the ascending aorta. Initially, supra-aortic debranching with various re-routing strategies significantly contributed to the proximalization of the sealing zones. This progression has made complete aortic arch debranching and Zone 0 landing possible.[1] For the newly developed branched and fenestrated aortic arch prostheses, the healthy Zone 0 increasingly served as the sealing zone. This facilitated the acquisition of new experiences in the planning and executing procedures.[2] The next goal in endovascular development is treating ascending aorta pathologies, a mobile segment with unique anatomical features and specific requirements for endovascular materials.[3] The objectives of this chapter are to describe the anatomical peculiarities of the ascending aorta and their implications for the treatment of ascending aorta pathologies. Moreover, the technical prerequisites for the safe performance of these therapies are summarized. Additionally, this chapter aims to highlight the challenges and potential solutions for the endovascular aortic valve, aortic root, and ascending aorta replacement—the "Endo-Bentall" procedure.

TREATMENT OF THE ASCENDING AORTA PATHOLOGIES

Chronic pathologies of the ascending aorta include ascending aortic aneurysm, penetrating aortic ulcer, and chronic Stanford type A dissection, whereas acute pathologies of the ascending aorta typically encompass acute Stanford type A dissection and intramural hematoma of the ascending aorta. The gold standard for treating these pathologies is open surgical replacement, with tubular replacement of the ascending aorta being the minimal variant. The isolated open tubular replacement can be combined proximally with aortic root reconstruction and distally with partial (hemi-arch) or complete arch replacement.[4] The extent of the pathology in aneurysms or the location of the entry tear in Stanford type A aortic dissection determines the scope of the open surgical intervention. This flexibility to address adjacent diseased segments is a clear advantage of classical surgery over isolated ascending aorta stent grafting, which currently offers no off-the-shelf therapeutic options for the aortic root. However, the invasiveness of the open surgical method is a significant disadvantage, particularly for patients with severe heart failure, lung- and liver dysfunctions, posing a substantial challenge for the intraoperative and postoperative course.[5] With the increasingly aging population in Europe, these comorbidities are on the rise, prompting the search for less invasive endovascular alternatives. The endovascular tubular endograft of the ascending aorta can serve as an alternative for localized pathologies of the ascending aorta, including the closure of the entry tear in Stanford type A dissection, treatment of a penetrating aortic ulcer, or a saccular ascending aneurysm (Figure 3.6.1).

The next chapter will delve deeper into the prerequisites for endovascular therapy and the challenges associated with this treatment approach.

ANATOMICAL REQUIREMENTS FOR THE ENDOVASCULAR ASCENDING TREATMENT

As described in previous chapters, the healthy ascending aorta is used as the proximal sealing zone for endovascular therapy in the treatment of aortic arch pathologies. Guidelines recommend a proximal and distal sealing zone of ≥25 mm in length.[4] When the pathology is located in the ascending aorta, meeting this requirement poses a challenge. The proximal and distal sealing zones of an isolated ascending aorta replacement are limited by the coronary arteries and the brachiocephalic trunk,

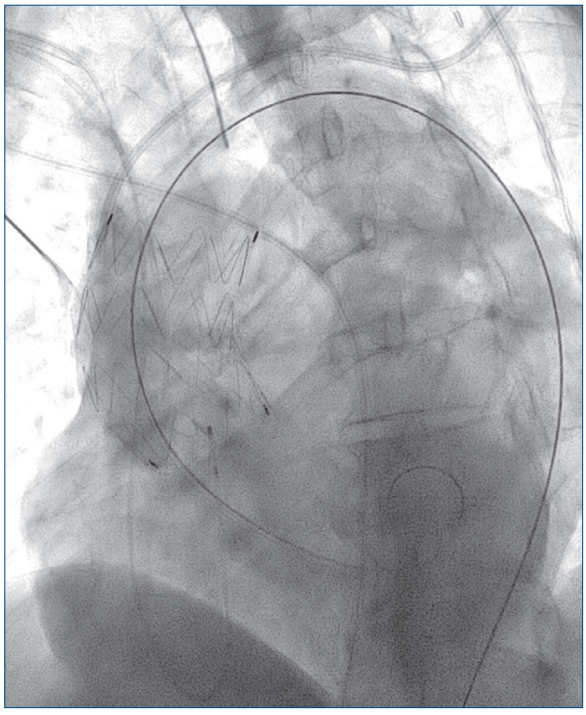


FIGURE 3.6.1 ● Isolated custom-made ascending endograft.

respectively. Additionally, this segment of the aorta is rather short, averaging 70-80 mm in length, making the placement of an isolated ascending aorta endograft feasible only for localized lesions with sufficient distance from the coronary arteries and the brachiocephalic trunk.[6, 7] The extension of the distal sealing zone can be achieved using fenestrated and branched aortic arch prostheses along with rerouting procedures. In contrast, the proximal extension of the sealing zone with an "*Endo-Bentall*" is still in the development phase and will be discussed separately later in the text. Beyond the length of the ascending aorta and the extent of the pathology, the diameter of zone 0 may play a crucial role. Endovascular therapy of the ascending aorta with diameters >38 mm is associated with a higher risk of retrograde type A dissection and should therefore be avoided.[4, 8] Other factors that limit endovascular therapy of the ascending aorta include the presence of left ventricular thrombi, as the procedure could lead to thrombus embolization and previous intact coronary bypasses that originate directly from the ascending aorta.[5] Although mechanical aortic valve replacement has occasionally been considered a surmountable contraindication, passing the mechanical aortic valve with the deployment system is not considered a standard procedure and should be reserved for centers with extensive cardiac surgical and endovascular expertise.[9]

PLANNING, PERSONNEL AND TECHNICAL REQUIREMENTS FOR THE ENDOVASCULAR ASCENDING TREATMENT

Planning and personnel requirements

The first prerequisite for the successful execution of ascending aorta therapy involves careful planning of the procedure with an assessment of the risk for possible complications. This includes determining whether a custom-made endograft should be used for the treatment of chronic pathology or if an off-the-shelf device is suitable. A major limiting factor, particularly for acute pathologies but also for severe chronic cases, is the production time of custom-made endografts, which may contribute to increased mortality during the manufacturing phase.[10] The endograft is measured using appropriate 3D software, addressing the short length of the ascending aorta, its diameter, and the recommended sealing length of 25 mm. Given that the ascending aorta has a pronounced angulation with a long outer curvature and a significantly shorter inner curvature, the sealing length is measured along the inner curvature. The recommended oversizing of the endograft is 15-20% for chronic pathologies, while for acute pathologies (intra-mural hematoma [IMH], Stanford type A dissection), an oversizing of 0-10% should be targeted.[4] During the planning phase, additional procedures are considered, such as rerouting the brachiocephalic trunk in cases of a short distal landing zone or the use of branched aortic arch prostheses to extend the ascending aorta endograft.[11] Potential imaging morphological risk factors for complications are also identified during the planning phase: the angulation of the ascending aorta may affect the tube graft apposition, the presence of calcifications in the sealing zones is a risk factor for endoleaks and stroke, and the presence of aortic wall-adherent "shagginess", poses an embolization risk.[12-14] Furthermore, potential complications must be discussed during the planning phase, and bailout strategies should be established. The implantation should be carried out by a dedicated aortic team, with contributions from all relevant disciplines.[4] In the case of the ascending aorta, the team necessarily includes cardiac surgeons, vascular surgeons, cardiologists, radiologists, and other specialties. Advanced interventional and surgical expertise and experience are required due to the complexity of interventions in this sensitive area of the aorta, which may require high precision and complex bailout strategies. For the successful execution of these procedures, the involvement of anesthesiology is essential already in the planning phase to establish preoperative evaluation, operability, monitoring measures, and anesthesiologic interventions during the procedure (anesthesia techniques, heparinization, near-infrared spectrometry, transesophageal echocardiography, and left ventricular output reduction).

Technical requirements

In addition to procedural planning, the technical requirements must be mentioned, with endograft playing an important role. They should allow for safe and precise deployment in the ascending aorta, demonstrate high conformability in the angulated anatomy, and be adapted to the anatomy of the ascending aorta with a short inner and long outer curvature to counteract malposition and wrinkling. This latter feature is already present in the ascending aorta module of the Nexus endograft (Endospan Ltd., Israel).[15] Furthermore, to achieve a deep sealing zone in the ascending aorta, they should not have a proximal bare stent and should be coupled with a deployment system that allows for bird-beak-free deployment in curved anatomy. Examples with various deployment mechanisms that address this quality feature include the Relay NBS endograft (Terumo Aortic, Inchinnan, UK) and the C-TAG conformable endograft with "active control" (Gore Medical, Newark, DE, USA).[16, 17] Complete apposition of the endograft ensures that the entire landing zone is utilized as a sealing zone without being shortened by proximal bird-beaks. In contrast to the descending aorta, where the proximal curve progressively straightens distally, the ascending aorta transitions directly into the angulated aortic arch. This results in a risk of distal malposition in this short aortic segment, where sealing zones are already limited by the natural length of the ascending aorta.[18] The ideal isolated ascending aorta endograft should, therefore, also include fixation in the distal landing zone proximal to the brachiocephalic trunk, either with the option for active angulation (C-TAG) or for stabilizing and guiding the distal end of

the endograft (Relay) to the inner curvature of the ascending aorta. The ability to reposition the endograft in the ascending aorta may be advantageous, particularly in the presence of short sealing zones.

Procedural standards

The standardization of endovascular repair of the ascending aorta should be established in an institutional protocol. The standards presented here are derived from experiences with hybrid and totally endovascular aortic arch replacement. These operations should be performed in a multifunctional hybrid operating room, fully equipped with advanced imaging, including radiation protection measures and trained personnel. The use of fusion imaging to reduce radiation and contrast media exposure, as well as to increase patient safety through better anatomical orientation for the operator, is increasingly becoming the standard.[19]

The transfemoral endograft implantation is performed under aortic valve passage with the aid of a left ventricular implantation wire. This approach allows for access to areas of the ascending aorta neighboring the aortic root. Alternatively, a transapical through-and-through wire can be used to guide the transfemoral implanted endograft along the inner curvature of the ascending aorta.[20] In cases of a short distal sealing zone, where precise distal landing is crucial, the transapical approach is advantageous. This approach also provides a valuable alternative in the presence of narrow or highly tortuous access vessels.[21] The elimination of air from the deployment system is considered an important factor in intraoperative stroke prevention. Extensive system flushing with saline, with or without prior insufflation of CO_2 into the system, reduces the amount of trapped air and thus, may prevent intraoperative stroke.[22] CO_2 has significantly higher solubility in blood compared to air and is therefore used to displace trapped air before flushing the endograft with saline.[23] The deployment of the endograft in the ascending aorta requires precision in a highly mobile aortic segment with circumferential and longitudinal wall movement. Controlled deployment is therefore only possible with measures to reduce left ventricular output. These measures include rapid pacing, administration of atropine, occlusion of the vena cava, and reduction of venous inflow through the ventilation-induced Valsalva maneuver (MuVIT method).[24] The transesophageal echocardiography (TEE) examination should be available during implantation to monitor the position of the left ventricular wire, assess aortic valve function, and document intraoperative results. Retrograde type A dissections and pericardial tamponades can occur during the intervention, and TEE can contribute to their early diagnosis. If there is a risk of over stenting the supra-aortic vessels, particularly the brachiocephalic trunk, in cases of a short distal landing zone, retrograde wires can be introduced through the supra-aortic branches for a bailout procedure. This allows for the rapid implantation of a chimney graft or in-situ fenestration to ensure cerebral perfusion.

PRESENT STATUS OF THE ASCENDING REPAIR AND RECENT RESULTS

The key reports on isolated endovascular replacement of the ascending aorta are shown in Table 3.6.I. In summary, the literature mostly consists of smaller series and case reports. In the systematic review by Muetterties *et al.*, 46 publications were analyzed, encompassing a total of 118 patients.[25] These patients were treated with 13 different endografts, of which only 10% were custom-made. The remaining endografts were thoracic off-the-shelf endografts in 71% of cases and abdominal cuffs in 11%.[25] The main indications for ascending aorta treatment in this study were acute type A dissection in 50% of cases, followed by pseudoaneurysms of the ascending aorta (30%).[25] The endografts were implanted via transfemoral, transapical, trans carotid, and trans axillary access in 63%, 14%, 13%, and 7% of cases, respectively. As shown in Table

Table 3.6.I ● Ascending endovascular repair reports (in English) including more than 5 patients.

Study	N.	Endograft specification	Technical success	30-day mortality	Stroke or TIA
Bernardes *et al.* 2014[29]	7	Valiant (Medtronic) and TAG (Gore)	86%	14%	0%
Preventza *et al.* 2014[30]	7	TAG (Gore), Excluder (Gore), Talent (Medtronic)	86%	14%	0%
Roselli *et al*, 2015[31]	21	TAG (Gore), Valiant (Medtronic) and Zenith (Cook)	not reported	14%	14%
Tsilimparis *et al*, 2016[28]	10	Zenith (Cook)	100%	10%	20%
Li *et al.* 2016[26]	15	Zenith (Cook)	100%	0%	0%
Piffaretti *et al*, 2021[32]	9	Relay (Terumo aortic)	100%	0%	0%
Yen *et al*, 2022[33]	11	Valiant (Medtronic) and TAG (Gore)	Not reported	9%	9%
Patel *et al.* 2023[27]	19	ASG (Gore)	not reported	16%	5%
Total	99		96% (42/44)	10% (10/99)	7% (7/99)

3.6.I, the technical success of the procedure improved over time, likely due to increasing experience and improved endograft design. In the studies, the 30-day mortality rate ranged from 0-16%,[26, 27] and the stroke rate d from 0% to 20%.[26, 28] Thus, perioperative stroke remains a significant concern in the treatment of the ascending aorta with tubular endografts, as has already been observed in the endovascular therapy of aortic arch pathologies. Additionally, a type I endoleak rate of 18% and a re-intervention rate of 9% were reported.[25] The conversion rate to open surgical repair was 3%, which is higher compared to the endovascular aortic arch repair. This may be partly due to a high percentage of interventions in acute Stanford type A dissection, which inherently carries a higher potential for intra- and postoperative complications.[25]

THE CHALLENGE OF ENDO-BENTALL PROCEDURES

The Bentall procedure was developed for the combined open surgical treatment of the aortic root and ascending aorta. In this repair, a biological heart valve prosthesis is housed at the proximal end of a tube prosthesis, allowing for the replacement of the aortic valve, aortic root, and ascending aorta with reimplantation of the coronary arteries in one single operation.[34] The endovascular counterpart is currently under development (Endo-Bentall). It aims to replace the invasive surgery (median sternotomy, use of the cardiopulmonary bypass) with a less invasive endovascular approach. The anatomical challenges of the Endo-Bentall resemble the above-mentioned critical features encountered for the ascending tube grafts, mainly including the short distance from the coronary arteries to the brachiocephalic trunk and the necessity of an endovascular solution to maintain the perfusion of the coronary arteries. In Stanford type A aortic dissections, the coronary segment between a transcatheter aortic valve and the ascending aorta endograft could remain fenestrated (Figure 3.6.2), as the primary entry tear is frequently not located in the aortic root.

Courtesy of: Moreover, the optimal anchoring of the Endo-Bentall in the aortic valve annulus may be the most sustainable proximal anchoring zone.[35] It is estimated that approximately one-third of acute type A dissections could be treated with such an endograft technique.[6] In particular, for aneurysms extending to the aortic root or Stanford type A dissections with entries in that area, this solution with an uncovered section between the TAVI and the ascending endograft would lead to endoleaks. For these pathologies, only a prosthesis that ensures complete sealing is suitable. In the aortic root area, this implies a branched prosthesis with branches for the coronary arteries. The first custom-made prosthesis with these features was implanted by Gaia *et al.* in 2019 *via* a transapical approach. Thus, this endograft may serve as a prototype for future development.[36]

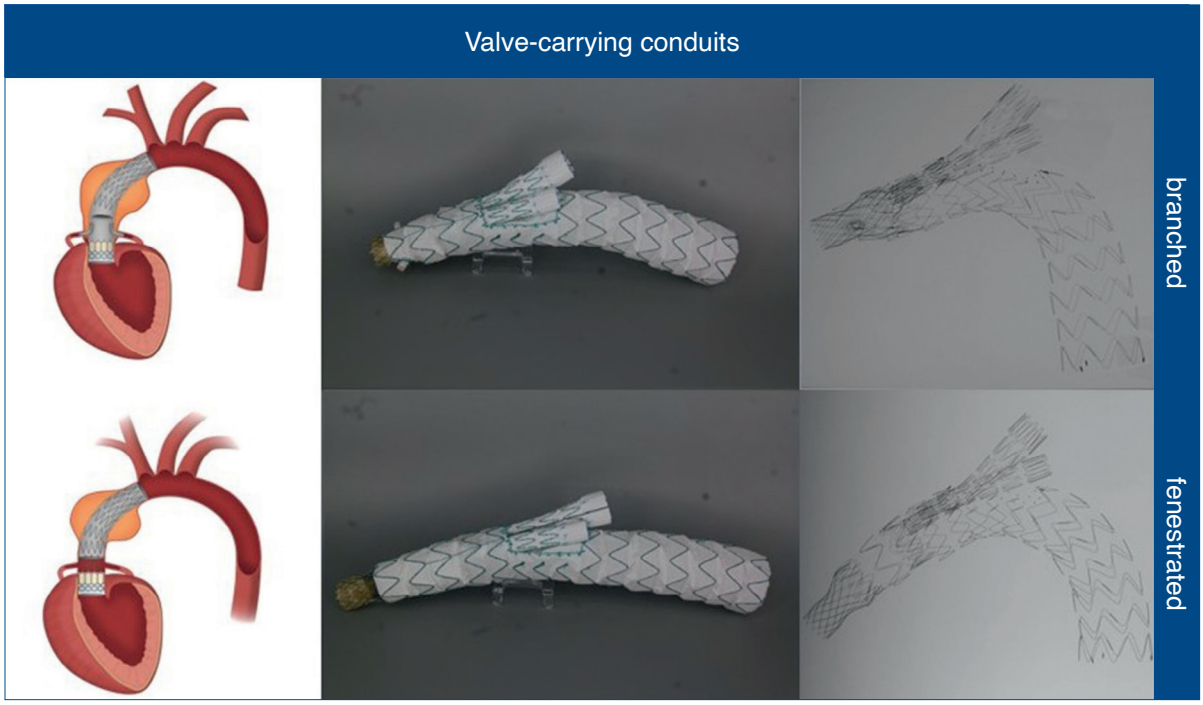


FIGURE 3.6.2 ● Conceptional valve carrying conduits. Courtesy of: Hauck SR et al. Structural failure in bridging stentgrafts for branched endovascular aneurysm repair: a case-control study. Insights Imaging 2022;13:62. Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Both variants of the Endo-Bentall were evaluated for their technical feasibility in type A dissections. Compared to endografts without an aortic valve prosthesis, which showed a feasibility of 4-21%, these two Endo-Bentall variants achieved a technical feasibility of 31-80%. The technical challenges primarily lie in the uncertain durability of the various materials. The biological aortic valve prosthesis used in the Endo-Bentall degenerates over time, potentially necessitating a reintervention at the valve level as a valve-in-valve procedure.[37] Furthermore, the aortic root and ascending aorta are highly mobile segments, which places high demands on the materials. In particular, stent fractures due to material fatigue can lead to complications such as endoleaks and aortic ruptures. Additionally, bridging stent graft fractures could lead to occlusion and subsequent myocardial infarction.[38, 39]

CONCLUSIONS AND FUTURE PERSPECTIVES

Endovascular therapy has already reached the ascending aorta. It is regularly used as a landing zone for total endovascular aortic arch replacement. Moreover, ascending pathologies are increasingly treated with short, isolated ascending aorta endografts. Various materials with unclear durability are being used in this highly mobile aortic segment which may affect the material fatigue. The secure anchoring of the ascending endografts needs to be further evaluated. Open questions are the necessary length of the healthy proximal landing zone and the oversizing of the endografts in different pathologies. An alternative for the secure anchoring of ascending aorta endografts is selecting the aortic valve annulus as the proximal landing zone. However, this procedure also requires improvements in endovascular material components, such as the conformability of the endograft and the bridging stent grafts to the coronary arteries. Research into new materials and concepts, and the scientific reporting of results from controlled studies, will be crucial in the coming years.

REFERENCES

1. Czerny M, Pfannmuller B, Borger MA, *et al.* Hybrid debranching technique for aortic arch replacement. Multimed Man Cardiothorac Surg 2011;2011:mmcts 2011 005108.
2. Czerny M, Berger T, Kondov S, *et al.* Results of endovascular aortic arch repair using the Relay Branch system. Eur J Cardiothorac Surg 2021;60:662–8.
3. Wittek A, Karatolios K, Fritzen CP, *et al.* Cyclic three-dimensional wall motion of the human ascending and abdominal aorta characterized by time-resolved three-dimensional ultrasound speckle tracking. Biomech Model Mechanobiol 2016;15:1375–88.
4. Czerny M, Grabenwoger M, Berger T, *et al.* EACTS/STS Guidelines for diagnosing and treating acute and chronic syndromes of the aortic organ. Eur J Cardiothorac Surg 2024;65.
5. Czerny M, Schmidli J, Adler S, *et al.* Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). Eur J Cardiothorac Surg 2019;55:133–62.
6. Moon MC, Greenberg RK, Morales JP, *et al.* Computed tomography-based anatomic characterization of proximal aortic dissection with consideration for endovascular candidacy. J Vasc Surg 2011;53:942–9.
7. Huang C, Zhou M, Liu Z, *et al.* Computed tomography-based study exploring the feasibility of endovascular treatment of type A aortic dissection in the Chinese population. J Endovasc Ther 2014;21:707–13.
8. Gandet T, Canaud L, Ozdemir BA, *et al.* Factors favoring retrograde aortic dissection after endovascular aortic arch repair. J Thorac Cardiovasc Surg 2015;150:136–42.
9. Konstantinou N, Peterss S, Stana J, *et al.* Passing a Mechanical Aortic Valve With a Short Tip Dilator to Facilitate Aortic Arch Endovascular Branched Repair. J Endovasc Ther 2021;28:388–92.
10. Katsargyris A, Uthayakumar V, Marques de Marino P, *et al.* Aneurysm Rupture and Mortality During the Waiting Time for a Customised Fenestrated/Branched Stent Graft in Complex Endovascular Aortic Repair. Eur J Vasc Endovasc Surg 2020;60:44–8.
11. Canaud L, Albat B, Hireche K, *et al.* Reverse extra-anatomic aortic arch debranching procedure allowing thoracic endovascular aortic repair of a chronic ascending aortic aneurysm. J Vasc Surg Cases Innov Tech 2018;4:102–5.
12. Shahbazian N, Romero DA, Forbes TL, *et al.* Identification of geometric and mechanical factors predictive of bird-beak configuration in thoracic endovascular aortic repair using computational models of stent graft deployment. JVS Vasc Sci 2022;3:259–73.
13. Wyss TR, Dick F, Brown LC, *et al.* The influence of thrombus, calcification, angulation, and tortuosity of attachment sites on the time to the first graft-related complication after endovascular aneurysm repair. J Vasc Surg 2011;54:965–71.
14. Hosaka A, Motoki M, Kato M, *et al.* Quantification of aortic shagginess as a predictive factor of perioperative stroke and long-term prognosis after endovascular treatment of aortic arch disease. J Vasc Surg 2019;69:15–23.
15. Planer D, Elbaz-Greener G, Mangialardi N, *et al.* NEXUS Arch: A Multicenter Study Evaluating the Initial Experience with a Novel Aortic Arch Stent Graft System. Ann Surg 2023;277:e460–e466.
16. Bockler D, Bischoff MS, Kronsteiner D, *et al.* Outcome analysis of the Gore Conformable Thoracic Stent Graft with active control system for the treatment of arch and descending thoracic aortic disease. Eur J Cardiothorac Surg 2021;60:1455–63.
17. Zipfel B, Czerny M, Funovics M, *et al.* Endovascular treatment of patients with types A and B thoracic aortic dissection using Relay thoracic stent-grafts: results from the RESTORE Patient Registry. J Endovasc Ther 2011;18:131–43.
18. Berezowski M, Morlock J, Beyersdorf F, *et al.* Inaccurate aortic stent graft deployment in the distal landing zone: incidence, reasons and consequences. Eur J Cardiothorac Surg 2018;53:1158–64.
19. Bachrati PZ, La Torre G, Chowdhury MM, *et al.* A State-of-the-Art Review of Intra-Operative Imaging Modalities Used to Quality Assure Endovascular Aneurysm Repair. J Clin Med 2023;12:3167.
20. Chiang WC, Ling-Lin Pai E, Chen PL, *et al.* Endografting under Assistance of Transapical Body Floss Through-and-Through Wiring Technique and Rapid Ventricular Pacing for an Ascending Aortic Tuberculous Pseudoaneurysm. Ann Vasc Surg 2017;45:270 e7-70 e11.
21. Hoogewerf M, van Geldorp MWA, Scholten JGF, *et al.* Endovascular repair of a ruptured, extremely tortuous, descending thoracic aorta aneurysm with aortic coarctation. J Vasc Surg Cases Innov Tech 2022;8:480–3.
22. Rylski B, Mayer F, Beyersdorf F, *et al.* How to minimize air embolisms during thoracic endovascular aortic repair with Relay Pro? Interact Cardiovasc Thorac Surg 2020;30:293–5.
23. Kolbel T, Rohlffs F, Wipper S, *et al.* Carbon Dioxide Flush-

ing Technique to Prevent Cerebral Arterial Air Embolism and Stroke During TEVAR. J Endovasc Ther 2016;23:393–5.
24. Stana J, Prendes CF, RG EM, *et al.* First Experience with the Munich Valsalva Implantation Technique (MuVIT) for Cardiac Output Reduction During Standard and Complex Thoracic Endovascular Aortic Repair. Eur J Vasc Endovasc Surg 2022;63:817–26.
25. Muetterties CE, Menon R, Wheatley GH, 3rd. A systematic review of primary endovascular repair of the ascending aorta. J Vasc Surg 2018;67:332–42.
26. Li Z, Lu Q, Feng R, *et al.* Outcomes of Endovascular Repair of Ascending Aortic Dissection in Patients Unsuitable for Direct Surgical Repair. J Am Coll Cardiol 2016;68:1944–54.
27. Patel HJ, Preventza O, Roselli EE, *et al.* Emergency and Compassionate Use of a Novel Ascending Endograft for Ascending and Arch Aortic Pathology. J Endovasc Ther 2023:15266028231208644.
28. Tsilimparis N, Debus ES, Oderich GS, *et al.* International experience with endovascular therapy of the ascending aorta with a dedicated endograft. J Vasc Surg 2016;63:1476–82.
29. Bernardes RC, Navarro TP, Reis FR, *et al.* Early experience with off-the-shelf endografts using a zone 0 proximal landing site to treat the ascending aorta and arch. J Thorac Cardiovasc Surg 2014;148:105–12.
30. Preventza O, Henry MJ, Cheong BY, *et al.* Endovascular repair of the ascending aorta: when and how to implement the current technology. Ann Thorac Surg 2014;97:1555–60.
31. Roselli EE, Idrees J, Greenberg RK, *et al.* Endovascular stent grafting for ascending aorta repair in high-risk patients. J Thorac Cardiovasc Surg 2015;149:144–51.
32. Piffaretti G, Czerny M, Riambau V, *et al.* Endovascular repair of ascending aortic diseases with custom-made endografts. Eur J Cardiothorac Surg 2021;59:741–9.
33. Yen YT, Chen YY, Kao PH, *et al.* Zone 0 thoracic endovascular aortic repair in high risk patients: A retrospective case series. Catheter Cardiovasc Interv 2022;100:787–94.
34. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax 1968;23:338-9.
35. Rylski B, Szeto WY, Bavaria JE, *et al.* Development of a single endovascular device for aortic valve replacement and ascending aortic repair. J Card Surg 2014;29:371–6.
36. Felipe Gaia D, Bernal O, Castilho E, *et al.* First-in-Human Endo-Bentall Procedure for Simultaneous Treatment of the Ascending Aorta and Aortic Valve. JACC Case Rep 2020;2:480–5.
37. Sathananthan J, Nigade A, Meier D, *et al.* Hydrodynamic Assessment of Explanted Degenerated Transcatheter Aortic Valves: Novel Insights Into Noncalcific and Calcific Mechanisms. JACC Cardiovasc Interv 2024;17:1340–51.
38. Hauck SR, Kupferthaler A, Freund MC, *et al.* Structural failure in bridging stentgrafts for branched endovascular aneurysm repair: a case-control study. Insights Imaging 2022;13:62.
39. Lescan M, Andic M, Bonorden C, *et al.* Bare Stent Fracture After TEVAR With the Modified Restrictive Bare Stent (RBS) Technique in Type B Aortic Dissections. J Endovasc Ther 2023:15266028231170114.

3.7 REPLACING THE USE OF X-RAYS FOR ENDOVASCULAR AORTIC REPAIR: OPTICAL FIBER BASED-TECHNOLOGY (FORS)

Jurre Klaassen, Gemmi Sufali, Constantijn E.V.B. Hazenberg, Joost A. Van Herwaarden

INTRODUCTION

The advent of endovascular aortic repair by Nikolai Volodos[1] in 1987 marked a pivotal moment in the treatment landscape for aortic pathologies.[2] Especially in recent decades, rapid progress has been made, leading to a remarkable transition from conventional open to the widespread use of endovascular techniques during aortic surgery. Although these endovascular approaches offer advantages such as lower complication rates and reduced hospital stay, they are not without limitations.[3–5] Endovascular procedures require the use of fluoroscopy for visualization of the required endovascular devices. The treatment of increasingly complex vascular diseases has led to longer procedure times, increasing radiation exposure for both patients and the treatment team.[6, 7] Given the recognized risks of DNA damage and the potential long-term health effects associated with fluoroscopic exposure, contemporary radiation safety guidelines adhere to the "as low as reasonably achievable" (ALARA) principle, whereby the emphasis is placed on the need to minimize radiation doses while ensuring procedural safety.[8–12]

Another challenge associated with the use of fluoroscopy is that three-dimensional structures are displayed in two dimensions and in grayscale images on the monitors in the operating room. Consequently, the lack of spatial perception for tortuosity and depth complicates navigation and increases the risk of procedural failure. In recent years, efforts to address this issue have led to the development of so-called image fusion or 3Droadmapping.[13–15] These tools enhance volumetric perception by overlaying three-dimensional segmentations of preoperatively acquired Magnetic Resonance Angiography (MRA) or Computed Tomography Angiography (CTA) images onto real-time two-dimensional grayscale fluoroscopy images. The overlay of preoperative images with live fluoroscopy during the procedure may be achieved via two registration methods. With a 2D-3D registration the alignment is performed using two fluoroscopy images, while with a 3D-3D registration, a cone-beam computed tomography (CBCT) acquisition is needed. A 2D-3D registration saves radiations, while a 3D-3D registration enhances accuracy only if the CBCT is performed after the introduction of endovascular stiff materials, since these usually deform the vascular anatomy. While studies have shown that these tools can reduce procedural time, radiation dose, and contrast agent usage, they are still limited to projecting a three-dimensional outline of anatomical structures.[13–15] Consequently, endovascular devices are still projected two-dimensionally, making it difficult to distinguish their orientation and precise spatial configuration within the surrounding anatomy. Moreover, the mechanical constraints of fluoroscopy systems limit the range of viewing angles, which can hinder optimal visualization during endovascular procedures.

To address the limitations of device visualization and overuse of fluoroscopy for navigation during endovascular procedures, Philips (Philips Koninklijke N.V., Best, The Netherlands) has developed Fiber Optic RealShape (FORS) technology in collaboration with clinical experts. FORS combines image fusion with a specially designed endovascular guidewire embedded with optical fibers, enabling the use of laser light instead of fluoroscopy for three-dimensional visualization of guidewires and catheters. Implementation of FORS technology enhances spatial perception of devices within anatomical imaging and offers potential reductions in radiation exposure during the navigation phase of endovascular procedures. This chapter aims to provide insights into the principles of this innovative technology and supply updates on its ongoing advancements.

FORS TECHNOLOGY

The FORS technology encompasses equipment that emits laser light through a multicore optical fiber integrated within a specially designed guidewire. At this moment, there is one single-use, 0.035-inch hydrophilic floppy guidewire available (Figure 3.7.1). This FORS-enabled guidewire is linked to the system that emits laser light through the optical fibers. Alternations in the shape of the integrated optical fiber, caused by twisting and bending of the device, cause shifts in the returning light spectrum.[16] By analyzing these shifts in the returning light spectrum, the system is able to generate a three-dimensional reconstruction of the FORS guidewire along the entire length of the integrated optical fiber, facilitating real-time visualization without requiring the use of fluoroscopy.[16] Although the FORS guidewire is fully fluoroscopically compatible and has mechanical and radiopaque properties similar to comparable conventional guidewires, it can only be front loaded due to its fixed connection to the system. In addition, the system uses the FORS 3D Hub to visualize conventional endovascular catheters (Figure 3.7.2). This is a so-called catheter-agnostic device that is attachable to the back of compatible[a] catheters. Combined with the FORS guidewire, the

a A compatible catheter has a Luer-lock complying with [Standard.80369-7], a length of equal or less than 95cm and an ID compatible with a 0.035" OD guide wire. In layman terms, it means that most standard 0.035" Sos, Cobra, Berenstein catheters etc. should be able to run over our FORS 0.035" navigation wire.

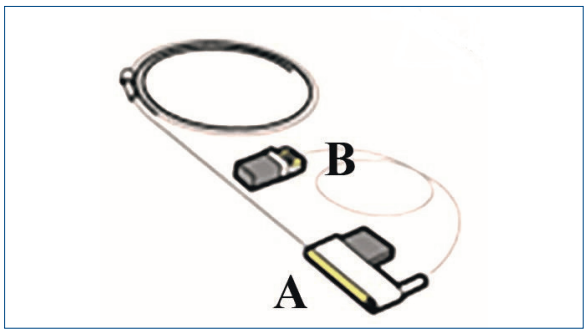


FIGURE 3.7.1 ● FORS enabled 0.035 inch angle hydrophilic floppy guidewire. Guidewire is connected to the FORS system by placing the docking fin (A) into the docking top and subsequently connecting the optical connector (B) to the docking base.

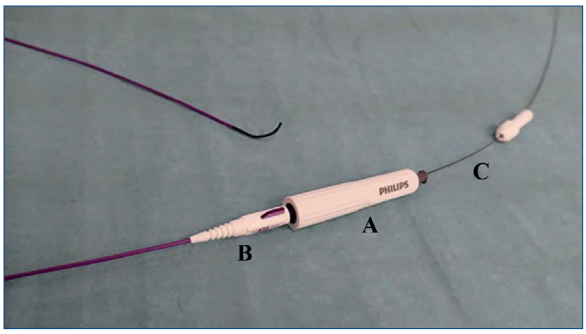


FIGURE 3.7.2 ● FORS 3D Hub (A). The 3D Hub is connected to a compatible conventional catheter (B; Merit Medical systems Inc., South Jordan, Utah, United States) that has a luer lock complying with [Standard.80369-7], a length of equal or less than 95cm and an ID compatible with a 0.035" OD guide wire. When the 3D hub is used in combination with the FORS guidewire (C), the system is able to reconstruct the conventional catheter over its full length.

FIGURE 3.7.3 ● Overview of the FORS system with (1) workstation, (2) trolley, (3) docking base and (4) docking top which connects FORS enabled devices. All FORS enabled devices are visualized in context of an anatomical roadmap of digital subtraction angiograph on the screen (5). Copyright © (2020) Koninklijke Philips N.V. All rights reserved.

system is also able to visualize[b] conventional catheters in real-time in full 3D, without the need for fluoroscopy.[17]

FORS reconstructs and visualizes all FORS enabled devices with three-dimensional attributes such as shading and a white dot at the distal tip of the displayed device. Incorporating these reconstruction features enhances understanding of the spatial trajectory and orientation of the devices. However, the added value of spatial visualization of FORS-enabled devices would be limited without information about their surrounding anatomical structures. Therefore, FORS technology is always utilized in conjunction with a fixed fluoroscopy system, such as the Philips Allura Xper FD20 system or the Philips Azurion 7 FD20 system (manufactured by Philips Medical Systems Netherlands, located in Best, Netherlands). This combination allows FORS users to employ a roadmap consisting of perioperative X-ray imaging (i.e., fluoroscopy, single exposure, or digital subtraction angiography) or preoperative CTA imaging to provide anatomical context during navigation.

The FORS system has received CE mark approval and is Food and Drug Administration (FDA) 510(k) cleared. It comprises four main components: (1) a workstation, (2) a trolley, (3) a docking base, and (4) a docking top, in addition to the FORS-enabled devices (Figure 3.7.3). The workstation, situated in the control room of the hybrid operating room, serves to connect the FORS technology to the fixed fluoroscopy system, create and refine

b When the FORS Guidewire is at the tip of the conventional catheter or beyond.

roadmaps derived from preoperative CTA, and register the FORS-compatible devices. The trolley serves as the operational hub of the FORS technology, housing the primary software and hardware components of the system. During procedures, the trolley is positioned in the operating room near the operating table and connected to the workstation via a local network connection. The docking base is attached to the surgical table's rail preoperatively, providing a fixed reference point relative to the changing position coordinates of the fluoroscopy system during procedures. This is necessary for coupling of the coordinate systems of the fixed fluoroscopy system and FORS-enabled devices through a shape registration step, enabling the FORS system to compute and visualize the spatial position of the FORS-enabled devices relative to X-ray images or created anatomical route maps. Finally, the docking top is placed atop the docking base. Similar to the FORS guidewire, the docking top is disposable and contains three slots into which the FORS devices can be docked. The devices are then connected to the system by linking the optical connector of the devices to the optical port on the docking station.

FIGURE 3.7.4 ● Example of bi-plane view during Fiber Optic RealShape (FORS) guided cannulation of Celiac trunk of Fenestrated endovascular aortic repair (FEVAR) stent graft using 0.035 inch angled hydrophilic floppy FORS guidewire (yellow) and a conventional 5F Berenstein catheter (purple; Merit Medical systems Inc., South Jordan, Utah, United States). The background on the left side of the image is a real time or single shot fluoroscopy image acquired at 57 degrees right anterior-oblique (RAO) angle, while the background on the right side of the image is a single shot fluoroscopy image acquired with anterior-posterior (AP) view.

FORS WORKFLOW

The FORS workflow encompasses three distinct steps: 1) visualizing anatomical context, 2) registering FORS-enabled devices, and 3) navigating with the use of FORS-enabled devices. While each step can be executed independently, device registration in step 2 must precede navigation in step 3.

- ***Step 1: visualizing anatomical context***
  FORS technology facilitates anatomical visualization using either a preoperatively acquired CTA-based roadmap or intraoperatively acquired digital subtraction angiography (DSA) or single-shot exposure images. The intraoperatively acquired DSA or single exposure images can be selected in the FORS software and overlaid to provide anatomical context. Conversely, the anatomical roadmap is constructed by segmenting vascular structures in preoperatively acquired CTA imaging. Additionally, the software allows placement of "ring landmarks" at significant anatomical locations, such as the origin of a visceral vessel of the aorta. Alignment of the roadmap with the live situation is achieved through volume registration, which can be done manually by adjusting the volume position based on two single exposure images taken with different fluoroscopy system orientations (≥Δ45°), or semi-automatically by identifying corresponding anatomical landmarks, such as calcified plaques, in both preoperative and intraoperative Conebeam CT scans.
- ***Step 2: registration of FORS-enabled devices***
  To accurately calculate and visualize the spatial location of FORS-enabled devices, the coordinate systems of the FORS technology and the fixed fluoroscopy system must be aligned using the FORS software. This alignment is achieved during the "shape registration" process, where the user manually marks the device tip in two single exposure images acquired with different fluoroscopy system orientations (≥Δ30°). Subsequently, the system automatically records and reconstructs the full length of the devices, projecting the result over the single-shot images. Finally, the user can confirm the registration or make manual adjustments to the reconstructed device length, after which the coordinate systems of both systems are linked.
- ***Step 3: navigation with the use of FORS-enabled devices***
  Once successfully registered, FORS-enabled devices are visualized in relation to the chosen anatomical context (Figure 3.7.4). The software offers a biplane viewing option to simultaneously view the anatomical context and devices from two different directions. Moreover, when using a CTA-based roadmap, the software allows positioning of the anatomical roadmap in desired viewing angles, overcoming orientation limitations of fluoroscopy systems. In addition to enhanced visualization of anatomical context, FORS reconstructed devices are visualized in three dimensions (3D), enhancing spatial understanding of these devices in relation to anatomical context.

ACCURACY AND SAFETY OF FORS TECHNOLOGY

A preclinical study by Jansen *et al.*[18] demonstrated the accuracy and safety of FORS technology. Experienced

and less experienced physicians performed various endovascular navigation tasks in both phantom and porcine models, with no adverse events or potential hazards identified. Accuracy was assessed through tip-to-tip distance measurements, resulting in a mean tip-to-tip distance of 2.7±2.2 mm.

CLINICAL IMPLEMENTATION

The First in Human clinical FORS study was conducted at UMC Utrecht.[19] This study utilized FORS technology during the navigation phase of 21 endovascular procedures, comprising 13 endovascular aortic repairs and 8 peripheral lesion repairs. Notably, a remarkable success rate was achieved, with no less than 90.9% of navigation attempts executed successfully using at least one FORS-enabled device. Success was defined as achieving stable positioning of FORS devices in the target following catheterization. Furthermore, this study validated the hypothesis proposed by Jansen *et al.*[18] in the preclinical study, affirming that FORS technology represents a clinical advancement owing to its three-dimensional display capability. In 76% of the procedures conducted in the First in Human study, the utilization of FORS-compatible image guidance was rated as "superior to conventional guidance." Particularly noteworthy was the perceived advantage of unlimited viewing possibilities afforded by FORS technology (Figure 3.7.5).

FORS appears to offer an excellent alternative to the use of radiation during endovascular procedures, which also reduces the risk of radiation damage for both the patient and the medical treatment team. Although FORS is expected to limit the use of radiation and preclinical research shows that it is possible to perform certain navigation tasks without the use of radiation, this has not yet been widely proven. The first published clinical studies demonstrated that the use of FORS during navigation tasks in (complex) EVAR procedures reduced radiation exposure.[20–23] However, this effect on reducing radiation exposure was only in one of these studies statistically significant for the entire procedure .[22] This may be explained by the fact that FORS in its current state can only be used during small and specific parts of the procedures.

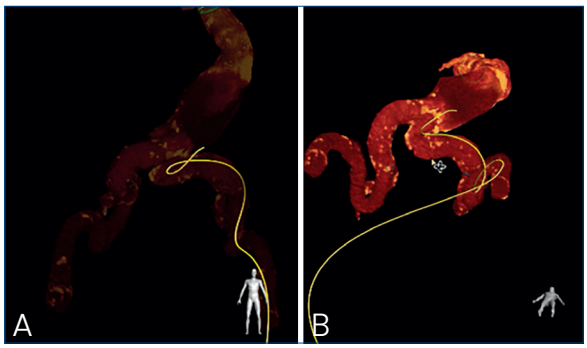


FIGURE 3.7.5 ● Example of FORS system's biplane view mode with unlimited viewing angles during catheterization of a tortuous iliac artery. Biplane view consists of an (A) anteroposterior view and a (B) caudocranial view that improves three dimensional understanding of the tortuous anatomy during insertion and advancement of the FORS enabled guidewire (yellow) into the iliac artery (from Van Herwaarden *et al.*, 2021).

FUTURE PERSPECTIVES

The promising initial clinical results indicating the role of FORS in reducing radiation exposure during endovascular procedures suggest a clear future for this technology. While the beneficial impact of FORS has been demonstrated in selective aspects of (complex) EVAR procedures, its application in other endovascular interventions and/or in conjunction with other radiation-reducing imaging modalities holds potential for further radiation reduction. Case reports have already highlighted the feasibility of using FORS for recanalization of superficial femoral artery lesions and the synergistic use of FORS and (intravascular) ultrasound to minimize the requirement for digital subtraction angiography, thus reducing fluoroscopy and nephrotoxic contrast use.[24, 25]

However, the current iteration of FORS technology is constrained by the availability of only one type of front-loadable guidewire. This limitation precludes access to lesions below the knee or cardiac lesions due to the wire's diameter (current version 0.035). To broaden the applicability of the technology, expansion of the FORS portfolio with guidewires of varying lengths and diameters is imperative. Furthermore, introducing back-loadability for the guidewire would enhance user convenience and facilitate quicker catheter transitions. This advancement would streamline the procedure workflow, allowing treating physicians to seamlessly switch between different catheters without the need for additional steps, thus enabling smoother integration into routine endovascular practices.

REFERENCES

1. Volodos' NL, Karpovich IP, Shekhanin VE, *et al.* [A case of distant transfemoral endoprosthesis of the thoracic artery using a self-fixing synthetic prosthesis in traumatic aneurysm]. Grudn Khir 1988:84–6.
2. Volodos NL. The 30th Anniversary of the First Clinical Application of Endovascular Stent-grafting. Eur J Vasc Endovasc Surg 2015;49:495–7.
3. Fanari Z, Weintraub WS. Cost-effectiveness of medical, endovascular and surgical management of peripheral vascular disease. Cardiovasc Revasc Med 2015;16:421–5.
4. Swerdlow NJ, Wu WW, Schermerhorn ML. Open and Endovascular Management of Aortic Aneurysms. Circ Res 2019;124:647–61.
5. Orandi BJ, Dimick JB, Deeb GM, *et al.* A population-based analysis of endovascular versus open thoracic aortic aneurysm repair. J Vasc Surg 2009;49:1112–6.
6. Ketteler ER, Brown KR. Radiation exposure in endovascular procedures. J Vasc Surg 2011;53:35S–38S.
7. Thakor AS, Winterbottom A, Mercuri M, *et al.* The radiation burden from increasingly complex endovascular aortic aneurysm repair. Insights Imaging 2011;2:699–704.
8. Ko S, Kang S, Ha M, *et al.* Health Effects from Occupational Radiation Exposure among Fluoroscopy-Guided Interven-

tional Medical Workers: A Systematic Review. Journal of Vascular and Interventional Radiology 2018;29:353–66.
9. Tang FR, Loganovsky K. Low dose or low dose rate ionizing radiation-induced health effect in the human. J Environ Radioact 2018;192:32–47.
10. Nyheim T, Staxrud LE, Jørgensen JJ, *et al.* Radiation exposure in patients treated with endovascular aneurysm repair: what is the risk of cancer, and can we justify treating younger patients? Acta Radiol 2017;58:323–30.
11. Hertault A, Maurel B, Midulla M, *et al.* Editor's Choice – Minimizing Radiation Exposure During Endovascular Procedures: Basic Knowledge, Literature Review, and Reporting Standards. Eur J Vasc Endovasc Surg 2015;50:21–36.
12. Writing Committee, ESVS Guidelines Committee, Document Reviewers. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Radiation Safety. European Journal of Vascular and Endovascular Surgery. Published online September 2022.
13. Ahmad W, Hasselmann HC, Galas N, *et al.* Image fusion using the two-dimensional-three-dimensional registration method helps reduce contrast medium volume, fluoroscopy time, and procedure time in hybrid thoracic endovascular aortic repairs. J Vasc Surg 2019;69:1003–10.
14. Doelare SAN, Smorenburg SPM, van Schaik TG, *et al.* Image Fusion During Standard and Complex Endovascular Aortic Repair, to Fuse or Not to Fuse? A Meta-analysis and Additional Data From a Single-Center Retrospective Cohort. J Endovasc Ther 2021;28:78–92.
15. Klaassen J, Vijn LJ, Hazenberg CEVB, *et al.* New tools to reduce radiation exposure during aortic endovascular procedures. Expert Rev Cardiovasc Ther 2022;20:567–80.
16. Megens M, Leistikow MD, van Dusschoten A, *et al.* Shape accuracy of fiber optic sensing for medical devices characterized in bench experiments. Med Phys 2021;48:3936–47.
17. Bydlon TM, Torjesen A, Fokkenrood S, *et al.* 3D Visualisation of Navigation Catheters for Endovascular Procedures Using a 3D Hub and Fiber Optic RealShape Technology: Phantom Study Results. EJVES Vasc Forum 2023;59:24–30.
18. Jansen M, Khandige A, Kobeiter H, et al. Three Dimensional Visualisation of Endovascular Guidewires and Catheters Based on Laser Light instead of Fluoroscopy with Fiber Optic RealShape Technology: Preclinical Results. Eur J Vasc Endovasc Surg 2020;60:135–43.
19. van Herwaarden JA, Jansen MM, Vonken E jan PA, *et al.* First in Human Clinical Feasibility Study of Endovascular Navigation with Fiber Optic RealShape (FORS) Technology. Eur J Vasc Endovasc Surg 2021;61:317–25.
20. Klaassen J, Hazenberg CEVB, Bloemert-Tuin T, *et al.* Radiation Dose Reduction During Contralateral Limb Cannulation Using Fiber Optic RealShape Technology in Endovascular Aneurysm Repair. European Journal of Vascular and Endovascular Surgery. Published online November 2023. doi:10.1016/j.ejvs.2023.10.041
21. Sanders AP, Swerdlow NJ, Jabbour G, *et al.* The effect of Fiber Optic RealShape technology on the reduction of radiation during complex endovascular surgery. J Vasc Surg. Published online November 2023.
22. Finnesgard EJ, Simons JP, Jones DW, *et al.* Initial Single Center Experience Using Fiber Optic RealShape Guidance in Complex Endovascular Aortic Repair. J Vasc Surg. Published online November 2022.
23. Panuccio G, Schanzer A, Rohlffs F, *et al.* Endovascular navigation with Fiber Optic RealShape technology. J Vasc Surg 2023;77:3–8.e2.
24. Klaassen J, van Herwaarden JA, Teraa M, *et al.* Superficial Femoral Artery Recanalization Using Fiber Optic RealShape Technology. Medicina (Lithuania). 2022;58(7).
25. Hazenberg CEVB, Wulms SCA, Klaassen J, *et al.* Reduction of Radiation Exposure during Endovascular Treatment of Peripheral Arterial Disease Combining Fiber Optic RealShape Technology and Intravascular Ultrasound. Journal of Visualized Experiments. 2023;(194).

3.8 THE CURRENT INSURMOUNTABLE LIMITS OF AORTIC ENDOVASCULAR APPROACH: WHEN OPEN SURGERY WILL REMAIN THE BEST (OR THE ONLY) STRATEGY

Andrea Kahlberg, Benedetta Mangili, Nicola Favia, Carlotta Bugna, Roberto Chiesa

A BRIEF HISTORY OF THE AORTIC ENDOVASCULAR ERA

Endovascular surgery has emerged from the necessity for a less invasive surgical approach, in particular for extensive aortic pathologies treatment. The year 1865 marked the inception of percutaneous endovascular aneurysm repairs, with Moore and Murchison pioneering attempts at inducing thrombosis within aneurysm sacs through direct needle cannulation and wire packing.[1] Their method involved the insertion of 26 yards of wire coils into a large thoracic aneurysm with a direct puncture. Although the aneurysm partially thrombosed, the patient died, compounded by evident complications of sepsis and distal embolism. In 1879 the incorporation of electricity in the procedure represented the evolution of this approach, the Moore-Corradi method.[1] This electrothrombosis technique entailed coiling with silver and copper wire, coupled with the passage of current through the wire to facilitate thrombosis.

In 1900 Rudolf Matas used electrothrombosis for the management of a huge abdominal aortic aneurysm (AAA).[1] Preceding this endeavor, Matas delineated the utility of endoaneurysmorraphy in peripheral aneurysm treatment, distinguishing three forms of aneurysmorraphy: obliterative, restorative, and reconstructive. Matas' innovative approach culminated in the successful management of an infrarenal AAA in 1923, with a 18-month patient postoperative survival before passing away due to complications related to pulmonary tuberculosis.

While preliminary attempts of "endovascular techniques" in aortic surgery date back nearly 125 years, a pivotal breakthrough emerged through the collaborative efforts of Parodi and Palmaz. They pioneered experiments involving stainless steel stents hand-sewn to thin-walled Dacron tube grafts, they initially trialed in canine models before advancing to human experimentation.[2] A noteworthy accomplishment happened on September 6th, 1990, when the first successful human endovascular aneurysm repair was performed. Subsequently, they elucidated their initial clinical experiences with five patients in the seminal paper titled "Transfemoral intraluminal graft implantation for abdominal aortic aneurysms".[2, 3] This milestone heralded a paradigm shift in aneurysm management, paving the way for the development of increasingly sophisticated endovascular devices characterized by enhanced accessibility, reduced profile, and intricate configurations.

The advancements in endovascular aneurysm repair highlights how surgical innovation evolves over time, with continuous improvement in techniques used (Figure 3.8.1). From rudimentary attempts in the 19th century to the contemporary era characterized by complex and always more precise endovascular technologies, each milestone reflects the collective efforts of pioneers striving to enhance patient outcomes and redefine the boundaries of surgical intervention in vascular pathology.

BEYOND BOUNDARIES

Nowadays, thanks to technology progresses, many barriers - considered impossible to overcome in the past- have been successfully surpassed.

Pre- and intra-operative imaging

One of these advancements is certainly represented by the progress in preoperative and intraoperative imaging techniques, which got greater diagnostic precision and a more accurate therapeutic approach.

In the historical practice of endovascular surgery, clinicians traditionally relied on two-dimensional (2D) intraoperative fluoroscopic imaging coupled with intravascular contrast opacification to address intricate three-dimensional (3D) pathological conditions. However, recent significant advancements in intraoperative imaging technology facilitated the development of image fusion methodologies. Many studies demonstrated that complex (fenestrated/branched) endovascular aneurysm repair (EVAR) carries a notable risk of acute renal failure due to the substantial amounts of contrast material employed.[4] While the exact causes are likely multiple, contrast-enhanced procedures remain the third most common cause of hospital-acquired acute renal failure.[5] Hence, any initiative aimed at minimizing contrast media volume in complex EVAR procedures is deemed crucial.

Additionally, the cumulative effect of exposure to radiation puts at risk both patients and physicians for deterministic and stochastic radiation injuries. Many studies, such as the meta-analysis conducted by Doelare *et al.*[4] confirm that fusion imaging method significantly reduces contrast volume, fluoroscopy time, and procedure time in complex EVAR procedures.

Another example is the utilization of the Intravascular Ultrasound (IVUS) system[6] or Fiber Optic RealShape (FORS) technology,[7] which have recently been introduced as adjunctive guidance technology enabling real-time three-dimensional visualization of specific endovascular devices, thus mitigating radiation exposure. IVUS allows to visualize vessel wall with identification of branch vessel landmarks using ultrasound technology alone. Using the pullback techniques, lumen diameters and cross-sectional area, wall thickness, lesion length, shape, and volume, lesion position within the lumen (concen-

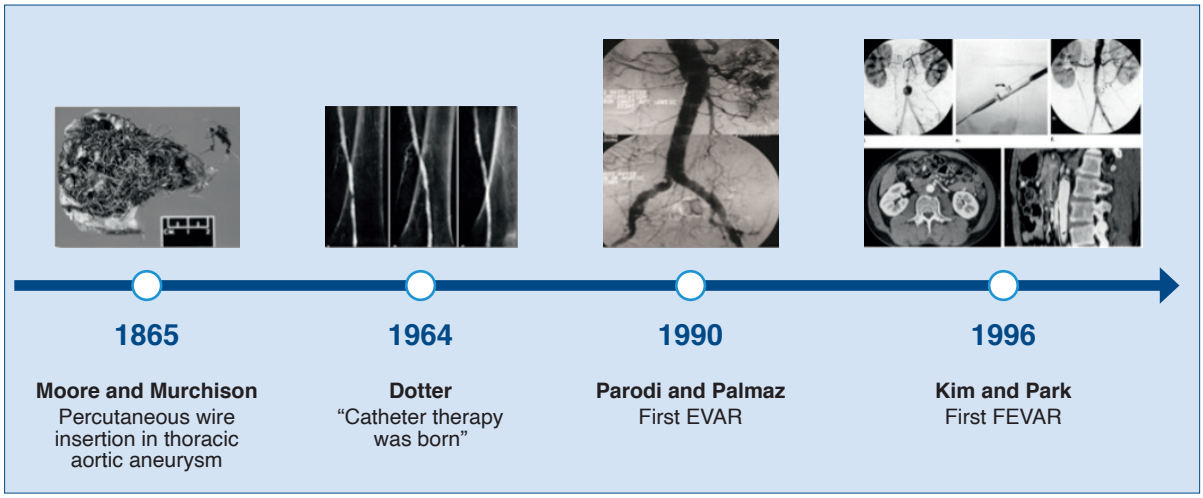


FIGURE 3.8.1 ● Milestones of the endovascular era.

tric vs eccentric), lesion type (fibrous vs calcific), presence and extent of flap, dissection, or ulceration, presence of thrombus an position of tears in dissected lamella can be determined.[6]

All these innovations, coupled with the increasing utilization of artificial intelligence, serve as, and will increasingly serve as, supportive tools for surgeons in accurate diagnosis and determinants for selecting the appropriate treatment.

Accessing the aorta

We are witnessing a competition between companies to present more advanced endografts with an increasingly low profile, adaptable to anatomies once considered prohibitive for endovascular treatment, thus allowing more patients to benefit from such treatment. These lower-profile delivery systems indeed allow us to consider endovascular treatment not only for patients with small-caliber arteries but also facilitate better navigability in challenging and tortuous anatomies[8]. New grafts are now becoming more "access friendly".

It has been over twenty years since Parodi *et al.* introduced the first endovascular repair technique for AAA treatment[2] and Marin conducted the inaugural endovascular AAA repair in the United States.[3] First-generation endografts were employed on a compassionate basis, they were implanted in patients deemed unsuitable for open AAA repair due to high surgical risk. Since then, EVAR has emerged as the preferred approach and is presently the most commonly performed procedure for AAA correction.

The challenge of hostile iliac access still represents a real obstacle to the technical success and increases the risk of intraoperative, perioperative, and postoperative complications in both elective and urgent/emergent AAA procedures. Studies from large cohorts and major trials[8-10] report that approximately 15% of patients undergoing EVAR have narrow or stenotic iliac arteries. Over the past decade, the introduction of low-profile endografts (Figure 3.8.2), which are smaller in both device and sheath size compared to first-generation aortic endografts, has been pivotal for patients with narrow iliac arteries.[9] Additionally, the development of hydrophilic introducers made easier the insertion of devices into challenging access. One other option to facilitate endograft insertion is the use of vessel dilators; however, this approach may not be suitable for heavily calcified lesions. In these cases, new vessel preparation techniques such as peripheral intravascular lithotripsy (IVL),[11] high-pressure balloon angioplasty with or without bare stents and/or endo-conduits, may serve as useful adjunctive procedures, particularly in complex cases.[12] The development of these new techniques made the endovascular approach feasible also for many more patients, especially for those that, a few years ago, would have been excluded due to hostile accesses (Figure 3.8.3).

Challenge of proximal (infrarenal) neck

In most of the commercially available endografts, a 15 mm neck length or longer is required according to the Instructions for Use (IFU); nevertheless, in clinical practice, a generally it is accepted minimum neck length of 10-15 mm to achieve infrarenal fixation. AAAs with shorter necks have a reduced contact surface area, leading to diminished frictional force and radial force along the neck's length, thus predisposing them to graft displacement and endoleaks. Neck lengths shorter than 15 mm relate with an increased incidence rate of early and late type Ia endoleaks necessitating secondary intervention.[13] Some of the newer devices have obtained approval for shorter neck lengths. Specifically, the Endurant II/Endurant IIs Stent Graft System (Medtronic, Minneapolis, MN, USA) and the Ovation Alto Abdominal Stent Graft System (Endologix LLC, Irvine, CA, USA) necessitate minimum neck lengths of 10 mm and 7 mm, respectively. In particular the Ovation Stent graft has an aortic

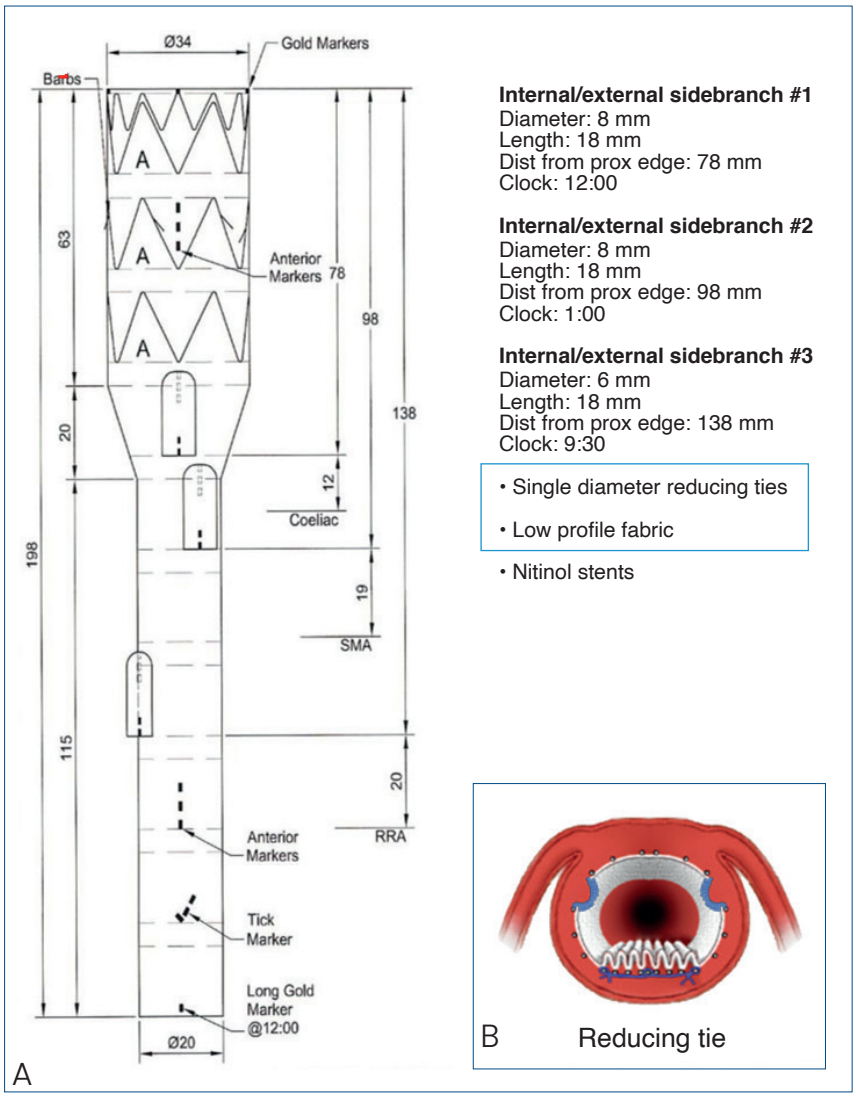


FIGURE 3.8.2 ● A) Schematic plan of a low-profile triple downward branch endograft (external diameter of 18 French, 6 mm); B) reducing tie for lower graft profile.

body provided with a suprarenal nitinol stent with anchors that offers active fixation, while a network of rings and channels that are inflated with a low-viscosity radiopaque polymer during stent-graft deployment, provides effective sealing.

Severe aortic neck angulation (≥60 degrees) is associated with peri-graft endoleaks secondary to poor proximal sealing and graft separation. The Heli-FX EndoAnchor (Medtronic, MN, USA) was designed to enhance endograft fixation and sealing and its use has also been shown to offer some protection against proximal neck dilatation (Figure 3.8.4). The system utilizes helical implants (4.5 mm in length, 3 mm in diameter) and an applier to engage the full thickness of aortic tissue and attach the endograft to the aortic wall. Conceptually, their use is intended to replicate a hand-sewn anastomosis between a graft and native vessel. Endoanchors can be used primarily either prophylactically in hostile necks or to manage an intraoperative type Ia endoleak during the initial endograft implantation procedure.

A new device manufactured by Gore Medical company, Gore Excluder Conformable AAA, has been designed to accommodate neck angulation and achieve a robust seal in this unfavorable anatomy.[14]

Challenge of distal landing zone

Isolated iliac artery aneurysms likely comprise 0.5% to 1.9% of all intra-abdominal aneurysms, but concurrent iliac artery aneurysms can complicate infrarenal aneurysms in 40% of patients.[15]

Before customized devices employment in the iliac region, various methods were employed to treat iliac arteries dilatations and they can be categorized into two groups: occlusive and inclusive. The predominant approach was typically occlusive. In these techniques, some form of occlusion was inserted into the internal iliac, followed by extension of the device limb into the external iliac artery. Both coils and plugs were utilized, with the prevailing consensus now favoring the placement of

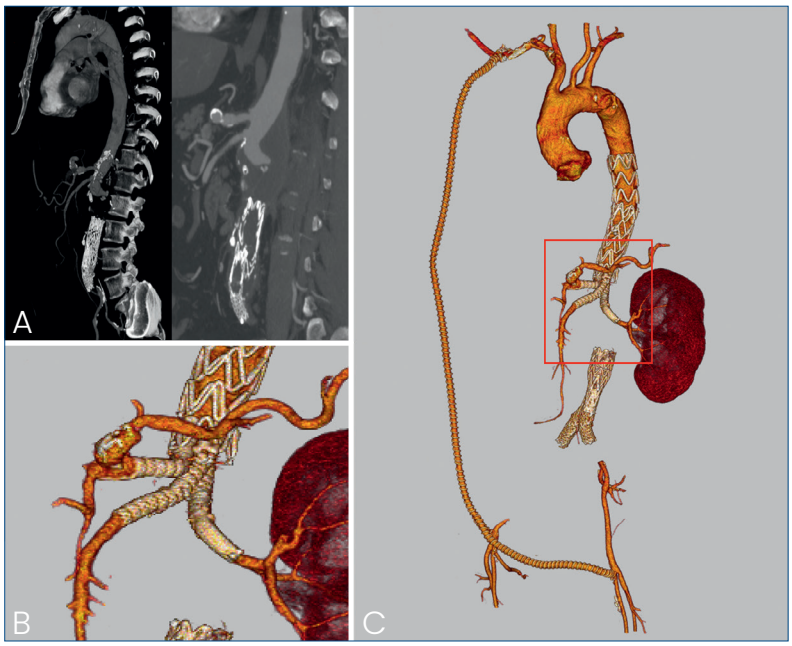


FIGURE 3.8.3 ● A) Preoperative CT of thoraco-abdominal aortic aneurysm in a patient with aorto-iliac occlusion after regular EVAR; B) focus on the distal part of the endograft with bridging stents; C) CT scan reconstruction of a B-EVAR deployed from axillary artery.

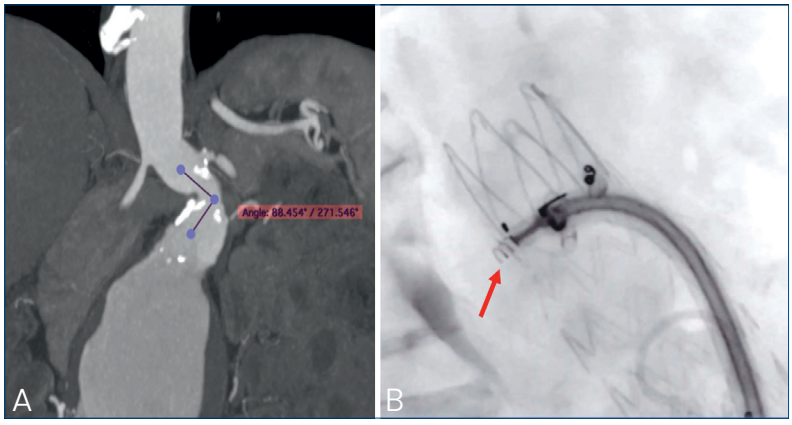


FIGURE 3.8.4 ● A) CT scan of a AAA with angulated neck; B) positioning of an EndoAnchor (indicated by the arrow).

an occlusive device in a patent internal iliac to prevent type II endoleak. Occluding the iliac region, the modification of pelvic circulation frequently resulted in buttock claudication in ambulatory patients and could potentially lead to more serious complications such as rectal or bowel ischemia and lumbar plexopathy.[15]

Despite not being widely recognized, iliac branch devices represent a significant advancement in aortic disease treatment. They validated the idea that branched devices could exhibit durability, offering a foundational platform for integrating branches into aortic repair and eliminating a prevalent criterion for anatomical exclusion.[16-18]

"Hot" districts

Nowadays, the available choices for aortic arch repair have expanded to include various endovascular techniques, including pure endovascular methods as well as "hybrid" approaches combining endovascular and surgical interventions. Primarily endovascular strategies are currently considered experimental and "off-label", and they are typically conducted only in specialized centers with high case-load. In these centers, the use of custom-made fenestrated/branched endoprostheses and physician-modified grafts is becoming always more common, letting offer a customize treatment to many more patients. The future direction of aortic arch repair is likely to incorporate advancements in both open and endovascular procedure.[19]

For example, Canaud and his group outline their innovative method of crafting a proximal scallop within a thoracic aortic stent graft to facilitate repair of aortic arch aneurysm (Figure 3.8.5). This inventive approach maintains the patency of the great vessels through the scalloped section of the aortic stent graft, positioned along the outer curve of the aortic arch, while providing a considerably larger proximal seal zone along the inner curve. The strength of this strategy lies in its simplicity, as it circumvents the technical complexities associated with cannulating the great vessels, a process related to high risk of

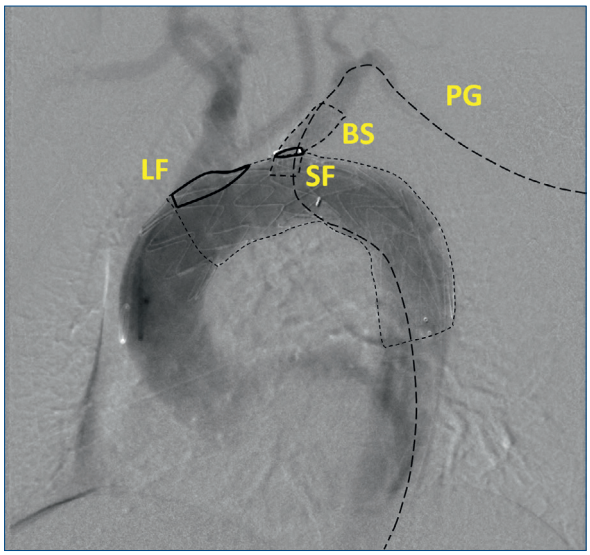


FIGURE 3.8.5 ● Aortic arch aneurysm exclusion with physician modified endograft (Canaud technique). LF: large fenestration for innominate and left common carotid artery; SF: small fenestration for left subclavian artery (LSA); BS: bridging stent for LSA; PG: preloaded guidewire.

stroke, long procedural time, and increased exposure to radiation and intra-arterial contrast agents.[20-22]

Pushing the boundary even proximally, the treatment of the ascending aorta and aortic valve, both in elective and emergency scenarios, is progressing towards endovascular surgery, facilitated by currently available physician-modified prostheses.[23] Since its inception in 1996, fenestrated endovascular aneurysm repair (F-EVAR) has catalyzed significant progress in endograft technology. Both custom-made and off-the-shelf fenestrated and branched endografts have been employed to manage patients with complex abdominal aortic and thoraco-abdominal aneurysms.[19, 24]

Rescue maneuvers

Despite technical advances of fenestrated and branched endografts, endovascular exclusion of complex aneurysms involving renal, visceral, and/or supra-aortic branches remains challenging. In situ fenestration of standard endografts or fenestration of a dissection lamella represents another endovascular means to maintain perfusion to such branches.

In recent years, increasingly advanced bail-out techniques have been developed for complex cases, such as novel "in situ" fenestration techniques and lamella dissection fenestration techniques[25, 26] (Figure 3.8.6). For instance, starting from needle fenestration, progressively precise and cutting-edge fenestration techniques using balloon, radiofrequency and diode laser have been developed.

Over the past two decades, there has been also a significant evolution in the treatment options for type B aortic dissection endovascular therapy emerged as a safe and effective approach, now it is considered the first-line treatment for acute/subacute complicated cases. While thoracic endovascular aneurysm repair (TEVAR) sometimes can achieve thoracic aorta remodeling and complete false lumen thrombosis, in the majority of cases, a remaining false lumen perfusion at some level is detectable, and usually it is due to additional distal tears. In chronic scenarios, false lumen perfusion has been identified as the primary contributor to late aneurysmal degeneration. A relatively novel technique, named STABILISE (stent-assisted balloon-induced intimal disruption and relamination in aortic dissection repair) technique, has been developed to improve true lumen perfusion.[27-29] This technique has outstanding outcomes, particularly in terms of alleviating malperfusion and reducing the long-term need for reintervention.

IMPASSABLE BOUNDARIES

Despite the numerous advances in endovascular surgery, which is increasingly accessible to many patients, there are nevertheless insurmountable limits for which in some cases, endovascular treatment remains and will likely remain the best or only strategy.

Connective tissue disorders

Connective tissue disorders (CTDs) comprise a cluster of syndromes distinguished by irregularities in connective

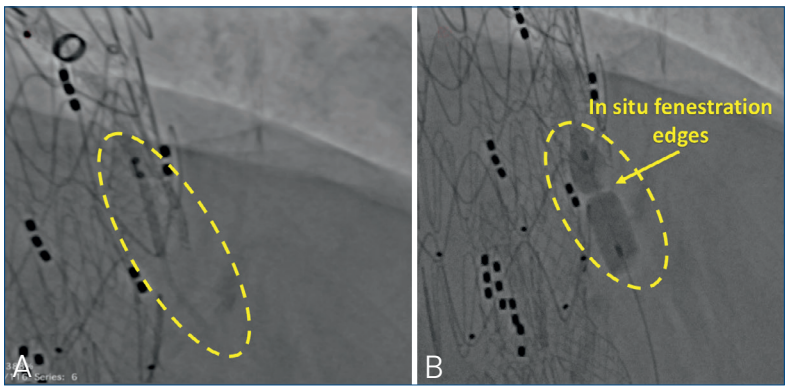


FIGURE 3.8.6 ● A) *In situ* fenestration with needle (marked with yellow circle) of a branch from a BEVAR; B) enlargement of the *in situ* fenestration with non-compliant balloon (marked with yellow circle).

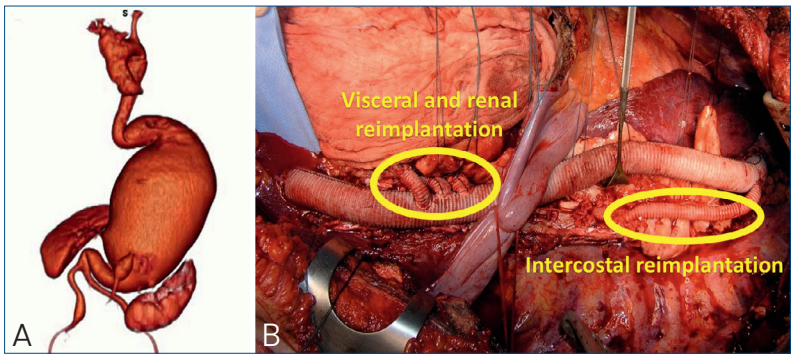


FIGURE 3.8.7 ● A) CT scan reconstruction of thoraco-abdominal aortic aneurysm in CTD patient; B) thoraco-abdominal aortic open repair with visceral and renal (on the left) and intercostal arteries (on the right) reimplantation.

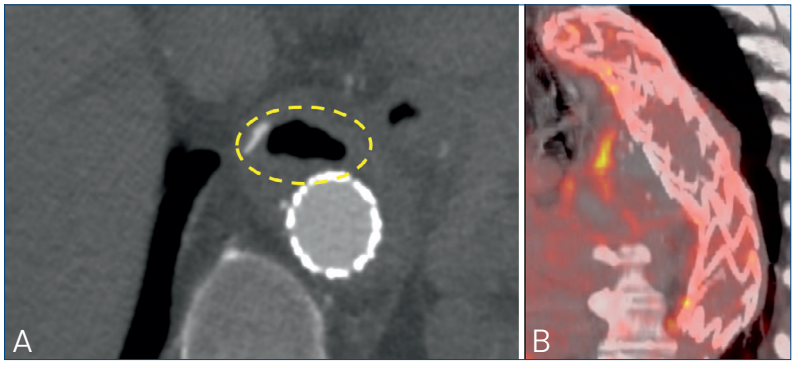


FIGURE 3.8.8 ● Radiological signs of infection of an endograft. A) CT scan of thoracic endograft with a large gas bubble; B) PET scan with intense capitation of the thoracic stent-graft.

tissue integrity, particularly in the vascular wall, resulting in varying degrees of weakness. Patients affected by CTDs like Marfan syndrome, Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrome are predisposed to significant cardiovascular abnormalities, including aortic dissection and aneurysm of the thoracoabdominal aorta, commencing from the aortic root (Figure 3.8.7). Aortic dissection serves as a predominant pathophysiological event necessitating aortic repair in CTD patients,[30] diverging from non-CTD patients where degenerative aneurysms commonly prompt repair. The distinctive inclination towards aortic dilation, especially post-dissection, in CTD patients, along with the specific challenges related to tissue integrity, underlines the significance of determining the most suitable aortic repair approach with optimal short- and long-term outcomes. If over the past two decades, endovascular repair has emerged as the main technique for treating aortic aneurysms in general population, it is not universally accepted in the CTD patient group.

However, the use of endovascular techniques in patients with CTDs remains a subject of controversy, given that these patients were consistently excluded from device trials. The enduring effectiveness of endovascular aortic repair in CTD patients, who typically undergo repair at a younger age compared to those with degenerative aneurysms, remains uncertain. Endovascular approaches may seem attractive, especially as patients with CTDs are now surviving to older ages, making them less suitable candidates for open surgery due to heightened operative risks, prior aortic procedures, or medical comorbidities. Nonetheless, CTD patients are prone to post-endovascular repair complications, often associated with high mortality rates. The use of self-expanding stent-grafts in the fragile and diseased aortas of CTD patients has been linked to increased occurrences of retrograde type A dissection (RTAD), stent migration, and stent-induced new entry (SINE).[30] Therefore, the endovascular repair is not the treatment of choice in CTD patients unless they are fragile with multiple comorbidities, unless there is an available Dacron graft to land in, or they are experiencing visceral malperfusion after aortic dissection (in this case it may be considered as bridging therapy before definitive open repair).[30, 31] A strict lifelong follow-up is essential in these patients to assess the necessity for reintervention. In conclusion, the gold standard for the treatment of aortic pathology in CTD patients remains open vascular repair.

Infections

Infection of prosthetic grafts presents a severe complication with a poor outcome (Figure 3.8.8); the first infection of an endograft was reported in 1993. Its incidence ranges from 0.3% to 6% following open surgery repair and 0.2% to 1% after EVAR.[32] In cases of infection, complete removal of the graft and debridement of infected tissue is the best options, as emphasized by the new guidelines worldwide.[32-35]

Factors contributing to prosthetic graft infection encompass prosthetic material placement in the groin, emergency surgeries, intestinal damage, perioperative infections, bacteremia, requirement for extra-anatomical

bypass in aorto-uni-iliac stent grafts, prior coil embolization of the hypogastric artery, diabetes, and immunosuppression. Given the high morbidity and mortality associated with prosthetic graft infection and graft-enteric fistula (ranging from 20% to 75% combined morbidity and mortality across various studies), prioritizing prevention, early detection, and aggressive intervention is paramount. The preferred approach for treating prosthetic graft infection involves in situ reconstruction with thorough debridement of infected tissues, utilizing infection-resistant materials such as autologous deep vein, cryopreserved allografts, or xeno-pericardial grafts. Alternatively, aortic ligation with extra-anatomical reconstruction stands as a viable option, particularly in cases of heightened patient risk or extensive local tissue infection.

In conclusion, as stated by international guidelines, endovascular surgery will not find a place in the treatment of prosthetic infections, which can find their more definitive solution in traditional surgery.[32-35]

Multiple endo failures

With the increasing development and widespread adoption of endovascular techniques, a greater incidence of complications such as endoleak, graft migration, and graft failure has been encountered. In the majority of cases, the management of these complications may again involve endovascular procedures. However, in complex cases where repeated attempts at endovascular surgery have proven unsuccessful, open surgery appears to remain the only viable recourse.[36, 37]

FINAL CONSIDERATIONS

In conclusion, thanks to technological advancements, endovascular surgery has become increasingly accessible to patients who were previously excluded from these kind of treatments. Today, in many cases, it has become the main treatment option. However, it is important to consider that in patients for whom endovascular surgery is no longer effective or not suitable, the therapeutic decision will be more complex. Therefore, traditional surgery remains and must continue to be a cornerstone in the practice of every experienced vascular surgeon and must not be forgotten in the training of the young surgeon.

REFERENCES

1. Bobadilla JL. From Ebers to EVARs: A Historical Perspective on Aortic Surgery. Aorta (Stamford) 2013;1:89–95.
2. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5;491–9.
3. Veith FJ, Marin ML, Cynamon J, *et al.* 1992: Parodi, Montefiore, and the first abdominal aortic aneurysm stent graft in the United States. Ann Vasc Surg 2005;19:749–51.
4. Doelare SAN, Smorenburg SPM, van Schaiket TG, *et al.* Image Fusion During Standard and Complex Endovascular Aortic Repair, to Fuse or Not to Fuse? A Meta-analysis and Additional Data From a Single-Center Retrospective Cohort. J Endovasc Ther 2021;28:78–92.
5. Mohammed NM, Mahfouz A, Achkar K, *et al.* Contrast-induced Nephropathy. Heart Views 2013;14:106–16.
6. Kpodonu J, Ramaiah VG, Diethrich EB. Intravascular ultrasound imaging as applied to the aorta: a new tool for the cardiovascular surgeon. Ann Thorac Surg 2008;86:1391–8.
7. Panuccio G, Schanzer A, Rohlffs F, *et al.* Endovascular navigation with Fiber Optic RealShape technology. J Vasc Surg 2023;77:3–8.e2.
8. Etkin Y, Baig A, Foley PJ, *et al.* Management of difficult access during endovascular aneurysm repair. Ann Vasc Surg 2017 Oct:44:77–82.
9. Wortmann M, Bischoff MS, Hakimi M, *et al.* How to overcome challenging iliac artery anatomy in endovascular repair for AAA. J Cardiovasc Surg (Torino) 2018;59:4–13.
10. Spath P, Campana F, Gallitto E, *et al.* Impact of iliac access in elective and non-elective endovascular repair of abdominal aortic aneurysm. J Cardiovasc Surg 2024;65:85–98.
11. Piazza M, Squizzato F, De Massari C, *et al.* Intravascular lithotripsy angioplasty for treatment of atherosclerotic coral-reef occlusion of the infrarenal aorta and its bifurcation. J Vasc Surg Cases Innov Tech 2023;9:101106.
12. Vatakencherry G, Molloy C, Sheth N, *et al.* Percutaneous access planning, techniques and considerations for endovascular aortic repair (EVAR). Cardiovasc Diagn Ther 2018;8(Suppl 1):S184–S190.
13. Houser A. Martinez C, Tassiopoulos A. The Challenge of Treating Abdominal Aortic Aneurysms with Hostile Neck Anatomy: An Overview. J Clin Med 2024;13:1460.
14. Park KH, Lim C, Lee JH, *et al.* Suitability of endovascular repair with current stent grafts for abdominal aortic aneurysm in Korean patients. J Korean Med Sci 2011;26:1047–51.
15. Richardson JW, Greenfield LJ. Natural history and management of iliac aneurysms. J Vasc Surg 1988;8:165–71.
16. Oderich GS, Greenberg RK. Endovascular iliac branch devices for iliac aneurysms. Perspect Vasc Surg Endovasc Ther 2011;23:166–72.
17. D'Oria M, Tenorio ER, Oderich GS, *et al.* Outcomes of Unilateral Versus Bilateral Use of the Iliac Branch Endoprosthesis for Elective Endovascular Treatment of Aorto-iliac Aneurysms. Cardiovasc Intervent Radiol 2022;45:939–49.
18. Oussoren FK, Maldonado TS, Reijnen MMPJ, *et al.* Solitary iliac branch endoprosthesis placement for iliac artery aneurysms. J Vasc Surg 2022;75:1268–75.e1.
19. Bertoglio L, Melloni A, Bugna C, *et al.* HTA PRO-ENDO commission investigators. In-hospital cost-effectiveness analysis of open versus staged fenestrated/branched endovascular elective repair of thoracoabdominal aneurysms. J Vasc Surg 2023;78:300–12.e3.
20. Canaud L, Chassin-Trubert L, Abouliatim I, *et al.* Total Arch Thoracic Endovascular Aortic Repair Using Double Fenestrated Physician-Modified Stent-Grafts: 100 Patients. J Endovasc Ther 2024;31:89–97.
21. Canaud L, Gandet T, Khantalin I, *et al.* Homemade proximal scalloped stent graft for thoracic endovascular aortic repair of zone 2 acute aortic syndrome. J Thorac Cardiovasc Surg 2016;152:1301–6.
22. Canaud L, Morishita K, Gandet T, *et al.* Homemade fenestrated stent-graft for thoracic endovascular aortic repair of zone 2 aortic lesions. J Thorac Cardiovasc Surg 2018;155:488–93.
23. Gaia DF, Bernal O, Castilho E, *et al.* First-in-human Endo-Bentall procedure for simultaneous treatment of the ascending aorta and aortic valve. JACC Case Rep 2020;2:480–5.
24. De Niet A, Reijnen MM, Tielliu IF, *et al.* Fenestrated Endografts for Complex Abdominal Aortic Aneurysm Repair. Surg Technol Int 2016;29:220–30.
25. Baghbani-Oskouei A, Savadi S, Mesnard T, *et al.* Transcatheter electrosurgical septotomy technique for chronic post-dissection aortic aneurysms. J Vasc Surg Cases Innov Tech 2023;10:101402.
26. Tanenbaum MT, Figueroa AV, Lee KB, *et al.* Early results of

transcatheter electrosurgical aortic septotomy for endovascular repair of chronic dissecting aortoiliac aneurysms. J Vasc Surg Cases Innov Tech 2024;10:101467.
27. Kahlberg A, Mascia D, Bertoglio L, *et al.* New technical approach for type B dissection: from the PETTICOAT to the STABILISE concept. J Cardiovasc Surg (Torino) 2019;60:281–8.
28. Melissano G, Bertoglio L, Rinaldi E, *et al.* Satisfactory short-term outcomes of the STABILISE technique for type B aortic dissection. J Vasc Surg 2018;68:966–75.
29. Mascia D, Rinaldi E, Kahlberg A, *et al.* The STABILISE technique to address malperfusion on acute-subacute type B aortic dissections. J Cardiovasc Surg (Torino) 2022;63:131–6.
30. Sayed A, Munir M, Bahbah EI. Aortic Dissection: A Review of the Pathophysiology, Management and Prospective Advances. Curr Cardiol Rev 2021;17(4):e230421186875.
31. Ali-Hasan-Al-Saegh S, Halloum N, Scali S, *et al.* A systematic review and meta-analysis of retrograde type A aortic dissection after thoracic endovascular aortic repair in patients with type B aortic dissection. Medicine (Baltimore) 2023;102:e32944.
32. Wanhainen A, Van Herzeele I, Bastos Goncalves F, *et al.* European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2024;67):192–331.
33. Kahlberg A, Melissano G, Mascia D, *et al.* How to best treat infectious complications of open and endovascular thoracic aortic repairs. Semin Vasc Surg 2017;30:95–102.
34. Kahlberg A, Rinaldi E, Piffaretti G, *et al.* Results from the Multicenter Study on Aortoenteric Fistulization After Stent Grafting of the Abdominal Aorta (MAEFISTO). J Vasc Surg 2016;64:313–20.e1.
35. Kahlberg A, Grandi A, Loschi D, *et al.* A systematic review of infected descending thoracic aortic grafts and endografts. J Vasc Surg 2019;69:1941–51.e1.
36. Rinaldi E, Kahlberg A, Carta N, *et al.* Late Open Conversion Following Failure of EVAR and TEVAR: "State of the Art". Cardiovasc Intervent Radiol 2020;43:1855–64.
37. Loschi D, Santoro A, Rinaldi E, *et al.* Open and endovascular reinterventions after Candy Plug false lumen embolization of type B aortic dissection. J Vasc Surg 2023;78:1409–17.

4

THE CHALLENGE OF ARTIFICIAL INTELLIGENCE

4.1 DIGITAL PATIENT DATA: ARTIFICIAL INTELLIGENCE, MACHINE LEARNING AND SENSOR TECHNOLOGY IN THE NEW ERA OF RESEARCH AND CLINICAL DATA COLLECTION

Paolo Servi, Enzo Gentile, Emiliano Chisci, Stefano Michelagnoli

INTRODUCTION AND HISTORICAL CONTEXT

The evolution of modern medicine is intrinsically linked to the ability to effectively collect, interpret, and use clinical data. For a long time, paper documentation was the only source of information about patients, often with handwritten medical notes, charts made on paper, and physical files stored in hospital archives.

This approach, where it survives, is inefficient because it limits data sharing among different healthcare professionals and increases the risk of errors.

The shift to electronic health records marked a radical change in the way patient data is documented and utilized.

These electronic systems have enabled the organization and storage of large amounts of information in digital format, facilitating access for clinicians and allowing better collaboration among the various actors involved in healthcare. Despite this, simply moving data to electronic platforms has not been enough to fully exploit the potential of clinical information.

The advent of Artificial Intelligence (AI) and advanced technologies has further revolutionized the scenario. Machine learning and deep learning, two segments of AI, have begun to harness the enormous amount of digital clinical data, offering new perspectives for improving diagnoses, optimizing clinical decisions, and personalizing therapies.

At the same time, the increasing spread of wearable devices and implantable sensors has generated a constant flow of real-time data, providing doctors with a more detailed view of patients' conditions.

Despite these innovations, significant challenges remain. The quality of the clinical data collected is often heterogeneous and requires advanced processing to ensure accurate interpretation. Moreover, concerns about data privacy arise as the collection of sensitive information becomes more pervasive. Overcoming these challenges is essential to fully exploit the potential of artificial intelligence and new technologies in the field of medicine.

CLINICAL DATA COLLECTION: THE CURRENT LANDSCAPE

Currently, the collection of clinical data relies on a wide range of sources and technologies that are redefining how healthcare professionals gather, analyze, and use information. The main sources include the following issues.

Electronic Health Records

Electronic health records (EHRs) represent a fundamental pillar in the collection of digital clinical data. They offer physicians quick access to detailed information on medical history, blood test results, diagnostic tests, prescriptions, and treatment plans. These systems enable cross-sectional data integration, making communication smoother between different departments and facilitating the sharing of information for more efficient patient management (Figure 4.1.1).

However, challenges remain, such as the homogeneity and compatibility of procedures among different application providers and the need to maintain high security standards.

Wearable Devices and Implantable Sensors

The increasing prevalence of wearable devices, such as smartwatches and sensors for monitoring heart rate or blood glucose levels, provides a constant flow of clinical data directly from the patient.

Implantable sensors, such as pacemakers and defibrillators, transmit more specific data on heart function and potential anomalies. This real-time information allows doctors to continuously monitor patients' conditions, respond quickly in emergencies, and optimize post-operative follow-up.

In vascular surgery, sensors play a crucial role in monitoring vital parameters such as blood pressure, oxygen saturation, and blood flow, during both surgical procedures and in the postoperative period.

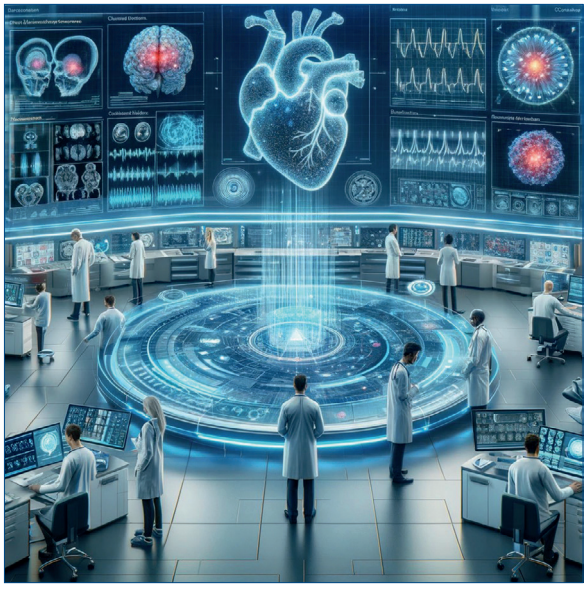


FIGURE 4.1.1 ● Artificial Intelligence-Assisted Medicine / @ AI generated.

These data can be transmitted in real time to a centralized monitoring system, allowing healthcare providers to detect anomalies early and intervene promptly. For example, our center is currently conducting a trial of remote blood pressure monitoring in all patients with acute aortic syndrome, such as type B aortic dissection.

During hospitalization, blood pressure is monitored both invasively and with standard non-invasive monitoring. This group of patients wears a bracelet (Aktiia, CE marked as a Class IIa medical device), and the device is calibrated.

Subsequently, the device is used for remote monitoring, as it can store all data in the cloud, facilitating transmission to the attending physician. It uses algorithms that process data collected from optical wrist sensors through photoplethysmography (PPG), analyzing the change in artery diameter with each heartbeat. The accuracy is high: 0.45±7.75 mmHg for systolic pressure and 0.38±6.86 mmHg for diastolic pressure. Thanks to accurate calibration and comparison of values from both invasive and non-invasive monitoring, blood pressure is constantly under control. Values are recorded throughout the day and night and then transmitted to the app (Figure 4.1.2).

The validity of Aktiia has been confirmed by peer-reviewed clinical studies published in scientific journals such as Nature.[1] Even in our preliminary experience, this device has provided significant support in monitoring patients and controlling blood pressure values. The literature is increasingly rich with experiences on the evaluation of wearable sensors in monitoring patients with cardiovascular disease.[2, 3]

FIGURE 4.1.2 ● Continuous arterial pressure and heart rate remote monitoring provided by wearable bracelets (Aktiia, CE marked as a Class IIa medical device). , It uses algorithms that process data collected from optical wrist sensors through photoplethysmography. (Courtesy of Aktiia SA, Rue du Bassin 8a, 2000 Neuchâtel, Switzerland).

Clinical Databases and Research Registries

Clinical databases and registries specific to diseases or procedures are another valuable source. They allow the systematic collection of information on large patient populations, facilitating clinical research and enabling specialists to identify epidemiological trends and risk factors. Registries established by national associations, for example, offer a comprehensive view of various patient types and different treatment modalities.

Data Derived from Clinical Research

Data from clinical studies provide insights into new therapies, devices, and medical procedures. The sharing and analysis of these data can accelerate the development of innovative treatments and improve existing clinical guidelines.

Artificial intelligence (AI) has become a fundamental pillar in the management of clinical data. Thanks to its advanced algorithms, AI can analyze large amounts of data in a very short time, providing healthcare professionals with valuable information to make informed clinical decisions. Machine learning (ML), a sub-discipline of AI, is based on the idea that computer systems can learn from data, identify patterns, and make predictions without being explicitly programmed to do so. We reviewed the literature, looking for publications with an impact factor (IF) higher than 3 to understand the most significant ones on the topic.

AI and ML are revolutionizing diagnostic procedures in vascular surgery. Through machine learning algorithms, it is possible to analyze diagnostic images, such as angiographies, ultrasounds, and CT scans, to detect vascular anomalies with unprecedented precision. Once standardized and validated, this could allow for faster and more accurate diagnoses, enabling healthcare providers to plan surgical interventions more effectively. AI can help reduce human errors during surgical procedures by providing real-time alerts regarding potential risks or complications. This can improve patient safety and reduce the rate of medical errors.

Another area of interest is AI's ability to predict the risks and complications associated with vascular surgeries. By analyzing clinical data such as patient history, laboratory test results, and diagnostic images, ML algorithms can identify patients at risk of developing postoperative complications. This allows healthcare providers to take preventive measures and personalize treatments to maximize clinical outcomes.

Imaging diagnostics represent a critical phase in the treatment offered to patients in vascular surgery, helping to confirm the diagnosis, evaluate the prognosis, and plan the surgical intervention. AI approaches can assist in optimizing image segmentation and pattern identification, as well as automating repetitive tasks, increasing repeatability, and reducing computation time. Various

AI-derived algorithms, for example, have been used to improve aortic aneurysm segmentation, allowing for a detailed assessment of the aneurysm's geometry and morphology.[4-8]

Machine learning has also been used to create fully automated pipelines for the detection and measurement of vascular calcifications in computed tomography (CT) images.[9, 10] Image segmentation and risk classification systems have been developed for patients with carotid artery stenosis.[11-13]

AI has promising applications in image segmentation, automation, data analysis from medical records, facilitating and improving data collection, and quantitative measures in large patient datasets. The risk to patients and the outcomes of the operation can be better assessed using a combination of these techniques. For example, several machine learning algorithms have been designed to assess the risk of aortic aneurysm development and rupture or to predict outcomes after surgical aneurysm repair.[14-19]

A recent study revealed significant cultural variations in the treatment of juxtarenal AAAs, with vascular surgeons recommending continuous monitoring, endovascular surgery, or open surgery for the same patient.[20] This underscores the critical need for new technologies to assist surgeons in determining the best treatment strategy. AI could potentially categorize patient status, better estimate the risk of pre- and post-operative complications, and advise surgeons on the most appropriate surgical method, enabling the formulation of multivariable scores that incorporate clinical, biological, and imaging parameters.

Radiomics is an emerging field in medical image analysis that focuses on extracting quantitative and qualitative information from diagnostic images, such as CT, MRI, and PET scans. Essentially, radiomics is based on the idea that medical images contain a vast array of information that can be extrapolated and analyzed to provide additional clinical insights beyond what is visible to the naked eye.

This approach involves the use of advanced algorithms to extract and analyze a wide variety of features from images, such as shape, texture, pixel intensity, and spatial relationships between tissues. These features are then statistically analyzed or processed using machine learning techniques to identify correlations with specific medical conditions, treatment responses, or prognostic outcomes.

Several decades ago, the term radiomics was introduced.[21] Radiomics refers to the analysis of medical images aimed at obtaining quantitative information from these images through appropriate mathematical methods and the use of computers, which is not detectable through simple visual observation by the operator.

Radiomics has the potential to improve diagnosis, prognosis, and the personalization of treatments through detailed analysis of medical images. It can also be used to identify predictive biomarkers of treatment response, monitor disease progression, and identify previously unrecognized disease subtypes. In summary, radiomics represents an important area of research that integrates computer science, engineering, statistics, and medicine to enhance the understanding and treatment of medical conditions.

Radiomic analysis offers an advanced approach to extracting quantitative and qualitative information from diagnostic images, allowing for a more in-depth assessment of patients with vascular conditions such as abdominal aortic aneurysms (AAA). By extracting radiomic features and performing advanced statistical analysis, radiomics can help identify significant correlations between aneurysm characteristics and crucial clinical outcomes, such as the risk of aneurysm rupture or disease progression.

This information can be used to personalize treatment plans, improve patient management, and identify new predictive biomarkers, providing important clinical benefits in vascular surgery practice.

A recent article by Wang et al.[22] describes the development of a radiomics model that uses machine learning techniques to predict the outcome of endovascular repair of an AAA. The proposed model could provide physicians with a predictive tool to guide treatment decisions and improve the planning of these procedures.

Another recent article[23] focuses on the use of radiomics of non-contrast computed tomography to detect endoleaks after AAA endovascular repair. The study demonstrated that radiomic analysis of non-contrast CT images can be effective in detecting endoleaks post-endovascular repair.

This approach showed promising sensitivity (88±10%) and specificity (78±5%) in detecting endoleaks, potentially offering a non-invasive and accurate method for postoperative monitoring of patients undergoing this procedure.

In summary, the results indicate that radiomic analysis of non-contrast CT images could be a useful technique for improving the clinical management of patients undergoing AAA endovascular repair, enabling early diagnosis and timely treatment of endoleaks.

Data from Social Media and Health Applications

Social media and wellness apps generate enormous volumes of data on patient behaviors and preferences. Although these data are often unstructured and less accurate compared to traditional sources, they can provide a detailed view of patients' daily living conditions, preferences, and experiences with the healthcare system. The growing use of these sources has generated vast amounts of clinical data, providing a basis for the application of AI and machine learning models. However, this proliferation also poses challenges in terms of management, integration, and analysis, requiring innovative approaches to extract maximum value in terms of usability from the collected data.

The Foundations of the SICVE Experimentation

The experimentation conducted by a small pool of AI experts, in collaboration with the Italian Society of Vascular Surgery (SICVE), represents an interesting example of how AI and machine learning can be harnessed to optimize the collection and analysis of specific clinical data (Figure 4.1.3).

This research is laying the groundwork for development in the following areas of intervention.

Data Collection

The aim is to develop a platform that collects and integrates clinical data from various sources, such as electronic health records, research registries, and monitoring devices, with the goal of creating one or more centralized and structured databases. The use of AI will allow for the automatic organization and analysis of these data, identifying patterns and correlations not always immediately recognizable by healthcare professionals.

Data Selection Criteria

The clinical data included in the immediate or near-term developments of the experimentation will encompass diagnostic test results, surgical records, vital signs, radiological images, and reports. Procedures will need to be designed to support the collection of both structured and unstructured data, enabling the integration of various formats.

Machine Learning Algorithms

The analysis of the collected data will be performed using machine learning algorithms, particularly classification and clustering models, to identify subgroups of patients with similar clinical characteristics. These algorithms can, to some extent, predict the outcome of certain surgical procedures based on pre-existing risk factors.

Conclusions

The investigation has highlighted the potential of AI technologies in vascular clinical practice, envisioning the effective integration and analysis of significant volumes of data. The synergy between digital experts and SICVE is crucial for understanding the specific needs of clinicians and adapting the analysis algorithms accordingly.

Methods of Clinical Data Analysis

Analyzing clinical data presents a complex challenge due to the heterogeneous and unstructured nature of the information. However, with the advent of advanced AI algorithms, innovative methods leveraging machine learning (ML) and deep learning (DL) have been developed. Let's explore some of these methods that are revolutionizing clinical research and practice.

Supervised Algorithms

Supervised algorithms are among the most used in the medical field. They rely on labeled data to "learn" to recognize specific patterns and predict clinical outcomes. Two of the most common approaches are:

FIGURE 4.1.3 ● The project in collaboration with SICVE aims to employ AI and machine learning to optimize the collection and analysis of specific clinical data.

- ***Classification*** This method categorizes patients into specific groups, such as those at high risk for postoperative complications. Models like Support Vector Machines (SVM) or Random Forests are often used to classify patients based on their clinical profiles.
- ***Regression*** Regression algorithms, such as logistic or linear regression, help predict continuous values. For example, linear regression can be used to estimate the length of hospital stay or predict the effectiveness of a drug.
- ***Unsupervised Algorithms*** Unsupervised algorithms are ideal for discovering hidden patterns in unlabeled clinical data. These methods include the following issues.
- ***Clustering*** Clustering groups patients with similar characteristics. Algorithms like K-means or hierarchical analysis can identify subgroups of patients with similar conditions, aiding clinicians in developing more personalized treatment strategies.
- ***Principal Component Analysis (PCA)*** PCA reduces the dimensionality of the data, simplifying the analysis and making it easier to identify significant variables.

Deep Learning (DL)

DL represents a recent but revolutionary development. DL models, such as Convolutional Neural Networks (CNN) and Recurrent Neural Networks (RNN), can process complex data like radiological images, signals from wearable devices, and even textual data from clinical reports. Convolutional Neural Networks (CNN): CNNs are particularly effective in image analysis. In

medicine, they are used to identify lesions, tumors, and other anomalies in radiographic or ultrasound images.

Recurrent Neural Networks (RNN): RNNs are ideal for analyzing sequential data, such as time series of vital parameters collected from monitoring devices.

Reinforcement Learning

Reinforcement learning is based on a reward model to teach algorithms to make optimal decisions. In the clinical field, it is used to optimize patient management, for example, by suggesting the best sequence of diagnostic tests or identifying the ideal treatment.

All the analysis methods mentioned have enabled the translation of large volumes of clinical data into useful knowledge, thereby improving patient diagnosis and management. Their continuous evolution will have a significant impact on medical practice.

AI is transforming the way clinical data is managed, leading to significant changes in diagnosis, treatment, and patient management. These innovations apply to various areas, offering increasingly promising results.

1. Early and predictive diagnosis
   - AI algorithms: AI algorithms are used to identify hidden patterns in clinical data that may suggest the presence of diseases in their early stages. For example, in cardiovascular diseases, AI can detect anomalies in electrocardiographic data or diagnostic images that might go unnoticed during a preliminary examination, facilitating timely diagnosis and preventive treatment.
   - Medical imaging: analysis of images through convolutional neural networks (CNN) allows for more precise identification of tumors and lesions. This technology is employed in the diagnosis of breast cancer, lung diseases, and other pathological conditions.
   - Natural Language Processing (NLP): analyzing clinical reports through NLP helps extract relevant information from unstructured documents, improving the quality of diagnostics.
2. Optimization of treatment plans
   - Personalized therapies: personalization of therapies is another important AI application. Machine learning can suggest the best treatment plan based on historical data from patients with similar characteristics.
   - Precision medicine: by integrating genomic, clinical, and wearable device information, AI can help identify the ideal treatment for each patient, reducing the risk of side effects and improving outcomes.
   - Therapy monitoring: AI algorithms can monitor patient adherence to prescribed therapies, providing real-time feedback and alerting clinicians in case of significant deviations.
3. Management of complications
   - Predictive algorithms: predictive algorithms can anticipate postoperative complications or adverse effects of therapies, allowing physicians to intervene proactively.
   - Intensive Care Units: in ICU settings, predictive models help monitor patients more efficiently, forecasting adverse events such as sepsis or multi-organ failure.
   - Adverse drug reactions: based on historical data and progressive learning, AI can identify drug combinations that may cause adverse reactions and suggest more reliable alternatives
4. Support for healthcare professionals
   - Decision support: AI-based decision support tools can suggest plausible diagnoses and treatment protocols, helping doctors make informed decisions.
   - Automation of repetitive tasks: administrative processes and repetitive tasks, such as filling out reports, can be automated, freeing up time for medical staff.
5. Medical training and specialization
   - Clinical simulations: AI can also be used to enhance the training of doctors and specialists. Simulation of clinical scenarios through virtual reality (VR) and reinforcement learning algorithms can help medical trainees improve their skills.
   - Personalized feedback: AI can analyze the performance of doctors and provide them with customized feedback to improve their abilities.

These applications demonstrate how AI is revolutionizing medical practice, setting new standards of care, and potentially improving clinical outcomes. However, ongoing progress requires attention to the ethical, legal, and technical challenges accompanying these innovations.

Finally, AI could be used in medical training and teaching through the simulation of clinical circumstances. Virtual reality simulations, for example, have been developed and could be used to teach aspiring surgeons basic endovascular operations.[24, 25]

IMPACTS AND CHALLENGES IN ADOPTING ARTIFICIAL INTELLIGENCE IN MEDICINE

The adoption of AI in medicine can significantly impact clinical processes but is also accompanied by challenges that require effective solutions to ensure its responsible and safe use. Let's explore the main potential impacts and related challenges in detail.

Impacts on healthcare

Improvement in Quality of Care: AI offers the potential to improve the quality of care by identifying patterns in clinical data that enable more accurate diagnoses and treatments.

Predictive algorithms help personalize therapies, while decision support systems provide physicians with data-driven suggestions.

Operational efficiency

Automating administrative tasks and standardizing clinical processes save time and resources, allowing healthcare professionals to focus more on patient care. For example,

automating report management can significantly reduce transcription errors.

Accessibility of care

AI tools, such as mobile applications for early diagnoses and monitoring vital signs, increase accessibility to care, especially in remote areas or for underserved populations. Remote consultations are facilitated by the remote analysis of clinical data.

Continuous training

AI promotes continuous training for doctors by providing advanced simulations, personalized feedback, and learning tools based on machine learning. This contributes to creating a more culturally complete clinical workforce.

Challenges in adopting Artificial Intelligence

1. Data privacy and security
   The collection and analysis of large volumes of clinical data pose serious privacy and security issues. Ensuring that patient data is protected and used responsibly (e.g., anonymizing references in cluster statistical analyses) while complying with local and international regulations is essential.
2. Algorithm bias
   AI algorithms can reflect the inherent biases present during the training phases, leading to discrimination or inequalities in treatments. It is necessary to develop fair and transparent algorithms to avoid these issues.
3. Acceptance by clinical staff
   Healthcare professionals may be reluctant to trust AI-based systems. It is important to involve them in the development and implementation of these systems and in machine learning itself, ensuring they understand the functionality and opportunities offered to improve clinical practice.
4. Legal responsibility
   Determining legal responsibility for AI errors, especially in the medical field, is a significant challenge. Who is responsible in the event of incorrect diagnoses or inappropriate treatments suggested by an AI system? Legislation and common sense suggest that the human clinical supervisor is responsible, but this consideration needs to be well formalized to build a culture and practice to be disseminated in medical schools and training programs.
5. Integration into existing systems
   Integrating AI systems into current healthcare infrastructures can be practically complex. Electronic health records (EHRs) are often not compatible between different healthcare units and medical centers or across different regions of the country, posing obstacles to unifying data from various sources. This issue has repeatedly surfaced in the definitions of standard clinical tracks undertaken by the Ministry of Health and the National Institute of Health, with the support of university research centers.

Addressing all these challenges is crucial to fully harness the potential of AI in medicine. Collaboration between healthcare specialists, technology developers, and research institutions will be essential to overcome these barriers.

CONCLUSIONS AND FUTURE PERSPECTIVES

Interoperability and Integration

Creating interoperable systems that allow the collection and analysis of data from various sources will be crucial. This will enable AI algorithms to have a more comprehensive view of the global clinical picture on national and international scales.

Multidisciplinary collaboration

Developing effective AI solutions will require close collaboration between doctors, computer engineers, legal experts, and patients to ensure a holistic approach.

Regulation and standardization

Establishing guidelines and ethical standards for the responsible use of AI in medicine will be necessary, ensuring that data is always managed securely and that algorithms are fair.

Continuous algorithms evolution

Algorithms need to be continuously updated and improved with new data and feedback, ensuring they reflect changes in clinical practices and population characteristics.

Education and awareness

It is important to educate healthcare professionals about the advantages and limitations of AI, involving them in decision-making processes and making them active partners in developing these solutions.

AI is redefining clinical data research and collection, paving the way for personalized medicine and patient management. Although there are obstacles to overcome, collaborative efforts among scientists, clinicians, and institutions will be essential to create an ethical and innovative technological ecosystem that revolutionizes healthcare for the future.

In conclusion, the use of artificial intelligence (AI), machine learning (ML), and sensor technology is revolutionizing the collection and analysis of clinical data in vascular surgery. These technologies offer unprecedented opportunities to improve diagnostic precision, predict risks and complications, and monitor patients in real time. However, it is crucial to address the challenges related to data integration and security to maximize the benefits of these technologies. With further developments and investments in research, AI, ML, and sensors are expected to play an increasingly important role in vascular surgery, leading to tangible improvements in the quality of care and clinical outcomes for patients.

Nevertheless, it is important to note that while AI

holds great promise in vascular surgery, it is still in the development and implementation stages. It is essential to conduct further clinical research and validate the effectiveness and safety of these technologies before their widespread adoption in clinical practice.

REFERENCES

1. Hughes A, Shandhi MMH, Master H, et al. Wearable Devices in Cardiovascular Medicine. Circ Res 2023;132:652-70.
2. Kario K. Management of Hypertension in the Digital Era: Small Wearable Monitoring Devices for Remote Blood Pressure Monitoring. Hypertension 2020;76:640-50.
3. Sola J, Vybornova A, Fallet S, et al. Validation of the optical Aktiia bracelet in different body positions for the persistent monitoring of blood pressure. Sci Rep 2021;11:20644.
4. Lareyre F, Adam C, Carrier M, et al. A fully automated pipeline for mining abdominal aortic aneurysm using image segmentation. Sci Rep 2019;9:13750.
5. Maiora J, Papakostas GA, Kaburlasos VG, et al. A Proposal of Texture Features for Interactive CTA Segmentation by Active Learning. IOS Press, Amsterdam, Netherlands; 2023.
6. Joldes GR, Miller K, Wittek A, et al. BioPARR: a software system for estimating the rupture potential index for abdominal aortic aneurysms. Sci Rep 2017;7:4641.
7. Zhuge F, Rubin GD, Sun S, et al. An abdominal aortic aneurysm segmentation method: level set with region and statistical information. Med Phys 2006;33:1440-53.
8. Subasic M, Loncaric S, Sorantin E. 3-D Image Analysis of Abdominal Aortic Aneurysm . IOS Press, Amsterdam, Netherlands; 2003.
9. Graffy PM, Liu J, O'Connor S, et al. Automated segmentation and quantification of aortic calcification at abdominal CT: application of a deep learning-based algorithm to a longitudinal screening cohort. AbdomRadiol (NY) 2019;44:2921-8.
10. Kurugol S, Come CE, Diaz AA, et al. Automated quantitative 3D analysis of aorta size, morphology, and mural calcification distributions. Med Phys 2015;42:5467-78.
11. Gao S, van ,t Klooster R, Kitslaar PH, et al. Learning-based automated segmentation of the carotid artery vessel wall in dual-sequence MRI using subdivision surface fitting. Med Phys 2017;44:5244-59.
12. Kumar PK, Araki T, Rajan J, et al. State-of-the-art review on automated lumen and adventitial border delineation and its measurements in carotid ultrasound. Comput Methods Programs Biomed 2018;163:155-68.
13. Kolias VD, Stamou G, Golemati S, et al. A semantically-aided architecture for a web-based monitoring system for carotid atherosclerosis. Annu Int Conf IEEE Eng Med Biol Soc 2015;2015:1373-6.
14. García G, Maiora J, Tapia A, et al. Evaluation of texture for classification of abdominal aortic aneurysm after endovascular repair. J Digit Imaging 2012;25:369-76.
15. Karthikesalingam A, Attallah O, Ma X, et al. An artificial neural network stratifies the risks of reintervention and mortality after endovascular aneurysm repair; a retrospective observational study. PLoSOne 2015, m10:e0129024.10.1371/journal.pone.0129024
16. Monsalve-Torra A, Ruiz-Fernandez D, Marin-Alonso O, et al. Using machine learning methods for predicting inhospital mortality in patients undergoing open repair of abdominal aortic aneurysm. J Biomed Inform 2016;62:195-201.
17. Turton EP, Scott DJ, Delbridge M, et al. Ruptured abdominal aortic aneurysm: a novel method of outcome prediction using neural network technology. Eur J VascEndovasc Surg 2000;19:184-9.
18. Wise ES, Hocking KM, Brophy CM. Prediction of in-hospital mortality after ruptured abdominal aortic aneurysm repair using an artificial neural network. J Vasc Surg 2015;62:8-15.
19. Lee R, Jarchi D, Perera R, et al. Applied machine learning for the prediction of growth of abdominal aortic aneurysm in humans. EJVES Short Rep 2018;39:24-8.
20. Atkins E, Mughal NA, Ambler GK, et al. Is management of complex abdominal aortic aneurysms consistent? A questionnaire-based survey. J Cardiovasc Surg (Torino) 2020;61:73-7.
21. Lambin P, Rios-Velazquez E, Leijenaar R. Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer 1990;48:441–6.
22. Wang Y, Zhou M, Ding Y, et al. A radiomics model for predicting the outcome of endovascular abdominal aortic aneurysm repair based on machine learning. Vascular 2023;31:654-63.
23. Hu G, Ding N, Wang Z, et al. Unenhanced computed tomography radiomics help detect endoleaks after endovascular repair of abdominal aortic aneurysm. EurRadiol 2024;34:1647-58.
24. Aeckersberg G, Gkremoutis A, Schmitz-Rixen T, et al. The relevance of low-fidelity virtual reality simulators compared with other learning methods in basic endovascular skills training. J Vasc Surg 2019;69:227-35.
25. Winkler-Schwartz A, Bissonnette V, Mirchi N, et al. Artificial intelligence in medical education: best practices using machine learning to assess surgical expertise in virtual reality simulation. J Surg Educ 2019;76:1681-90.

4.2 WHAT IS BIG DATA IN VASCULAR SURGERY AND HOW MAY BE USED WITH AI: WILL RANDOMIZED CONTROLLED TRIALS BE REPLACED?

Jean-Baptiste Ricco, Farid Guetarni, Aurélien Hostalrich

INTRODUCTION

Since its introduction at the Dartmouth College Conference in 1956, tremendous advances in artificial intelligence (AI) have been made, leading to applications using big data (BD) in numerous fields from industry to finance, education, media, and telecommunications.

In health care, the constant increase of computer data led professionals, hospitals and states to take into consideration the management of BD requiring AI and sophisticated technical platforms to run the information systems (IS) of hospitals together with extra-hospital data from connected devices.

AI in healthcare is needed as physician's decisions are becoming more evidence-based, relying on guidelines and large databases as opposed to solely schooling and expert opinion. Moreover, considering the rising costs of health care worldwide, current incentives are also changing. States and private insurance companies are switching from fee for service to plans that prioritize patient outcomes. The rise of AI and BD is also answering that need.

Together with data analysts, clinicians should now take over the development of AI and BD. If they fail to do so, it is likely they will be quickly overwhelmed by high performance proprietary systems from the commercial world, such as Google and Facebook. However, prerequisites are essential to make this digital transition.

Convergence of data requires collecting them from multiple heterogeneous hospital databases and making the necessary modifications to direct the data flows into a single BD warehouse. Subsequently, it is necessary to clean and apply the correct algorithm for AI with the help of data scientists (Figure 4.2.1).

ARTIFICIAL INTELLIGENCE, BIG DATA AND MACHINE LEARNING

These new professions, at the interface of algorithm coding and statistical analysis, well beyond the scope of current biostatistical competencies, will lead to a major change at the very heart of the medical profession. In Europe, experience with BD healthcare is being built in pilot university hospitals, with networks between several institutions to analyze millions of data. In this context, feasibility studies involving the construction of cohorts leading to multicenter studies are the first step in the use of AI and BD.

These steps became possible thanks to the intro-

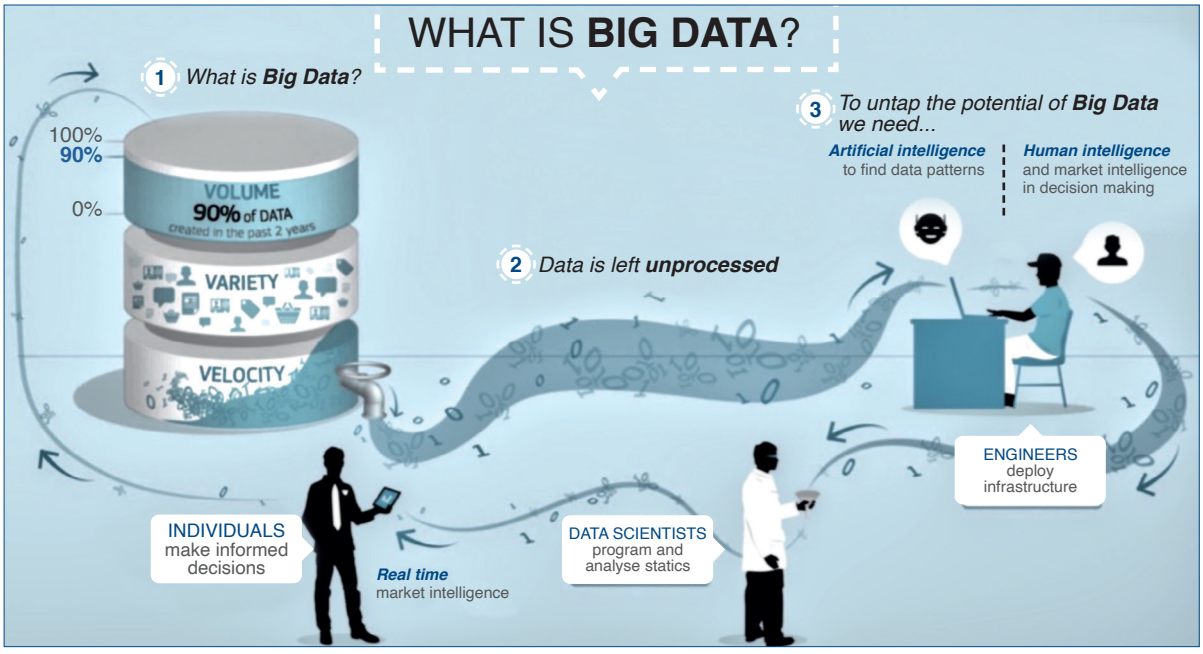


FIGURE 4.2.1 ● What is Big Data? Using big data requires not only artificial intelligence, but also people. 1) Convergence of data requires collecting them from multiple heterogeneous databases to direct the data flows into a single Big Data warehouse. 2) At this point, data is left unprocessed. 3) Engineers deploy the infrastructure, clean the data and make the data readable by an analysis tool (AI) with the help of data scientists. from the European Commission on Research and Innovation.

duction of AI and machine learning. AI is the ability of a machine to make an autonomous decision based on data collected with a self-learning ability, in repetitive data processing and adaptation to new data evolving over time. In machine learning, a model learns from examples rather than being programmed with rules. A key difference between human learning and machine learning is that humans can learn to make general associations from small amounts of data. For example, a child does not need many examples of a cat to differentiate it from a dog. Machines require many more examples than humans to learn the same task.

In this context, AI for precise predictions about the distant future is sometimes risky, and definitely inappropriate. As an example, the rise and fall of "Google Flu" showed us that forecasting an annual event based on one year's data runs into time series problems. The apparent solution is to pile on greater varieties of data, including social, demographic, genomic, and mobile sensor records to a patient's history and web browsing logs.

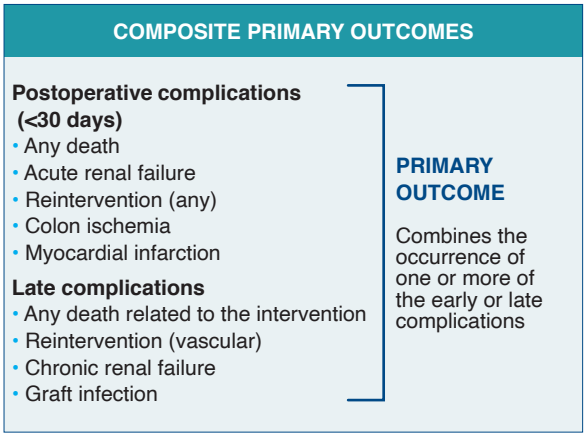


FIGURE 4.2.2 ● Composite primary outcomes of the study. The composite primary outcomes combined the occurrence of one or more early or late complications to search for risk factors. This list was elaborated before starting the analysis of data.

THE MAGIC OF BIG DATA AND RELATED RISKS

By analyzing BD, AI is constantly learning and introduces the concept of predictive medicine, that has already been tested and appreciated in some specific areas, such as medical imaging, cancer care, and dermatology. AI learning may allow to build diagnostic and therapeutic programs, individualized to each patient thanks to the large analysis of his or her clinical, biological, and even genetic characteristics.

The management of BD may result in a useful repository of patients advanced clinical data, provided that hospitals will be able to make a true "revolution", by introducing new professions and pedagogical figures aimed to guide its use into the clinical environment. The interaction with medical practitioners is a key-point to help engineers to avoid irrelevant data collection, misleading analyses, and possible confounding indications.

USE OF BIG DATA AND MACHINE LEARNING IN VASCULAR SURGERY

In our specific field, our group evaluated the use of BD analysis and its possible advantages in clinical practice, by comparing the usual methodology for clinical research using electronic health records (EHRs) *versus* novel BD queries to search for factors influencing the outcome of open surgical repair of abdominal aortic aneurysms (AAA). The composite primary outcome was defined as the occurrence of one or more early or late complications (Figure 4.2.2).

Two research teams were involved in the analysis. Each team was blinded to the findings of the other team. In team A (traditional), three vascular surgeons analyzed a panel of patients using codes corresponding to open surgical repair of infrarenal AAA through EHRs (N.=722) with appropriate univariate and multivariate analyses. In team B (BD), two data scientists and one vascular surgeon extracted from a "massive data" environment of 10 male patients, a sample based on a semantic detection for open surgery of infrarenal AAA. This pilot study was integrated as part of a collaboration between different French University Hospitals using a common information technology system. The way Team B (BD) worked is shown in Figure 4.2.3. The clinician wrote a request with all criteria corresponding to AAA open surgical repair. A first DataMart was produced by the scientists and revised by the clinicians, because of many aberrant findings to end up with a 'basket' corresponding to the criteria pertinent to the study. Results of team A (traditional method) are shown in Figure 4.2.4, and results of team B (BD) are shown in Figure 4.2.5. Team A found six predictors for early and late complications and team B (BD) only 5 same predictors. "Level of aortic clamping" could not be analyzed through neural networks by team B.

Time and cost for team A and B were also analyzed. Time spent was 362 hours for team A and 68 hours for team B (P=0.01). Total cost was 300.000 € for team A and 90.000 € for team B. Cost for Big Data does include the training of the data analysts but not the quarterly updates of the Big Data system.

This study highlighted that extreme caution is needed in the manipulation of a cluster of BD. The role of a bedside physician is essential to avoid that "nonsense" input data might produce misleading output data. Other limitations of BD use are heterogeneity (semantic search with AI), ethical and legal constraints (EU regulation), and the need for validation by large clinical studies. Despite these limitations, it seems appropriate to use BD to rapidly assess a surgical practice and particularly innovative techniques, avoiding costs and delays associated with randomized controlled trials. Yet, it's still not the time for "big data" approaches to overturn the results of carefully conducted randomized controlled trials.

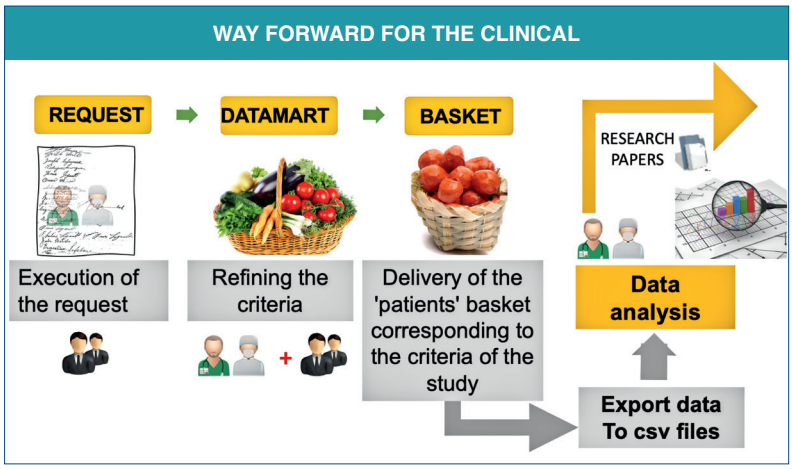


FIGURE 4.2.3 ● The way Team B (BD) works. This figure shows the different steps of data analysis when using BD and the close collaboration between clinician and scientists.

RESULTS: Traditional Method

Team A (CLASSIC) found six predictors for early and late complications

N=722	ID	VARIABLES	ODDS RATIO	*p* value
Logistic Regression	1	Chronic Kidney Disease (CKD)	2.70 [1.40-5.22]	.01
	2	Level of Aortic Clamping	1.47 [1.05-3.21]	.04
	3	Duration of Aortic Clamping	3.20 [1.30-4.54]	.01
	4	Pre-existing Myocardial Infarction	1.05 [1.01-1.90]	.01
		VARIABLES	**HAZARD RATIO**	***p* value**
Cox Proportional Hazards	5	Diabetes	4.90 [1.34-10.25]	.01
	6	Chronic Kidney Disease (CKD)	1.93 [1.19-3.20]	.01

FIGURE 4.2.4 ● Results of team A (traditional method). Team A found six predictors for early and late complications.

RESULTS: Using Big Data

Team B (BIG DATA) identified the following predictors (1,3,4,5,6)

N=745	ID	VARIABLES	ODDS RATIO	*p* value
Logistic Regression	1	Chronic Kidney Disease (CKD)	2.95 [1.30-5.00]	.01
	2	Level of Aortic Clamping	?	?
	3	Duration of Aortic Clamping	3.70 [1.45-5.54]	.01
	4	Pre-existing Myocardial Infarction	1.45 [1.21-2.90]	.01
		VARIABLES	**HAZARD RATIO**	***p* value**
Cox Proportional Hazards	5	Diabetes	5.80 [1.28-9.35]	.01
	6	Chronic Kidney Disease (CKD)	1.78 [1.02-2.70]	.01

The level of aortic clamping could not be analyzed through neural networks

FIGURE 4.2.5 ● Results of team B (BD). Team B found only 5 same predictors. The level of aortic clamping could not be analyzed through neural networks by team B.

BIG DATA IN EUROPE

In Europe, the speed of the implementation of these systems is not happening as quickly as expected. The necessary economic investments and the paradigm shift has taken time, especially as public authorities have also had to consider the protection of patient data within the European Union's General Data Protection Regulation, which came into effect in May 2018. Health systems have developed sophisticated mechanisms to ensure the safe delivery of pharmaceutical agents to patients. The wide applicability of AI and BD will require a similarly thorough regulatory oversights.

Hospitals in Paris are trialing BD and AI with machine learning systems to forecast admission rates, aiming

to obtain a more efficient employment of resources, and improve patient outcomes. For this purpose, in 4 hospitals taking part of the Assistance Publique-Hôpitaux de Paris (AP-HP), data from internal and external sources, including 10-year values of hospital admissions records and several external data sets such as weather, public holidays, and flu patterns, have been crunched to come up with day and hour-level predictions of the number of patients expected through the doors. AI was employed to determine which algorithms provide the best indicator of future trends when they are fed data from the past. The system, built upon an open-source platform, resulted in a web browser based interface designed for doctors, nurses, and hospital administration not trained in data science, to forecast visit and admission rates for the next 15 days. Extra staff members were drafted in when high numbers of visitors were expected, leading to reduce waiting times for patients and a better quality of care.[1]

With the cost of providing health care increasing at more than the rate of gross domestic product in every developed country, smart, intelligent systems like those of the AP-HP are likely to play an important part in the future of healthcare.

By more accurately predicting the demand for services, waste can be reduced and insuring can become more efficient. Following oncology with genetic profiling now being used to identify patients for whom tailored chemotherapy directed toward personal cancer mutation is used,**2** several applications derived from AI are to be expected in vascular surgery with the management of registries including clinical, biological, and imaging data.

ETHICAL AND LEGAL ASPECTS OF ARTIFICIAL INTELLIGENCE IN THE HEALTHCARE SYSTEM

The use of intelligent systems may complicate liability issues for hospitals in several ways, although this is a reason for implementation rather than a reason to reject this innovation.

First, in the case of adverse events for patients, the information recorded by the system may be sought by the plaintiffs in bringing their claims against healthcare workers or the hospital. To speak in general terms, if a hospital system is able to explicitly destroy video recordings from cases involving medical injuries, this might constitute "spoliation" of evidence, which in some states might not only be held against the hospital system in court, but subject it to liability. By contrast, if data collected by AI-powered systems are dealt using appropriate document retention/destruction algorithms, and retained for a reasonable time, the hospital will likely be on safer ground.

Second example, when AI might detect repeated alerts signals regarding a specific employee or a care-team, if this critical issue is not correctly reported and subsequently managed, the hospital may be vulnerable to a claim of liability for failing to act. Again, planning is essential. Before the first recording is taken, the hospital should carefully develop updated plans considering how it will respond if various problems are uncovered. Ideally, this can be done in a cooperative way with healthcare personnel, but the key is to be transparent with preventive explanations about what is planned.

In the future, it is likely that new AI-powered tools will be widely used in hospitals to improve patients' care and overall efficiency of the medical system. Nonetheless, it is essential to consider the ethical and legal implications of such technology, and the appropriate frameworks for implementation - as soon as possible.

BIG DATA IN VASCULAR SURGERY: NEW AREAS OF INTEREST

Ross *et al.*[3] built several models to identify peripheral arterial disease (PAD) that frequently goes undiagnosed.[4] They compared their models to standard logistic regression ones, and showed that AI was able to produce more accurate predictive algorithms, thought either to identify patients with PAD, and to predict mortality. As a matter of fact, PAD population is still currently missing strong risk prediction models. For example, Ross *et al.*[3] used a variety of patient data, including genomic, imaging, and socio-economic variables not obtainable within the usual clinical research pathway to identify patients at risk.

As shown in the AP-HP experience, we will soon be able to provide real time predictive analysis for patient care in large data sets, and to extract more granular information from the electronic health records with natural language processing techniques.[5]

In vascular surgery, imaging is a key step in the care provided to patients, and several AI-powered methods have been applied to improve aortic aneurysm segmentation, allow precise characterization of aneurysm geometry, pre-operative modelling for endograft insertion, calculation of expected risk of aortic aneurysm growth, and outcome prediction after surgical repair.[6-8]

Programs have also been developed for image segmentation, and risk stratification in patients with carotid artery stenosis.[9] Finally, AI has also been used to improve simulation quality for educational activities, mainly practical simulation-based training in endovascular surgery.[10]

ARTIFICIAL INTELLIGENCE AND BIG DATA FOR SURGICAL EDUCATION

With technological progress, university students and Vascular Surgery residents have access to large amounts of data, sometimes excessive, and can be confounded by an overload of information. A challenge for tomorrow's medical education is to help residents to organize and use properly selected information, throughout the course of their studies. With the use of BD and machine learning, AI can help to better organize information content and literature search. AI also offers the opportunity to develop new teaching methods, and highly support a qualified training, such as the use of tutoring systems, virtual

facilitators, robots, or virtual-reality simulators for complex endovascular and open vascular procedures. It can also be used to assess surgical expertise in virtual reality simulated environments. AI has been used to assess surgical skills during vascular procedures, and automatically rate the trainee skills during a suturing task. In the future, it could help to identify specific patterns predicting technical success, that may help vascular surgeons to optimize outcomes.

Indeed, BD analytics and AI have being already used to drive decisions in human professions. Although scientists must set the algorithms up, once in place, machine learning will progressively run independently from human intervention. This may make life safer and will probably remove much undesirable *tedium*, but will definitely expose us to new and important dangers. For the foreseeable future in vascular surgery, it will remain critical for clinicians to be deeply engaged in the process, carefully supervising and maintaining a rigorous science-guided and ethically acceptable medical care. What can be said with reasonable certainty, is that AI and Big Data revolution will change vascular science over the next decades - in both predictable and unpredictable ways.

CONCLUSIONS

Current development of AI - together with BD analysis - is a major opportunity for vascular surgeons as part of the whole medical community, since these techniques have the potential to significantly improve patient care, evidence-based medicine, education, and training. AI has raised promises but, on the downside, has created hype derived from fantasy. There remain many challenges to be still discovered, under the algorithm black-box. The involvement of vascular surgeons in these technological changes is therefore of utmost importance, to guide scientific research and industry projects, to help developing relevant applications, and to guarantee a safe and tailored use in clinical practice.

REFERENCES

1. The Datapine blog. https://www.datapine.com/blog/big-data-examples-in-healthcare, pages 1-10, 2018.
2. Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol 2013;3:1803-5.
3. Ross EG, Shah NH, Dalman RL, *et al.* The use of machine learning for the identification of peripheral artery disease and future mortality risk. J Vasc Surg 2016;64:1515-22.
4. Hirsch AT, Criqui MH, Treat-Jacobson D, *et al.* Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317-24.
5. Leeper NJ, Bauer-Mehren A, Iyer SV, *et al.* Practice-based evidence: profiling the safety of cilostazol by text-mining of clinical notes. PLoS One 2013;8:e63499.
6. Zhuge F, Rubin G, Sun S, *et al.* An abdominal aortic aneurysm segmentation method: level set with region and statistical information. Med Phys 2006;33:1440-53.
7. Acosta Santamaría VA, Daniel G, Perrin D, *et al.* Model reduction methodology for computational simulations of endovascular repair. Comput Methods Biomech Biomed Engin 2018;2:139-48.
8. Karthikesalingam A, Attallah O, Ma X, *et al.* An Artificial Neural Network Stratifies the Risks of Reintervention and Mortality after Endovascular Aneurysm Repair; a Retrospective Observational study. PLoS One 2015;10:e0129024.
9. Gao S, van ,t Klooster R, Kitslaar PH, *et al.* Learning-based automated segmentation of the carotid artery vessel wall in dual-sequence MRI using subdivision surface fitting. Med Phys 2017;44:5244-59.
10. Aeckersberg G, Gkremoutis A, Schmitz-Rixen T, *et al.* The relevance of low-fidelity virtual reality simulators compared with other learning methods in. basic endovascular skills training. J Vasc Surg 2019;69:227-35.

4.3 ENHANCING CLINICAL DECISION MAKING IN AAA DIAGNOSIS AND TREATMENT WITH AI: HOW CAN IT HELP WITH PREDICTION OF AAA GROWTH, ENDOLEAKS AND SPINAL CORD ISCHEMIA

Venkat Ayyalasomayajula, Stefan P.M. Smorenburg, Dieuwertje Alblas, Patryk Rygiel, Lotte Rijken, Kaj O. Kappe, Jelmer Wolterink, Kak Khee Yeung

INTRODUCTION

Aortas that are affected by disease can dilate, leading to an abdominal aortic aneurysm (AAA). The rupture of an AAA has fatal consequences. Patients above 60 years of age, with hypertension, peripheral atherosclerotic vascular disease, familial predisposition as well as certain genetic conditions (*e.g.* Marfan syndrome and Ehlers-Danlos syndrome) have a high risk of suffering AAA.[1] Currently, little is known about the pathophysiology of aneurysmal disease, limiting the ability to develop non-surgical treatments for the prevention and/or stabilization of aneurysms. Next to that, patients with AAA are at higher risk of developing further cardiovascular complications than the normal population.[2]

Currently, clinicians mostly rely on medical imaging techniques in determining optimal management and surgical treatment regimens for AAA and applying general cardiovascular risk management. However, it is difficult for experts to predict treatment success through imaging analysis alone because the progression of a disease is influenced by different factors, *e.g.*, smoking, genetic disorder, and age. Hence, it remains unknown which AAA patients will have cardiovascular events or in which patients the AAA will progress. There is a need for a better selection of patients to prevent AAA rupture and unnecessary surgery (for patients who will never rupture) and to provide personalized cardiovascular risk management. Moreover, to relieve patients' burden and to prevent complications even before surgery, providing personalized follow-up is necessary.

Artificial Intelligence (AI) is a concept in which a computer can replicate human cognition, enabling the execution of intricate tasks. The idea of AI and the corresponding scientific field have been around for decades, and different approaches have been explored. Machine learning (ML) is a subset of AI focusing on algorithms that learn patterns and make predictions from data without explicit programming. Machine learning algorithms play a crucial role in disease classification tasks. In vascular surgery, these tasks often include the identification and categorization of various vascular conditions based on medical imaging data, patient characteristics, and clinical parameters, thereby aiding in diagnosis.[3] Some commonly used algorithms in this domain include logistic regression, support vector machines (SVMs), and random forests, which are all powerful models that can unravel both linear and non-linear relations. Further, they handle high-dimensional data, making them suitable for classifying vascular diseases based on features extracted from medical images or patient data.

Most of the recent developments in AI have been driven by deep learning. Deep learning is a specialization within machine learning that involves artificial neural networks. These networks are an abstraction of biological networks, containing thousands or millions of weights that define the relation between inputs and outputs. By far the most common way to use these networks is through supervised learning. In supervised learning, the values of these weights are optimized during training, an iterative process in which samples and targets are shown to the model and an error is minimized. This requires datasets of input samples and desired outputs. Ideally, once a model has been trained this way, it is able to make predictions on new and unseen cases. Neural networks can have complex architectures, which allow them to learn hierarchical representations of data. Convolutional neural networks (CNNs) are a type of deep learning architecture commonly used for image analysis. A U-Net is an example of a CNN architecture for image-to-image translation tasks, *e.g.*, obtaining a segmentation for a medical image. By training AI methodologies using thousands of cases, the optimal combination (weighting) of different factors can be unraveled, leading to improved decision-making.[3–5]

In this chapter, we introduce and discuss AI methods for three challenges in AAA management. First, for image-based and multi-modal AAA growth prediction. This information is relevant, as high-quality estimates of growth rate in an individual patient could help optimize surveillance frequency. Second, automatic detection and localization of endoleaks during and after surgery. Endoleak detection can be challenging in completion digital subtraction angiography (DSA), with high inter-observer variability. AI could help alleviate this issue, to better determine the success of an intervention and the risk of reintervention. Third, for the pre-operative prediction of the risk of spinal cord ischemia (SCI) in patients undergoing repair of a thoracoabdominal aortic aneurysm (TAA). SCI has a major impact on the quality of life of patients, and proper pre-operative estimates of SCI risk could aid in clinical decision-making. Finally, we conclude with a discussion of the practical, legal, and ethical implications of AI in vascular surgery.

THE ROLE OF AI IN AAA GROWTH PREDICTION

Abdominal aortic aneurysm (AAA) growth depends on many patient-specific factors, *e.g.* AAA shape, presence

of intraluminal thrombus (ILT), hemodynamic quantities, internal wall mechanics and morphological parameters, but also smoking status, and BMI.[6] Uncovering the exact contributions of these parameters to AAA growth requires large-scale studies, which are challenging to conduct because of two main reasons.

1. ***Labor intensive data collection.*** Computation of morphological and hemodynamic parameters requires a 3D model of the patient's aortic vasculature. Extracting such vascular models is time-consuming and requires expert knowledge, limiting their use to small-scale studies.
1. ***Complex underlying process.*** The full set of parameters underlying AAA growth is unknown. This means that the process cannot fully be explained by parameters that we can extract clinically and from imaging. Moreover, the relation between these parameters and AAA growth is likely to be non-linear, and there might be interactions between parameters.

AI can aid in solving both problems. First, AI models exist that operate directly on image data, *e.g.* 3D computed tomography angiographies (CTAs), and acquire a 3D vascular model automatically, from which morphological and hemodynamic parameters can be extracted.[7-9] Second, AI models operating on these parameters may be used to learn their relationships and predict AAA growth. Besides their use in a research setting, these AI models could be used in a clinical setting to aid tailored clinical decision-making in AAA patient management.

AI-DRIVEN ACQUISITION OF 3D VASCULAR MODELS FROM IMAGE DATA

3D models of the AAA including lumen and thrombus together with surrounding vasculature contain a wealth of morphological patient-specific information. They can be acquired from the CTA by a process commonly referred to as *segmentation*: in each axial slice, the boundary of the lumen and thrombus are delineated (Figure 4.3.1A) which are combined into a 3D model (Figure 4.3.1B). Manual segmentation is laborious and requires expert knowledge, hence it is infeasible on large-scale datasets. Therefore, AI has been deployed to automatically segment 3D models of the aneurysm from 3D CTA's.[7-9] Accurate segmentation of the thrombus remains challenging, as its boundary is irregular and may be hard to distinguish in CTAs.[10] Nevertheless, these 3D vascular models can be used to extract morphological features, such as diameter and volume measurements, or to simulate blood flow and extract hemodynamic features.[11] Moreover, vascular models can be used in clinical practice to automatically measure stent graft sizes or to create a 3D printed version of the aneurysm that can be used to prepare surgical intervention in complex cases.

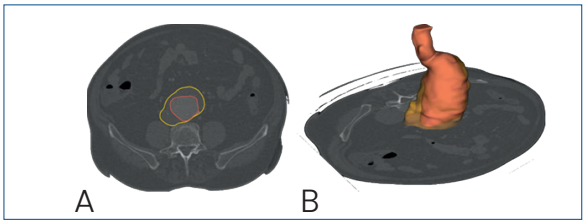


FIGURE 4.3.1 ● A) 2D axial slice with segmentation of lumen and intraluminal thrombus. B) 3D rendering of the infrarenal section of the AAA lumen and intraluminal thrombus.

AI-DRIVEN GROWTH PREDICTION

Computational models can be used to shed light on the contributions of patient-specific parameters towards AAA growth. These methods all lie on a spectrum between model-driven and data-driven approaches. Model-driven approaches try to describe the underlying AAA growth and remodeling process by a set of equations.[12] Although these methods rely on well-understood physics laws and are thus explainable, they may depend on parameters that cannot be measured in each patient. Alternatively, data-driven methods use an AI-model that operates on patient-specific data and tries to predict the AAA growth.[13-15] AI models require *training data*, which is used to calibrate the model's input to its output. Although data-driven approaches obviate the need for finding explicit relationships between the parameters, they are often seen as black boxes and therefore not as explainable as the model-driven approaches.

Aneurysm growth can be represented in many ways, involving various degrees of simplification. For example, class-based systems have been adapted, *e.g.* whether an AAA reaches the surgical decision threshold within four years or slow, medium, or quick increase of the maximal diameter.[14] Global quantification is also an option, *e.g.* the growth rate of the maximal diameter or lumen and thrombus volume.[16] Expressing AAA growth using a single class or quantity may be an oversimplification. Alternatively, AAA growth can be expressed as local deformations of the 3D vascular model[13, 15, 17] or a changing diameter profile.[18, 19] Figure 4.3.2 shows an evolving aneurysm on a continuous time scale. Here, AI was used to represent the local AAA growth patterns continuously, even though the data was only captured at a few irregularly spaced moments in time.

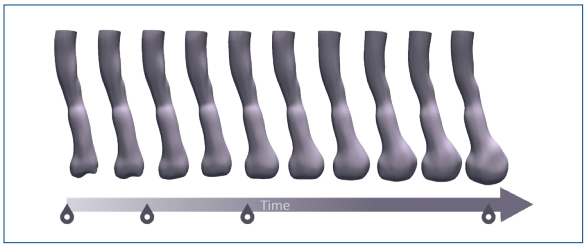


FIGURE 4.3.2 ● Treating AAA growth locally results in a continuous 3D representation of the evolving AAA lumen. Pointers indicate the moments in time CTA scans were made and thus a 3D model was available. Image adapted from Alblas *et al.*[17]

AI models predict AAA growth on a digital representation of the AAA patient, but the content and structure of such a digital twin can vary wildly. A patient can be represented in terms of a vector consisting of quantitative or class-based parameters, including: age, sex, smoking status, AAA diameter, thrombus volume, thrombus texture, peak wall shear stress, etc.[14, 20] Basic AI models can be trained to learn the effect on AAA growth of all these parameters based on a retrospectively constructed training dataset. However, these handcrafted patient-specific features leave out intricate details that could be crucial in aneurysmal development. As an alternative, more realism and detail can be included by using the AAA outer wall and local features, *e.g.* hemodynamic forces, as input data for AI models.[13, 15] Furthermore, some AI models can operate on the surface of 3D vascular models directly, allowing for a realistic representation of the patient with very limited loss of data.[21] Changing the structure of the input data requires careful adaptation of the AI model: AI models operating on tabular data cannot be used to operate on 3D shape data and vice-versa.

CHALLENGES

We have given an overview of the role of AI in AAA growth prediction. Although significant advances have been made, we identified some challenges before these methods can be applied in clinical settings.

- ***Acquisition of large-scale longitudinal data*** AI methods require large amounts of data to be trained on. To assess AAA progression, a large set of longitudinal patient data should be acquired, preferably from multiple centers across the world. The cohort of patients included in this dataset should be representative of the general AAA population, as there may be biases that may be unintentionally learned by the model. There are obvious patient characteristics that should be considered, such as sex, age, but also less obvious characteristics including hemodynamic features and presence of thrombus.
- ***Reliability*** In clinical practice, AI models will be used to predict the growth of a recently diagnosed aneurysm. With most current models, it is not possible to infer if the model is sure about its prediction. Quantification of the uncertainty in the predicted growth given a new patient is needed for the clinician to assess its clinical value.

INTRA-OPERATIVE ANALYSIS AND ENDOLEAKS

Since the introduction of endovascular aneurysm repair (EVAR) for treating abdominal aortic aneurysms (AAA), endoleaks have continued to persist in patients. Despite numerous attempts to mitigate the risks associated with endoleaks — AAA growth, loss of proximal and distal seal, and eventual AAA rupture — an effective clinical solution has yet to be established.[22] Endoleaks, if not managed properly, can significantly compromise stent graft seal by AAA growth and eventual aortic rupture, leading to life-threatening scenarios.

THE COMPLEXITY OF ENDOLEAK CLASSIFICATION

It is crucial to recognize that endoleaks can be benign or malignant. Typically, type Ia-Ic endoleaks, which revolve around the loss of the stent graft seal, and type IIIa-IIIc endoleaks, which revolve around device integrity should be treated aggressively. Type II endoleaks however can be benign and occur without AAA growth. Moreover, classifying the type of endoleak still presents a challenge in contemporary endovascular practices. Some type II endoleaks may eventually reveal themselves as type 1 or 3 endoleaks and type v endoleaks (endotension) may eventually be undetected endoleaks.[23, 24]

In fenestrated and branched EVAR, classifying endoleaks is complicated by the presence of multiple branches and/or fenestrations. A branch losing access over time to the renal or visceral artery results in a type Ic endoleak, a fabric tear or fracture might cause a type IIIb endoleak, or the detachment between a side branch and the main body might lead to a type IIIc endoleak. This complexity necessitates a robust diagnostic framework to ensure accurate classification and clinical management.[25]

Furthermore, the hemodynamics of endoleaks are poorly understood—both slow-flowing and fast-flowing endoleaks exist, along with various AAA intrasac pressures post-EVAR.[26, 27] Understanding these intrasac hemodynamics is crucial for predicting the risk of rupture and planning appropriate interventions. Correct classification of endoleak type is crucial for ensuring patients receive appropriate treatment. Misclassification of endoleaks can lead to incorrect treatment.

AI FOR ENDOLEAK DETECTION: A NEW FRONTIER IN ENDOLEAK MANAGEMENT

Current imaging modalities at most hospitals for detecting endoleaks consist of computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or duplex ultrasound (DUS). These modalities generally visualize major endoleaks quite accurately. However, these examinations result in static imaging of the patient, and assessment is performed by the radiologist finding large but also subtle endoleaks.

A new frontier in endoleak management is the detection using artificial intelligence techniques. Some reports have developed algorithms for endoleak detection utilizing CTA imaging.[28-30] By employing automatic anatomical segmentation of the aorta and its side branches, the entire arterial system can be visualized, allowing for the automatic classification of endoleaks. This approach eliminates the need for cumbersome visual inspections by physicians.

More specifically, the arterial tree can be detected

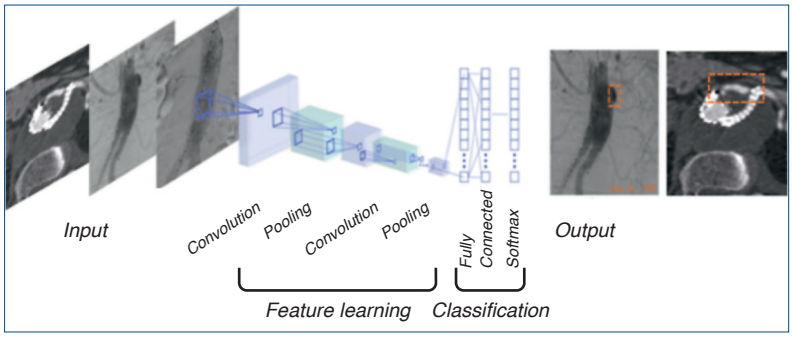


FIGURE 4.3.3 ● Example of an automatic endoleak detection pipeline with two modalities as input, CTA and DSA. After feature learning and classification, the endoleak can be detected, with a bounding box for instance, orange.

with central luminal lines and subsequently the central lumen line can be transformed into a straight multiplanar reconstruction (sMPR). By visualizing the aorta, side branches and EVAR stent as sMPR, endoleaks and other anomalies can be detected by developed algorithms.

The automation of imaging tasks, such as the segmentation of patient anatomy, calculation of aortic diameters, seal zone lengths, and stent graft apposition, can standardize and improve EVAR follow-up by identifying high- and low-risk patients.

This can be achieved through a pixel-by-pixel or voxel in-depth analysis. Every voxel in medical imaging contains information about a specific location in 3D, allowing for quantitative analysis. For instance, if the seal zone of the proximal aortic neck contains thrombus or calcification, this can be detected by the intensity value of the voxel at that specific location. All this information can be used as input for deep learning models, enabling automatic segmentation of structures and making the process fully automatic. An illustration of this workflow is shown in Figure 4.3.3.

The integration of artificial intelligence techniques and imaging modalities represents a significant advancement in understanding and implementing care for EVAR patients. AI can further refine these processes by predicting potential complications before they become clinically evident, thus offering a proactive approach to patient management.

SPINAL CORD ISCHEMIA

Spinal cord ischemia (SCI), leading to paraparesis or paraplegia, is one of the most feared and devastating complications for patients and physicians after endovascular aortic repair of thoracoabdominal aortic aneurysms (TAA). Recent studies have shown SCI rates (including all severities) varying between 7% and 18% after endovascular repair of TAA, though the incidence is hugely impacted by the extent of disease and treatment strategy.[31-33] Presentation of SCI symptoms typically occur immediately postoperatively, but late onset of SCI symptoms can also occur.[31] About half of the patients have resolution of symptoms over time, while the other half of the patients have permanent SCI.[32, 33] The impact of SCI on the quality of life of patients is large, with a significantly worse life expectancy.

Over the years, improvements in perioperative management of TAA patients treated with endovascular aortic repair have reduced the incidence of SCI. Dias-Neto *et al.*, demonstrated a reduction of over 30% SCI in patients with multi-stage treatment compared to single-stage treatment.[32] Implementation of a institutional bundled protocol for SCI risk demonstrated a reduction of the overall SCI rate from 13% to 3%, while the reduction was even more for high-risk patients, from 19% to 4% after protocol implementation.[34]

Amongst many others, these mentioned strategies have improved outcomes for patients and multiple risk analysis studies have identified risk factors for SCI.[31, 35, 36] However, the multifactorial etiology of SCI is yet to be fully understood and individual evaluation of all risk factors in prospective randomized trials is unfeasible. Therefore, the optimal weighting of the currently known risk factors, while considering the heterogeneity of the patient's disease and condition, remains unknown, making accurate stratification of high and low risk patients a challenge for physicians.

Artificial intelligence can aid in the next phase of individual patient-tailored risk prediction of SCI. Artificial intelligence models can analyze large amounts of data to identify patterns for the prediction of outcomes in individual patients. The weights of individual input parameters to the model are optimized for the prediction of the outcome. Li, *et al.* demonstrated the capability of predicting major adverse events after open and endovascular abdominal aortic aneurysm repair based on large datasets.[37, 38] Similar methods could be applied for the prediction of SCI after endovascular aortic repair.

The key challenge to the application of artificial intelligence for the prediction of SCI after endovascular aortic repair is the availability of data. The rarity of the complication makes the availability of data at individual centers scarce, opting for extensive collaboration between centers to establish large datasets required for training of artificial intelligence models. A new challenge that arises with the collaboration with multiple centers is the heterogeneous databases with missing data as result. To overcome these challenges, prospective registry-based data collection should be considered.

Given the homogeneous data collection in a multicenter collaboration, artificial intelligence can be utilized in various ways for the prediction of SCI. Machine

learning models, a subcategory of artificial intelligence, can be used to predict outcomes based on patient and procedure-related factors, as demonstrated by Li, *et al.*[37, 38] Another aspect in which artificial intelligence can be used is image analysis. Most risk analysis studies in the literature focus on patient- and procedure-related risk factors.[31, 32, 36] Preoperative imaging has not been investigated extensively for the prediction of SCI, due to the high workload of analyzing and extracting patient specific features. However, information extracted from the preoperative CTA such as intra-aortic thrombus characteristics, psoas muscle area and a high number of visible segmental arteries have shown to be predictors of SCI.[39] Artificial intelligence, and in particular deep learning models, have the capability to automatically analyze and extract similar patient specific characteristics from preoperative imaging with a minimal burden on the physician. The automatic analysis of imaging enables the large-scale inclusion of imaging-related risk factors for the prediction of SCI.

Multimodal models can enhance the prediction of SCI after endovascular aortic repair. Within these multimodal models, patient-, procedure- and imaging-related risk factors can be optimally weighted and combined for the patient-tailored prediction of SCI. Better preoperative risk prediction, and thus stratification of high and low risk patients, can aid the physician in optimizing the treatment strategy for the individual patient and benefit the patient by lowering the risk of SCI.

MULTI-MODAL DATA IN PERSONALIZED MEDICINE

In healthcare, multi-modality indicates the presence of different types of data to be used as input to the AI model. Even though AI is frequently leveraged to tackle problems in healthcare, its use has been focused on single-modal data, as seen above. However, in personalized medicine, integrating multi-modal data is emerging as a transformative tool to enhance decision-making and improve patient outcomes.[40] Various modalities of data are useful in developing AI tools for cardiovascular diseases. These include but are not limited to electronic health records (EHR), medical imaging (*e.g.*, CT, MRI, US, etc), multi-omics data (proteomics, transcriptomics, lipidomics, genomics, and metabolomics), and wearable device data (Figure 4.3.4). This heterogeneity poses several problems in AI to use data from different sources to build accurate models. As such, dealing with heterogeneous data requires careful processing to put the data into the form required for a single AI model.[41] As the data is processed, it is transformed into meaningful information through techniques such as structuring EHRs, feature extraction from medical imaging, polygenic risk score modeling of multi-omics data, and analysis of wearable device data.

KEY ASPECT OF MULTI-MODAL AI: DATA FUSION

The practice of consolidating data from multiple modalities is called data fusion.[43] In data fusion, given the infancy of the field, there is no consensus on how best to combine different data, especially since there are three different techniques.[44] They are:

- early fusion: the simplest form of data fusion in which disparate data sources are merged into a single feature vector before being used by a single machine learning algorithm: Linear models such Linear Regression, Logistic Regression, Stochastic Regression, Support Vector Machines (SVMs), etc.; Tree based models such as Decision trees, Random Forests, etc.; or Neural

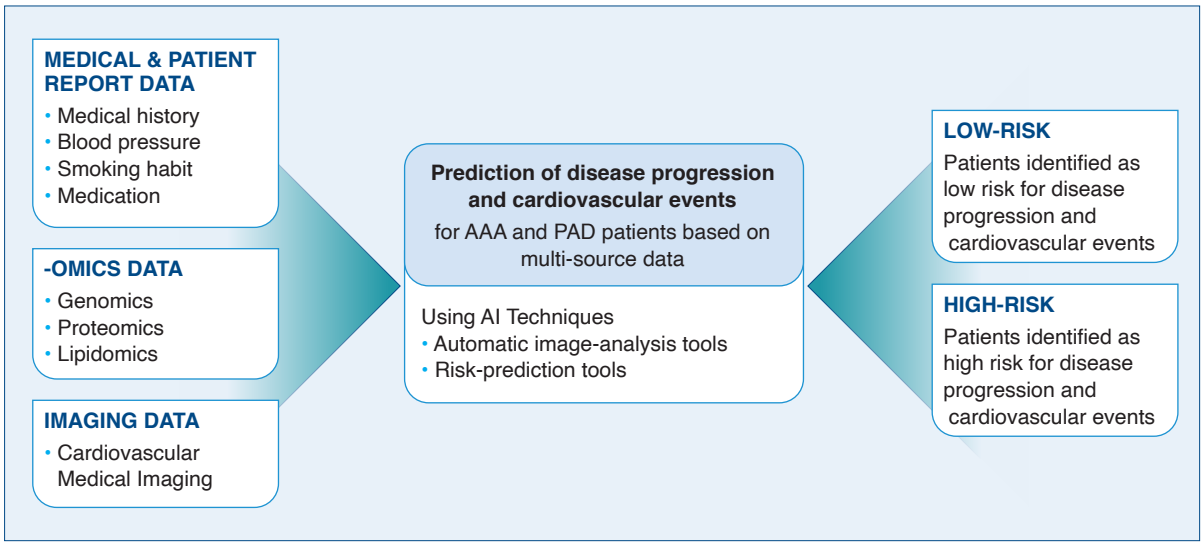


FIGURE 4.3.4 ● An example of a multi-modal AI framework for abdominal aortic aneurysm (AAA) and peripheral arterial disease (PAD) disease progression and risk stratification from the VASCUL-AID platform.[42]

Networks such as Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), Long Short-Term Memory Networks (LSTMs); Graph based models such as Graph Neural Networks (GNNs), Graph Convolutional Networks (GCNs), etc.
- Intermediate fusion: data fusion occurs in the intermediate phase between the input and output of an AI architecture when all data sources have the same representation format.
- Late fusion: the aggregation of decisions from multiple ML algorithms mentioned above,

each trained with different data sources. In addition, various rules are used to determine how decisions from different classifiers are combined.

Early fusion has the advantage of converting all data into the same representation that can be classified using robust classical models. However, when the input modalities are particularly uncorrelated and have widely varying dimensionality and sampling rates, it is easier to use a late fusion approach. Alternatively, intermediate fusion provides more flexibility in terms of how and when representations learned from multi-modal data are fused.

MULTI-MODAL AI MODELS FOR CARDIOVASCULAR DISEASES

To date, there are very few applications of multi-modal AI related to cardio- vascular diseases, a few of which are examined here. Chen *et al.* developed a multi-modal data fusion model using EHR, medical imaging data, and genomics data to predict the risk of cerebral infarction.[45] Compared to existing prediction algorithms, their prediction accuracy reached 94.8% with a convergence speed faster than convolutional neural network (CNN) based uni-modal disease risk prediction models. In the same context, the data fusion model reported by Hao *et al.* to classify patients at potential cardiovascular risk fuses structured clinical and medical imaging data with unstructured textual data (clinical notes).[46] Based on their multi-modal recurring neural network model, they report an accuracy of 96% outperforming several state-of-the-art methods. Zihni *et al.* investigated whether multi-modal fusion enhances the prediction of stroke outcomes.[47] They analyzed neuroimaging data and clinical metadata extracted from the Hotter dataset using two multi-modal fusing strategies. They demonstrated that combining neuroimaging data with clinical metadata has the potential to enhance stroke outcome prediction, further advocating end-to-end fusion for greater robustness. Bagheri *et al.* developed a multi-modal model that integrates laboratory results with free-text radiology reports extracted from the Second Manifestations of ARTerial Disease (SMART) Study to predict cardiovascular risk.[48] Their proposed hybrid-fusion model demonstrated state-of-the-art performance. Similarly, Brugnara *et al.* developed a data fusion model using a series of cardiac CT images with EHR data and endovascular treatment data to predict Acute Ischemic Stroke.[49] They concluded that integrative assessment of clinical, multimodal imaging, and angiographic characteristics allowed accurately predict the clinical outcome following endovascular treatment for acute ischemic stroke.

CHALLENGES

Multi-modal Machine Learning continues to face numerous challenges stemming from the utilization of heterogeneous data featuring diverse structures and formats. Consequently, the primary challenges can be succinctly outlined as follows.

Data standardization

Collecting and processing large amounts of high-quality data in cardiovascular healthcare can be challenging, especially for multi-center studies. To develop more robust and effective multi-modal AI models, researchers must seek to standardize data collection to improve data quality, integration, and reusability. However, the development of such standards requires collaborative expert input, analysis, and consensus.

Electronic data capture systems such as Castor EDC enable standardized data collection by enforcing consistency, uniformity, and quality. It offers structured data entry forms with predefined fields and formats which helps ensure that data is captured invariably according to predetermined standards and harmonized terminology (data dictionary).

Data fusion

It is not easy to learn the ability to merge information from two modalities and determine the optimal fusion strategy. This is due to the different predictive capacities and noise structures of the different information coming from different senses. In addition, the ability to deal with missing data at various levels has a significant impact on the ability to perform fusion tasks.

Explainability

Multi-modal AI models have shown great promise in healthcare by enabling more accurate and tailored diagnosis and treatment recommendations. However, these models can be complicated to understand, making it difficult for physicians to understand how the models arrived at a particular decision or recommendation. The lack of interpretability and openness of these models can affect their clinical acceptance and confidence.

CONCLUDING REMARKS

The integration of multi-modal AI in cardiovascular disease risk prediction and progression significantly contributes to the advancement of precision medicine, primarily by enabling more personalized treatment strategies. A key aspect of multi-modal data in cardiovascular disease is its complex and diverse nature, which necessitates advanced AI tools developed through collaborative effor-

ts with clinicians.[50] Such a collaboration ensures that the developed tools are not only technologically sound but also clinically relevant.

Certain aspects that can serve as future recommendations to improve multi-modal AI models for cardiovascular diseases include increasing data collection through tools such as internet-of-things and smart wearables, developing explicit methodological tools to handle missing data, employing advanced data integration tools, embedding modern techniques to enhance explainability, and optimizing computation cost. Lastly, future research directions should focus on prospective studies comparing differences in care derived from multi-modal fusion modeling compared to conventional modeling or standards of care, as this can provide additional validation.

FUTURE PERSPECTIVES AND CHALLENGES OF AI

AI tools have shown their power in classifying imaging, genomics, and proteomics data in other fields. AI algorithms can be trained with patient's data considering their lifestyle to improve the prediction of disease progression. To guarantee acceptance of AI-assisted tools in the medical field, it is key that they comply with the Ethics Guidelines for Trustworthy AI which means that their development, deployment, and use is lawful, ethically and socio-technically aligned. In 2019, the EU High Level Expert Group on AI published the Ethics Guidelines for Trustworthy AI (Ethics Guidelines),[51] as a guidance for AI development and use in line with European values.

Unfortunately, the massive amount of clinical data available to date is not yet efficiently used to serve the medical community and patients in vascular diseases. An international collaboration is needed for collection of data and standardization of data. Specific infrastructure with trusted data input in different countries and electronic health care systems can aid in using AI. Next is prospective validation of the designed AI-tools in different cohorts. When using AI for clinical decision making, all the above-mentioned challenges need to be addressed. One European research consortium VASCUL-AID (www.vascul-aid.eu) is focusing on all the above challenges while using AI to predict cardiovascular progression in AAA and patients with peripheral arterial diseases. The project will show results in the upcoming years (May 2029 is the end of the project).

REFERENCES

1. Groeneveld ME, Meekel JP, Rubinstein SM, *et al.* Systematic review of circulating, biomechanical, and genetic markers for the prediction of abdominal aortic aneurysm growth and rupture. J Am Heart Assoc 2018;7:e007791.
2. Xiao J, Borné Y, Bao X, *et al.* Comparisons of Risk Factors for Abdominal Aortic Aneurysm and Coronary Heart Disease: A Prospective Cohort Study. Angiology 2021;72:24–31.
3. Chung TK, Gueldner PH, Aloziem OU, *et al.* An artificial intelligence based abdominal aortic aneurysm prognosis classifier to predict patient outcomes. Sci Rep 2024;14:3390.
4. Summers KL, Kerut EK, To F, *et al.* Machine learning-based prediction of abdominal aortic aneurysms for individualized patient care. J Vasc Surg 2024;79:1057-67.e2.
5. Ullah N, Kiu Chou W, Vardanyan R, *et al.* Machine learning algorithms for the prognostication of abdominal aortic aneurysm progression: a systematic review. Minerva Surg 2024;79:219–27.
6. Singh K, Bønaa KH, Jacobsen BK, *et al.* Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: The Tromsø study. Am J Epidemiol 2001;154:236–44.
7. Rygiel P, Alblas D, Brune C, *et al.* Global Control for Local SO (3)-Equivariant Scale-Invariant Vessel Segmentation. arXiv preprint arXiv:240315314. 2024.
8. Lareyre F, Adam C, Carrier M, *et al.* A fully automated pipeline for mining abdominal aortic aneurysm using image segmentation. Sci Rep. 2019;9:13750.
9. López-Linares K, García I, García-Familiar A, *et al.* 3D convolutional neural network for abdominal aortic aneurysm segmentation. arXiv preprint arXiv:190300879. 2019.
10. Raffort J, Adam C, Carrier M, *et al.* Artificial intelligence in abdominal aortic aneurysm. J Vasc Surg. 2020;72:321-33.e1.
11. Soudah E, Ng EYK, Loong TH, *et al.* CFD modelling of abdominal aortic aneurysm on hemodynamic loads using a realistic geometry with CT. Comput Math Methods Med 2013:2013:472564.
12. Gasser TC, Miller C, Polzer S, *et al.* A quarter of a century biomechanical rupture risk assessment of abdominal aortic aneurysms. Achievements, clinical relevance, and ongoing developments. Int J Numer Method Biomed Eng 2023;39:e3587.
13. Kim S, Jiang Z, Zambrano BA, Jang Y, *et al.* Deep Learning on Multiphysical Features and Hemodynamic Modeling for Abdominal Aortic Aneurysm Growth Prediction. IEEE Trans Med Imaging 2023;42:196–208.
14. Lindquist Liljeqvist M, Bogdanovic M, Siika A, *et al.* Geometric and biomechanical modeling aided by machine learning improves the prediction of growth and rupture of small abdominal aortic aneurysms. Sci Rep 2021;11:18040.
15. Do HN, Ijaz A, Gharahi H, Zambrano B, *et al.* Prediction of Abdominal Aortic Aneurysm Growth Using Dynamical Gaussian Process Implicit Surface. IEEE Trans Biomed Eng 2019;66:609–22.
16. Siika A, Bogdanovic M, Liljeqvist ML, *et al.* Three-dimensional growth and biomechanical risk progression of abdominal aortic aneurysms under serial computed tomography assessment. Sci Rep 2023;13:9283.
17. Alblas D, Hofman M, Brune C, *et al.* Implicit Neural Representations for Modeling of Abdominal Aortic Aneurysm Progression. Vol. 13958 LNCS, Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics) 2023:356–36.
18. Jiang Z, Do HN, Choi J, *et al.* A Deep Learning Approach to Predict Abdominal Aortic Aneurysm Expansion Using Longitudinal Data. Front Phys. 2020;7.
19. Akkoyun E, Gharahi H, Kwon ST, *et al.* Defining a master curve of abdominal aortic aneurysm growth and its potential utility of clinical management. Comput Methods Programs Biomed 2021;208.
20. Garcia-Garcia F, Metaxa E, Christodoulidis S, *et al.* Prognosis of Abdominal Aortic Aneurysms: A Machine Learning-Enabled Approach Merging Clinical, Morphometric, Biomechanical and Texture Information. In: Proceedings - IEEE Symposium on Computer-Based Medical Systems. 2017. p. 463–8.
21. Suk J, Haan P, Lippe P, *et al.* Mesh Convolutional Neural Networks for Wall Shear Stress Estimation in 3D Artery Models. Vol. 13131 LNCS, Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). 2022. 93–102.
22. Kappe KO, Smorenburg SPM, Hoksbergen AWJ, *et al.* Deep Learning–Based Intraoperative Stent Graft Segmentation on Completion Digital Subtraction Angiography During Endovascular Aneurysm Repair. J Endovasc Ther 2023;30:822–7.

23. Perini P, Gargiulo M, Silingardi R, *et al.* Occult endoleaks revealed during open conversions after endovascular aortic aneurysm repair in a multicenter experience. Int Angiol 2023;41:476–82.
24. Madigan MC, Singh MJ, Chaer RA, *et al.* Occult type I or III endoleaks are a common cause of failure of type II endoleak treatment after endovascular aortic repair. J Vasc Surg 2019;69:432–9.
25. Chun JY, de Haan M, Maleux G, *et al.* CIRSE Standards of Practice on Management of Endoleaks Following Endovascular Aneurysm Repair. Cardiovasc Intervent Radiol 2024;47:161–76.
26. Antkiewicz M, Protasiewicz M, Kuliczkowski W, *et al.* Preliminary Assessment of Intra-Aneurysm Sac Pressure During Endovascular Aneurysm Repair as an Early Prognostic Factor of Aneurysm Enlargement. Vasc Health Risk Manag 2022; 18:677–84.
27. Sakata M, Takehara Y, Katahashi K, *et al.* Hemodynamic Analysis of Endoleaks After Endovascular Abdominal Aortic Aneurysm Repair by Using 4-Dimensional Flow-Sensitive Magnetic Resonance Imaging. Circ J 2016;80:1715–25.
28. Kappe KO, Smorenburg SPM, Hoksbergen AWJ, *et al.* Deep Learning-Based Intraoperative Stent Graft Segmentation on Completion Digital Subtraction Angiography During Endovascular Aneurysm Repair. J Endovasc Ther 2023;30:822–7.
29. Hahn S, Perry M, Morris CS, *et al.* Machine deep learning accurately detects endoleak after endovascular abdominal aortic aneurysm repair. JVS Vasc Sci 2020;1:5–12.
30. Macía I, Graña M, Maiora J, *et al.* Detection of type II endoleaks in abdominal aortic aneurysms after endovascular repair. Comput Biol Med 2011;41:871–80.
31. Spanos K, Kölbel T, Kubitz JC, *et al.* Risk of spinal cord ischemia after fenestrated or branched endovascular repair of complex aortic aneurysms. J Vasc Surg 2019;69:357–66.
32. Dias-Neto M, Tenorio ER, Huang Y, *et al.* Comparison of single- and multistage strategies during fenestrated-branched endovascular aortic repair of thoracoabdominal aortic aneurysms. J Vasc Surg [Internet] 2023;77:1588–97.e4.
33. Aucoin VJ, Motyl CM, Novak Z, *et al.* Predictors and outcomes of spinal cord injury following complex branched/fenestrated endovascular aortic repair in the US Aortic Research Consortium. J Vasc Surg 2023;77:1578–87.
34. Scali ST, Kim M, Kubilis P, *et al.* Implementation of a bundled protocol significantly reduces risk of spinal cord ischemia after branched or fenestrated endovascular aortic repair. J Vasc Surg 2018;67:409-23.e4.
35. Brisard L, El Batti S, Borghese O, *et al.* Factors for Spinal Cord Injury during Endovascular Repair of Thoracoabdominal Aneurysm: Review of the Literature and Proposal of a Prognostic Score. J Clin Med. 2023;12:7520.
36. Bisdas T, Panuccio G, Sugimoto M, *et al.* Risk factors for spinal cord ischemia after endovascular repair of thoracoabdominal aortic aneurysms. J Vasc Surg 2015;61:1408–16.
37. Li B, Verma R, Beaton D, *et al.* Predicting Outcomes Following Endovascular Abdominal Aortic Aneurysm Repair Using Machine Learning. Ann Surg 2024;279:521–7.
38. Li B, Eisenberg N, Beaton D, *et al.* Using machine learning to predict outcomes following suprainguinal bypass. J Vasc Surg 2024;79:593-608.e8.
39. Kölbel T, Nana P, Torrealba JI, *et al.* The Association of Sarcopenia and ASA Score to Spinal Cord Ischemia in Patients Treated With the t-Branch Device. J Endovasc Ther 2023 Jun 6:15266028231179414.
40. Yan K, Li T, Lobo Marques JA, *et al.* A review on multimodal machine learning in medical diagnostics. Mathematical Biosciences and Engineering 2023;20:8708–26.
41. Wang L. Heterogeneous data and big data analytics. Automatic Control and Information Sciences 2017;3:8–15.
42. Yeung KK. https://vascul-aid.eu/. 2024. VASCUL-AID.
43. Kline A, Wang H, Li Y, *et al.* Multimodal machine learning in precision health: A scoping review. NPJ Digit Med 2022;5:171.
44. Menegotto AB, Cazella SC. Multimodal Deep Learning for Computer-Aided Detection and Diagnosis of Cancer: Theory and Applications. Vol. 410, Studies in Fuzziness and Soft Computing. 2021:267–287.
45. Chen M, Hao Y, Hwang K, *et al.* Disease Prediction by Machine Learning over Big Data from Healthcare Communities. IEEE Access 2017;5:8869–79.
46. Hao Y, Usama M, Yang J, *et al.* Recurrent convolutional neural network based multimodal disease risk prediction. Future Generation Computer Systems 2019;92:76–83.
47. Zihni, E., Kelleher, J.D., Mada, V.I. et al (2020). Multimodal fusion strategies for outcome prediction in stroke. Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologiesvol. 5, pp.421-428.
48. Bagheri A, Groenhof TKJ, Veldhuis WB, *et al.* Multimodal learning for cardiovascular risk prediction using EHR data. arXiv preprint arXiv:200811979. 2020.
49. Brugnara G, Neuberger U, Mahmutoglu MA, *et al.* Multimodal Predictive Modeling of Endovascular Treatment Outcome for Acute Ischemic Stroke Using Machine-Learning. Stroke 2020;51:3541–51.
50. Rahate A, Walambe R, Ramanna S, *et al.* Multimodal Co-learning: Challenges, applications with datasets, recent advances and future directions. Information Fusion 2022;81:203–39.
51. AI H. High-level expert group on artificial intelligence. Ethics guidelines for trustworthy AI. 2019;6.

4.4 ARTIFICIAL INTELLIGENCE IN ULTRASOUNDS DIAGNOSTICS: THE FUTURE IS NOW

Nicola Reina, Alder Casadei

INTRODUCTION

The concept of Artificial Intelligence (AI) was first introduced by John McCarthy at the Dartmouth conference in 1956: "*The attempt to demonstrate that every aspect of learning and characteristic of human intelligence could be simulated by a machine*".[1]

Impressive advances in recent decades have introduced Al in our everyday life, with applications in across a wide range of fields. AI, a branch of computer science, encompasses Machine Learning (ML), Deep Learning (DL) and convolutional neural networks (CNNs) and nowadays, is even being referred to as "the fourth industrial revolution".[2]

When we synthesize the concepts, ML consists in enabling machines to learn through supervised, unsupervised, or reinforcement learning, while DL, a subset of ML is used when a machine is fed with a large quantity of raw data, so-called "big data".[3, 4] CNNs is explicitly assumed to be images and have proven highly effective and efficient in performing medical imaging tasks.[5]

In medicine, AI is transforming various aspects of the medical disciplines, like risk of the disease, diagnosis, prognosis, therapy and outcomes.

A bibliographic analysis research within vascular diseases that included 171 studies,[6] pointed out that the vascular system and aortic diseases were the most represented (N.=57; 32.2% and N.= 43; 24.3%, respectively), followed by peripheral artery disease (N.=20; 11.3%) and cardiovascular risk (N.=14; 7.9%). Imaging data (N.= 87; 43.1%), were the most commonly dataset used for developing the Al applications followed by clinical or behavioral patients' data (N.=42; 20.8%), and biological data (N.=22; 10.9%).[6]

Regarding Ultrasound (US),[5] this technique is applied extensively in disease diagnosis due to its safety and efficiency, becoming an indispensable tool for clinical practice thanks to its many advantages: it is easy to carry out, there is no ionizing radiation, it is low-cost, and it offer real-time imaging display. On top of all these advantages, US is a technique well accepted by patients.

US is also currently a multiparametric examination and the continuous development of ultrasonic diagnostic instruments and diagnostic technologies (*i.e.*, high-frequency US, Shear Wave Elastography (SWE), Contrast-Enhanced Ultrasound (CEUS), and three/four-dimensional (3D/4D) imaging), has made US widely preferred as a first-line imaging technique also in the fields of vascular diseases. As it is widely known, compared with Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), US is a type of imaging modality with high operator dependence, and high internal and external variabilities in the manual acquisition and evaluation of the images.[5]

US also presents other challenges such as noise, artifacts, limited field of view, and variability across the different manufacturers of US systems. With AI, ultrasonic imaging analysis has entered a new era. Supported by these technologies, the status of US image-variation factors such as operator-, scanner-, patient-dependent can be significantly improved.[5] It will be necessary to standardize image acquisition and additional cine images, regulate operator and interpreter qualification and performance, integrate clinical information, and provide performance feedback to maximize benefits for patient care.[7] DL technology with CNN is known to have outstanding performance in image pattern recognition, although variables in the US image acquisition process produce enormous amounts of unintentional image-data, making it difficult for either, the conventional method or DL, to create a usable algorithm in practice.

Therefore, one of the most interesting benefits of applying AI in US would be reduced variability between examiners. In this regard, AI may offer an excellent opportunity to improve the performance of US and deficiencies in clinical validation.[8]

Finally, clinical information should also be integrated into image data-analysis tools, both to improve performance and to maximize clinical usefulness.[8]

US AND AI: APPLICATION IN ATHEROSCLEROTIC VASCULAR DISEASES

Cardiovascular diseases are the leading cause of death in developed countries and represent a heavy burden on health care systems and society.[9] In countries such as the USA, every year 795,000 people experience a stroke, and approximately 240,000 suffer a Transient Ischemic Attack (TIA).[9, 10] Increasing amounts of highly diverse data are becoming available and AI techniques now can utilize them not only to improve diagnosis, but also provide better understanding of disease pathogenesis, more accurate outcome prediction and precision medicine approaches.[11]

Carotid disease, namely carotid plaque and stenosis, Peripheral Artery Disease (PAD), Aortic Aneurysm (AAA), are among the most common vascular diseases,[12-15] and we will describe the role of AI in these areas with a focus on US diagnostics in carotid disease (Figure 4.4.1).

Carotid artery disease

Following cardiac disease and cancer, stroke continues to be the third leading cause of death and disability due to chronic disease in the developed world. In a carotid artery, the presence of increased intima-media thickness, plaque, or stenosis is associated with an increased risk of a TIA or a stroke.[16] Clearly, in a field where other most sophisticated technologies like CTA, MRA or Positron

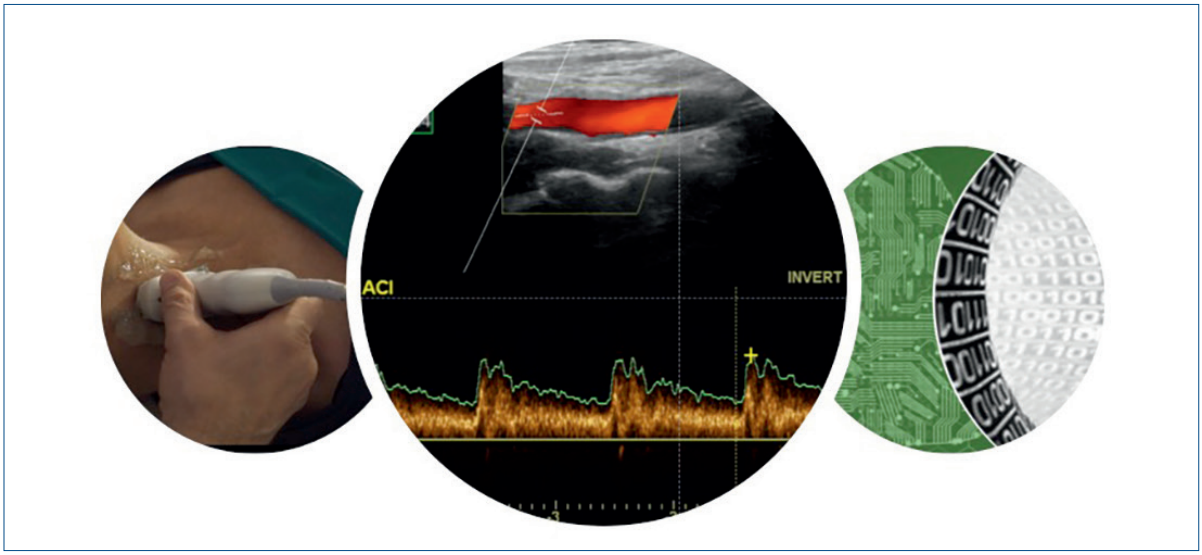


FIGURE 4.4.1 ● US diagnostics in carotid diseases: AI offers various applications to support and potentially improve the management of the patients.

Emission Tomography (PET), their combination and other more sophisticated methods have introduced novel concepts in detection of carotid plaque characteristics.[17] It should be stressed, however, that patients often have TIA or stroke with only mild to moderate carotid luminal stenosis.[18] Moreover, carotid plaque morphology, as recorded by high-resolution ultrasound images, can also have prognostic implications and assist in identifying asymptomatic individuals with carotid stenosis at risk for stroke.[19] Stable plaques are assumed to present as echogenic, smooth, and homogeneous, while vulnerable plaques typically are echolucent, irregular, and heterogeneous.[20, 21] Many different studies show that a more detailed plaque characterization expanding beyond luminal stenosis could provide additional value in predicting future events.[22-26]

The delineation of the carotid plaque using the manual technique has some limitations and difficulties, among them a quiet long analysis time and highly operator-dependent.[27] Thus, researchers have proposed various methods of delineating carotid IMT, plaque, and CAS.[28, 29]

However, a high percentage of patients have a delayed diagnosis of CAS as US is generally not used for routine health checkups and CAS is usually asymptomatic.[30]

With the rapid development of AI, ML algorithms have overcome the limitations of traditional statistical models and have been successfully applied in many medical scenarios and has also been used in CAS diagnosis with the aim to develop ML models to screen CAS in asymptomatic adults.[31, 32]

Yun *et al.*[33] tried to establish and validate ML models for early screening of CAS using routine health check-up indicators in northeast China. A total of 6315 records of patients undergoing carotid ultrasonography were collected. Of these, 1632, 407, and 1141 patients were diagnosed with CAS in the training, internal validation, and external validation datasets, respectively.[33]

The study, which developed and validated a screening model for CAS using ten ML algorithms based on routine clinical and laboratory features, showed that the GBDT models (Gradient Boosting Decision Tree) provided the best discriminatory performance.

In the interpretability analysis, individuals with diabetes or those over 65 years of age showed low negative predictive value. In fact, age was the most important factor influencing the performance of the GBDT model, followed by sex and non-high-density lipoprotein cholesterol.[33]

In a contest where several imaging techniques are available,[34] a recent review[35] summarized the main types of AI models that were used to analyze carotid plaques and identified patterns associated with symptomatic disease and plaque vulnerability based on MRA, CTA, or US.

Guang *et al.*,[36] evaluated the performance of their DL-based detection and classification system for carotid plaques on US compared with two experienced radiologists who manually classified plaque vulnerability. In a cohort of 205 patients, the DL system demonstrated a better AUC (0.84 *vs.* 0.69; P<0.01 and 0.87 *vs.* 0.66 in the training and validation cohorts, respectively). Other investigators used transfer-learning–based DL models to classify symptomatic and asymptomatic plaques: they augmented and optimized 10 AI models using a transfer learning approach and showed the potential of the method for plaque characterization.[37]

Huang *et al.*,[38] built a nomogram using US-based radiomics and clinical features to identify symptomatic carotid plaques. This model outperformed the clinical and conventional US model, with an AUC of 0.93 and 0.92

in the training and test cohorts (v 0.723 and 0.580), respectively. Other imaging techniques were also used to develop AI- based plaque characterization.

Le EPV *et al.*,[39] utilize carotid CTA to identify culprit carotid arteries in patients who had prior cerebrovascular events; Zhang *et al.*,[40] built a magnetic resonance imaging–based model using radiomics features and ML for differentiating symptomatic from asymptomatic carotid plaques and the model achieved an AUC of 0.99 in the test cohort.

Another more recent interesting study,[41] to accurately predict the risk of ischemic stroke, established a radiomics model of carotid atherosclerotic plaque-based high-resolution vessel wall magnetic resonance imaging (HR-VWMRI) and combined it with clinical indicators.

In the training and test cohorts, the radiomics T1CE model based on HR-VWMRI combined with clinical characteristics, had the highest AUC value of 0.84 and 0.82, respectively, demonstrating, that can accurately predict the risk of ischemic stroke.[41]

Also, for the detection of asymptomatic CAS through ML, AI can also utilize greyscale static DUS images.[42] In a dataset of 156 US images,[43] (with and without CAS), used to train a geometry group network based on convolutional neural network (CNN) architecture, the algorithm detected CAS of any grade with a sensitivity, specificity, and accuracy of 87%, 82%, and 90%, respectively.

Carotid plaque segmentation

Currently, Vessel Wall High-Resolution Magnetic Resonance Imaging (VW-HRMRI) is the most appropriate and cost-effective imaging technique to characterize carotid plaque vulnerability and plays an important role in promoting early diagnosis and guiding appropriate clinical therapy to reduce the risk of plaque rupture and acute ischemic stroke.

With regard to carotid plaque, US segmentation needs special attention because the delineation of the carotid plaque using the manual technique is quite difficult and error-prone because very operator-dependent. Thus, researchers have proposed various automated methods of delineating the carotid plaques.[44] Ronneberger *et al.*,[45] in 2015 proposed a segmentation network based on fully convolutional networks (FCN) for medical images, called U-Net, which has become the most common segmentation architecture in the medical field. The original U-Net can segment plaque morphology, but it has over-segmentation and under-segmentation problems.

Other studies,[46-48] also utilize U-Net for carotid atherosclerotic plaque segmentation, emphasizing the central role of this issue. A DL-based model was also applied for carotid IMT and lumen measurement.[49] It was the first artificial intelligence-based approach to US-based carotid artery segmentation and carotid IMT measurement that used 13 layers of convolution layers for feature extraction and three up-sample layers for segmentation.

A new method consisting of a novel design of 10 types of solo deep learning (SDL) and hybrid deep learning (HDL) models,[50] focused on automated plaque segmentation in the internal carotid artery (ICA), has shown to be very useful in identifying plaques at risk of rupture. The system is very fast and precise (it takes <1 s per image) and it may therefore be practical to introduce such an AI-based system to detect rupture-prone plaques (or vulnerable plaque detection).

Skandha *et al.*[51] also have explored the use of HDL models in a multicenter framework, making this study the first of its kind. Among the 17 AI models, the best performing HDL system was that comprising CNN and decision tree (DT), as its accuracy and area-under-the-curve were 99.78±1.05% and 0.99 (P<0.0001), respectively. The online system ran in <2 s and is a reliable, and effective tool for characterizing the carotid plaque for early stroke risk stratification.

Jain *et al.*[52] proposes an attention-channel-based UNet deep learning (DL) model that identifies the complex carotid plaques images in the ICA and common carotid artery (CCA) images. The study included 970 ICA and 679 CCA images from three different centers. The performance of Attention-UNet model was benchmarked against UNet, UNet++, and UNet3P models yielding an AUC value of 0.97, compared to 0.964, 0.966, and 0.965 AUC values for the three other models, respectively. They concluded that the Attention-UNet model is beneficial in segmenting very complex plaque images that are hard to diagnose using other methods.

Previous techniques for B-mode carotid atherosclerotic wall plaque segmentation and Total Plaque Area (TPA) used AI methods on mono-ethnic databases, where training and testing are from the "same" ethnic group ("Seen AI"). Therefore, the versatility of the system is questionable.[53-55]

The first study of its kind that uses the "Unseen AI" paradigm where training and testing are from "different" ethnic groups,[56] hypothesized that DL models should perform in 10% proximity between "Unseen AI" and "Seen AI". Two cohorts from multi-ethnic groups (330 Japanese and 300 Hong Kong [HK]) were used for the validation of the hypothesis and the authors used a four-layered UNet architecture for the segmentation of the atherosclerotic wall with low plaque. "Unseen AI" (training: Japanese, testing: HK or vice versa) and "Seen AI" experiments (single ethnicity or mixed ethnicity) were performed.

Evaluation was conducted by measuring the wall plaque area. When using the UNet DL architecture, the "Unseen AI" pair one (Training: 330 Japanese and Testing: 300 HK), the mean accuracy, dice- similarity, and correlation-coefficient were 98.55, 78.38, and 0.80 (P<0.0001), respectively, while for "Unseen AI" pair two (Training: 300 HK and Testing: 330 Japanese), these were 98.67, 82.49, and 0.87 (P<0.0001), respectively. Using "Seen AI", the same parameters were 99.01, 86.89 and 0.92 (P<0.0001), respectively. In conclusion the study demonstrated that "Unseen AI" was in proximity (<10%) to "Seen AI", validating the DL model for low atherosclerotic wall plaque segmentation. The online system runs <1 second.[56]

Carotid Plaque Volume (CPV) can be also measured by 3D ultrasound and may be a better predictor of stroke than stenosis,[57, 58] but analysis time limits clinical utility associated with intra-/interobserver variability.[59, 60]

The study of Phair *et al.*,[61] tested the accuracy, reproducibility, and time saved of using an AI derived semi-automatic software to measure CPV ("auto-CPV"). Three-dimensional (3D) US images for 121 individuals were analyzed by 2 blinded operators to measure auto-CPV. Corresponding endarterectomy specimen volumes were calculated, and measurement times were compared with previous manual CPV measurement. The mean difference between auto-CPV and surgical volume was small at 95% confidence interval (CI) 0.06 (0.24) (0.41 to 0.54) cm^3. Interobserver and intra-observer error was low with mean difference (95%CI) 0.01 (0.26) (0.5 to 0.5) cm^3 and 0.03 (0.19) (0.35 to 0.40) cm^3 respectively.

The study demonstrated that Auto-CPV assessment is accurate, reproducible, and significantly faster than manual planimetry and can be assessed in large population studies to stratify risk in asymptomatic carotid disease or assess response to medical treatment.[61]

Also, the 3D US reconstruction[62] was evaluated for CAS and qualitative and quantitative evaluation of the segmentation results were compared with CTA. Using 3D US reconstructions may help operators, but future studies using larger datasets are needed with quantitative evaluation methods of the results.

Prediction of outcomes of patients after carotid intervention

Several techniques can be used to treat CAS, including Carotid Endarterectomy (CEA) or Carotid Artery Stenting (CASt).[63, 64] Both techniques carry a risk of postoperative complications, and development of new prognostic tools may help clinicians to better anticipate and prevent them.

Some studies focused on the prediction of postoperative outcomes after CASt.

In a cohort of 317 patients,[65] some investigators used an Artificial Neural Network (ANN) to evaluate the risk of major adverse cardiovascular events. Based on input features composed of 13 clinical risk factors, the ANN model predicted the occurrence of major adverse cardiovascular events with a sensitivity of 85.8%, specificity of 60.8%, and accuracy of 80.8%.[65]

ML was also used for prediction of the risk of unplanned 30-day readmission after CASt.[66] From the US Nationwide Readmission Database 2017, 16.745 patients who underwent CASt were identified, of whom 7.4% were readmitted within 30 days. Septicemia or cerebral infarction/hemorrhagic cerebrovascular bleed, from the 42 clinical variables, where the major causes of all unplanned readmissions and the model produced an accuracy of 87.43% with a C-statistic of 0.802 using Deep Neural Network (DNN).[66]

Matsuo *et al.*,[67] built a 5 ML algorithms to predict the risk of ischemic stroke within 30 days after carotid intervention (CEA or CASt). From a cohort of 165 consecutive patients, 17 clinical factors were used as input data in an XG- Boost model, which demonstrated an accuracy of 86.2% to predict postoperative ischemic stroke. In this study, internal carotid artery peak systolic velocity, low-density lipoprotein cholesterol, and the type of procedure (*i.e.*, CEA or CASt) were identified as the most contributing factors of the predictive model.[67]

Li *et al.*,[68] have used ML to develop automated algorithms that predict outcomes following CEA. The primary outcome was stroke or death at 1 year following. Overall, 166.369 patients underwent CEA during the study period (between 2003 and 2022). In total, 7.749 patients (4.7%) had the primary outcome of stroke or death at 1 year. Patients with an outcome were older, with more comorbidities, had poorer functional status, and demonstrated higher risk anatomic features. ML models could accurately predict outcomes following CEA with excellent performance (AUROC ≥0.90).[68]

Although further studies are required, these results indicate the potential value of AI-based outcome prediction models to guide decision making and patient selection for CEA or CASt and have the potential to guide perioperative risk mitigation strategies.

Abdominal Aortic Aneurysm

Abdominal Aortic Aneurysm (AAA) is one of the most severe complications in the field of vascular disease, with a significant mortality risk due to rupture related to size and growth rate.[69] The role of US is crucial in the first diagnosis of AAA as well as in the follow-up; however, with the commonly recognized limitations of the US, starting with the intra-inter observer variability. Recently, some studies have proposed new techniques with interesting results to investigate which geometrical and mechanical factors, using 4D ultrasound or time-resolved 3D ultrasound (3D + t US), correlate with increased growth of the aneurysm.[70, 71] CTA is the gold-standard technique for the diagnosis, as well as the preoperative planning and postoperative outcome assessment in AAA; for this reason, many AI techniques in AAA management are CTA-based. AI has already been employed in the management of AAA, mainly in setting the diagnosis, predicting its growth and risk of rupture or in the preoperative planning and postoperative outcome prediction.[72]

Regarding cross-sectional outer to outer aortic wall measurements, the deep learning (DL) based method (Augmented Radiology for Vascular Aneurysm [ARVA]), can provide a potentially reliable solution for assisting clinical practice.[73] In addition, the study of Camara *et al.*,[74] even if these are preliminary data from a CNN model, have shown that the model can accurately screen and identify CTA findings of infrarenal AAAs.

ML algorithms, based on variables from different pathophysiological fields, taking into account clinical, biologic, morphologic, and biomechanical variables, are also utilized to develop a prediction model that could risk stratify AAAs into high and low growth rate groups.[75] In

the study of Forneris *et al.*,[76] three functional biomarkers, namely time-averaged wall-shear stress, *in vivo* principal strain, and intra-luminal thrombus thickness, encoded as regional averages on axial and circumferential sections perpendicularly to the aortic centerline, were helpful to predict rapid growth in individual patients.

Another study[77] assessed ML models using clinical, biomechanical, and morphological indices from 381 patients, the largest cohort of AAA patients that utilizes medical image and clinical data, to differentiate patient outcomes. The aneurysm prognosis classifier (APC) model demonstrated the ability to classifier AAA in stable, AAA that will require repair, or AAA that will rupture representing a objective clinical decision support tool for aneurysm management.[77]

The prediction of outcomes following open AAA repair or EVAR, is still challenging with a lack of widely used tools to guide perioperative management. Li *et al.*,[78, 79] develop ML models that accurately predict outcomes better than logistic regression with excellent performance, achieving an AUROC of 0.93 (95% confidence interval, 0.92-0.94), following open AAA.[78] ML models following EVAR also predicted MI, stroke, death, reintervention, other morbidity, non-home discharge, and readmission with AUROC's of 0.84 to 0.97.[79]

AI models have high accuracy and potential for important utility in the perioperative management of patients being considered for intervention for AAA.

Peripheral arterial disease

Peripheral Arterial Disease (PAD), which refers to the narrowing of the arteries that supply the upper and lower limbs, is most commonly due to atherosclerosis. It is estimated that more than 200 million patients worldwide suffer from PAD and more than 50% of these patients are asymptomatic and often remain undiagnosed and untreated.[80] The European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines[13] are an important reference for the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication Diagnostic methods and medical imaging in peripheral arterial disease.

AI can no doubt be used to facilitate the detection, the management and also the outcome prediction in PAD.[11] With regard to the detection of PAD, we found the work of McBane *et al.*,[81] extremely interesting as it applied DL for the detection of PAD *via* arterial (posterior tibial artery) Doppler waveform data. The proposed DL algorithm predicted normal (>0.9) or pathological (<0.9) post-exercise ABI based on posterior tibial artery Doppler waveforms recorded at the resting state. The clinical trial included 1.941 patients with PAD and 1.491 control subjects and detected PAD with an AUC of 0.94 (CI = 0.92–0.96).[81] McBane *et al.*[82] also have subsequently evaluated patients with diabetes mellitus (DM) that are at increased risk for PAD and its complications, and arterial calcification and non-compressibility may limit the test interpretation. Deep neural networks were trained on resting posterior tibial arterial Doppler waveforms to predict all-cause mortality, major adverse cardiac event (MACE), and major adverse limb event (MALE) at 5 years. 4.211 patients with DM met study criteria (mean age, 68.6±11.9 years; 32.0% female) and after allocating the training and validation subsets, the final test subset included 856 patients. During follow-up, there were 262 deaths, 319 MACE, and 99 MALE.

Machine Learning (ML) algorithms can also predict outcomes following interventions for PAD. A prognostic study[83] included 235.677 patients whose data were obtained from the Vascular Quality Initiative (VQI), a multicenter registry containing data from vascular surgeons and interventionalists at more than 1.000 academic and community hospitals. who underwent endovascular intervention for PAD (mean [SD] age, 68.4 [11.1] years; 94.979 [40.3%] female) and 71.683 (30.4%) developed 1-year MALE or death.[83]

The same Vascular Quality Initiative database was used to identify patients who underwent infrainguinal bypass for PAD between 2003 and 2023.[84] The primary outcome was 1-year MALE (composite of surgical revision, thrombectomy/thrombolysis, or major amputation) or death. Overall 59.784 patients underwent infrainguinal bypass and 15.942 (26.7%) developed major adverse limb event or death after a year. From the trained 6 ML models, the best preoperative prediction model was XG Boost achieving AUROC (95% CI) of 0.94 (0.93-0.95). In comparison logistic regression had an AUROC (95% CI) of 0.61 (0.59-0.63).[84]

A AI Markov-based model,[85] not ready for clinical application, was prospectively interrogated immediately after individual interventions for PAD over a 12-year period to test predictive performance.[86] Patient quality of life (cQoL) was determined at each patient follow-up visit. A total of 1.143 consecutive patients were evaluated, with a median follow-up of 18 months. Al can successfully predict treatment for PAD that maximizes patient quality of life in most cases, but it should be necessary to incorporate patient anatomic and physiological risk factors and refinement of the AI model that can assist but not assume vascular surgical decision-making.[86]

CONCLUSIONS

Carotid stenosis, aortic aneurysm, and lower extremity arterial disease are the top three cardiovascular diseases that are being managed in daily vascular surgical practice.

Ultrasound is the most widely available and affordable imaging methods. Computed tomography, magnetic resonance imaging, positron emission tomography, or their combination, have introduced novel concepts in detection of vascular diseases characteristics, risk assessment, therapy, prognosis and outcomes.[87]

Despite technical advances and innovations in diagnostics and treatment, management of vascular diseases is still challenging, and patient outcomes are often associated with high rates of morbidity and mortality.[63, 64]

Artificial Intelligence (AI) offers various applications to support and potentially improve the management of patients with vascular diseases and in particular machine-learning algorithms are already being employed in cardiovascular imaging applications, in vascular diseases management and vascular surgical practice.[88]

However, in real-life, AI algorithms require large amounts of high-quality data to be trained effectively. Furthermore, AI algorithms trained on data from one population may not perform as well on data from other populations due to differences in imaging protocols, patient demographics, and disease prevalence.[87]

Another extremely important issue is that physicians must learn how to work constructively with AI technology and other systems to best serve their patients' needs, develop personalized medicine and improve patient care.[88]

The use of AI in medical data raises also important ethical issues, such as data privacy and patient consent. Recently, the American Medical Association defined the role of AI in healthcare as "augmented intelligence", stating that AI should be designed and used to enhance human intelligence rather than to replace it.[89]

As research involving the development and implementation of AI technologies continues to grow in global health, important challenges for ethical governance should be posing around the world.[90, 91]

For this purpose, the European Commission approved, on March 13, 2024, the AI Act, the first-ever legal framework on AI, with the aims to provide AI developers and deployers with clear requirements and obligations regarding specific uses of AI.[92]

All these issues need to be addressed before AI-based approaches can be adopted on a large scale in clinical practice. Also, further research efforts are needed to validate such applications and investigate their accuracy and safety in large multinational cohorts before their implementation in daily clinical practice**.**

Notwithstanding, the future is now.

REFERENCES

1. Moor J. The Dartmouth College Artificial Intelligence Conference: The Next Fifty Years. AI Magazine, 2006. 27(4), 87. DOI: https://doi.org/10.1609/aimag.v27i4.1911.
2. Yoon D. What we need to prepare for the fourth industrial revolution. Healthc Inform Res 2017;23:75-6.
3. Panch T, Szolovits P, Atun R. Artificial intelligence, machine learning and health systems. Journal of global health. J Glob Health 2018;8:020303.
4. Badawi O, Brennan T, Celi LA, *et al.* Making big data useful for health care: a summary of the inaugural mit critical data conference. JMIR Med Inform 2014;2:e22.
5. Shen YT, Chen L, Yue WW, Xu HX. Artificial intelligence in ultrasound. Eur J Radiol 2021;139:109717.
6. Lareyre F, Lê CD, Ballaith A, *et al.* Applications of Artificial Intelligence in Non-cardiac Vascular Diseases: A Bibliographic Analysis. Angiology 2022;73:606-14.
7. Kim YK. Artificial intelligence in medical ultrasonography: driving on an unpaved road. Ultrasonography 2021;40:313-7.
8. Park SH. Artificial intelligence for ultrasonography: unique opportunities and challenges. Ultrasonography 2021;40:3-6.
9. Roth GA, Mensah GA, CO Johnson, *et al.* Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol 2020;76:2982–3021.
10. Martin SS, Aday AW, Almarzooq ZI, *et al.* 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation 2024;149:e347-e913.
11. Kampaktsis PN, Emfietzoglou M, Al Shehhi A, *et al.* Artificial intelligence in atherosclerotic disease: Applications and trends. Front Cardiovasc Med 2023;9:949454.
12. Paraskevas KI, Mikhailidis DP, Ringleb PA, *et al.* An international, multispecialty, expert-based Delphi Consensus document on controversial issues in the management of patients with asymptomatic and symptomatic carotid stenosis. J Vasc Surg 2024;79:420-35.
13. Nordanstig J, Behrendt CA, Baumgartner I, *et al.* Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. Eur J Vasc Endovasc Surg 2024;67:9-96.
14. Pratesi C, Esposito D, Apostolou D, *et al.* Guidelines on the management of abdominal aortic aneurysms: updates from the Italian Society of Vascular and Endovascular Surgery (SICVE). J Cardiovasc Surg 2022;63:328-52.
15. Wanhainen A, Van Herzeele I, Bastos Goncalves F, *et al.* Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2024;67:192-331.
16. Murray CSG, Nahar T, Kalashyan H, *et al.* Ultrasound assessment of carotid arteries: Current concepts, methodologies, diagnostic criteria, and technological advancements. Echocardiography 2018;35:2079-91.
17. Brinjikji W, Huston J 3rd, Rabinstein AA, *et al.* Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. Neurosurg 2016;124:27-42.
18. Saba L, Cau R, Spinato G, *et al.* Carotid stenosis and cryptogenic stroke. J Vasc Surg 2024;79:1119-31.
19. Zhu G, Hom J, Li Y, *et al.* Carotid plaque imaging and the risk of atherosclerotic cardiovascular disease. Cardiovasc Diagn Ther 2020;10:1048-67.
20. Alexandratou M, Papachristodoulou A, Li X, *et al.* Advances in Noninvasive Carotid Wall Imaging with Ultrasound: A Narrative Review. J Clin Med 2022;11:6196.
21. Saba L, Cau R, Murgia A, *et al.* Carotid Plaque-RADS: A Novel Stroke Risk Classification System. JACC Cardiovasc Imaging 2024;17:62-75.
22. Saba L, Scicolone R, Johansson E, *et al.* Quantifying Carotid Stenosis: History, Current Applications, Limitations, and Potential: How Imaging Is Changing the Scenario. Life (Basel) 2024;14:73.
23. Saba L, Antignani PL, Gupta A, *et al.* International Union of Angiology (IUA) consensus paper on imaging strategies in atherosclerotic carotid artery imaging: From basic strategies to advanced approaches. Atherosclerosis 2022;354:23-40.
24. Spanos K, Tzorbatzoglou I, Lazari P, *et al.* Carotid artery plaque echomorphology and its association with histopathologic characteristics. J Vasc Surg 2018;68:1772-80.
25. Aboyans V, Ricco JB, Bartelink M-L EL, *et al.* ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal. Eur Heart J 2017;39:763–816.
26. Nardi V, Benson J, Bois MC, *et al.* Carotid Plaques From Symptomatic Patients With Mild Stenosis Is Associated With Intraplaque Hemorrhage. Hypertension 2022;79:271-82.
27. He Z, Luo J, Lv M, *et al.* Characteristics and evaluation of atherosclerotic plaques: an overview of state-of-the-art techniques. Front Neurol 2023;14:1159288.

28. Cassola N, Baptista-Silva JC, *et al.* Duplex ultrasound for diagnosing symptomatic carotid stenosis in the extracranial segments. Cochrane Database Syst Rev 2022;7(7):CD013172.
29. Ospel JM, Kappelhof M, Ganesh A, *et al.* Symptomatic non-stenotic carotid disease: current challenges and opportunities for diagnosis and treatment. J Neurointerv Surg 2024;16:418-24.
30. van Dam-Nolen DHK, Truijman MTB, van der Kolk AG, *et al.* Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA: The PARISK (Plaque At RISK) Study. JACC Cardiovasc Imaging 2022;15:1715-26.
31. Fan J, Chen M, Luo J, *et al.* The prediction of asymptomatic carotid atherosclerosis with electronic health records: a comparative study of six machine learning models. BMC Med Inform Decis Mak 2021;21:115.
32. Yu J, Zhou Y, Yang Q, *et al.* Machine learning models for screening carotid atherosclerosis in asymptomatic adults. Sci Rep 2021;11:22236.
33. Yun K, He T, Zhen S, *et al.* Development and validation of explainable machine-learning models for carotid atherosclerosis early screening. J Transl Med 2023;21:353.
34. Saxena A, Ng EYK, Lim ST. Imaging modalities to diagnose carotid artery stenosis: progress and prospect. Biomed Eng Online 2019;18:66.
35. Saba L, Sanagala SS, Gupta SK, *et al.* Multimodality carotid plaque tissue characterization and classification in the artificial intelligence paradigm: a narrative review for stroke application. Ann Transl Med 2021;9:1206.
36. Guang Y, He W, Ning B, *et al.* Deep learning-based carotid plaque vulnerability classification with multicentre contrast-enhanced ultrasound video: a comparative diagnostic study. BMJ Open 2021;11(8) e047528.
37. Sanagala SS, Nicolaides A, Gupta SK, *et al.* Ten fast transfer learning models for carotid ultrasound plaque tissue characterization in augmentation framework embedded with heatmaps for stroke risk stratification. Diagnostics (Basel) 2021;11:2109.
38. Huang Z, Cheng XQ, Liu HY, *et al.* Relation of carotid plaque features detected with ultrasonography-based radiomics to clinical symptoms. Transl Stroke Res 2022;13:970-82.
39. Le EPV, Rundo L, Tarkin JM, *et al.* Assessing robustness of carotid artery CT angiography radiomics in the identification of culprit lesions in cerebrovascular events. Sci Rep 2021;11:3499.
40. Zhang R, Zhang Q, Ji A, *et al.* Identification of high-risk carotid plaque with MRI-based radiomics and machine learning. Eur Radiol 2021;31:3116–26.
41. Han N, Hu W, Ma Y, *et al.* A clinical-radiomics combined model based on carotid atherosclerotic plaque for prediction of ischemic stroke. Front Neurol 2024;15:1343423.
42. Kigka VI, Sakellarios AI, Tsakanikas VD, *et al.* Detection of Asymptomatic Carotid Artery Stenosis through Machine Learning. In: Proceedings of the 2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Glasgow, UK, 11–15 July 2022; p. 1041-4.
43. Kordzadeh A, Askari A, Abbassi OA, *et al.* Artificial intelligence and duplex ultrasound for detection of carotid artery disease. Vascular 2023;31:1187-93.
44. Han N, Ma Y, Li Y, *et al.* Imaging and Hemodynamic Characteristics of Vulnerable Carotid Plaques and Artificial Intelligence Applications in Plaque Classification and Segmentation. Brain Sci 2023;13:143.
45. Ronneberger O, Fischer P, Brox T. U-net: Convolutional networks for biomedical image segmentation. In: Proceedings of the Medical Image Computing and Computer-Assisted Intervention-MICCAI 2015, 18th International Conference, Munich, Germany, 5-9 October 2015; p. 234-41.
46. Meshram NH, Mitchell CC, Wilbrand S, *et al.* Deep Learning for Carotid Plaque Segmentation using a Dilated U-Net Architecture. Ultrasonic Imaging 2020;42:221-30.
47. Xie M, Li Y, Xue Y, *et al.* Two-stage and dual-decoder convolutional U-Net ensembles for reliable vessel and plaque segmentation in carotid ultrasound images. Proceedings of 2020 19th IEEE International Conference on Machine Learning and Applications (ICMLA), Miami, FL, USA, 14-17 December 2020; p. 1376-81.
48. Jiang M, Spence JD, Chiu B. Segmentation of 3D ultrasound carotid vessel wall using U-Net and segmentation average network. Proceedings of 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Montreal, QC, Canada, 20–24 July 2020; p. 2043-46.
49. Biswas M, Saba L, Chakrabartty S, *et al.* Two-stage artificial intelligence model for jointly measurement of atherosclerotic wall thickness and plaque burden in carotid ultrasound: a screening tool for cardiovascular/stroke risk assessment. Comput Biol Med 2020;123:103847.
50. Jain PK, Sharma N, Giannopoulos AA, *et al.* Hybrid deep learning segmentation models for atherosclerotic plaque in internal carotid artery B-mode ultra sound. Comput Biol Med 2021;136:104721.
51. Skandha SS, Nicolaides A, Gupta SK, *et al.* A hybrid deep learning paradigm for carotid plaque tissue characterization and its validation in multicenter cohorts using a supercomputer framework. Comput Biol Med 2022;141:105131.
52. Jain PK, Dubey A, Saba L, *et al.* Attention-based UNet deep learning model for plaque segmentation in carotid ultrasound for stroke risk stratification: an artificial intelligence paradigm. J Cardiovasc Dev Dis 2022;9:326.
53. Biswas, M, Kuppili, V, Saba L, *et al.* State-of-the-Art Review on Deep Learning in Medical Imaging. Front Biosci 2019;24:392-426.
54. Jena B, Saxena S, Nayak GK, *et al.* Artificial Intelligence-Based Hybrid Deep Learning Models for Image Classification: The First Narrative Review. Comput Biol Med 2021;137:104803.
55. Zhou R, Guo F, Azarpazhooh MR, *et al.* Deep Learning-Based Measurement of Total Plaque Area in B-Mode Ultrasound Images. IEEE J Biomed Health Inform 2021;25:2967-77.
56. Jain PK, Sharma N, Saba L, *et al.* Unseen Artificial Intelligence-Deep Learning Paradigm for Segmentation of Low Atherosclerotic Plaque in Carotid Ultrasound: A Multicenter Cardiovascular Study. Diagnostics (Basel) 2021;11:2257.
57. Wannarong T, Parraga G, Buchanan D, *et al.* Progression of carotid plaque volume predicts cardiovascular events. Stroke 2013;44:1859-65.
58. Spence JD. Vessel Wall Volume and Plaque Volume Should Replace Carotid Intima-Media Thickness. Am J Hypertens 2024;37:270-2.
59. Zhao Y, Jiang M, Chan WS, *et al.* Development of a Three-Dimensional Carotid Ultrasound Image Segmentation Workflow for Improved Efficiency, Reproducibility and Accuracy in Measuring Vessel Wall and Plaque Volume and Thickness. Bioengineering (Basel) 2023;10:1217.
60. Yu S, Zheng Y, Dai X, *et al.* The value of coordinated analysis of multimodal atherosclerotic plaque imaging in the assessment of cardiovascular and cerebrovascular events. Front Cardiovasc Med 2024;11:1320222.
61. Phair AS, Carreira J, Bowling FL, *et al.* Accelerated Measurement of Carotid Plaque Volume Using Artificial Intelligence Enhanced 3D Ultrasound. Ann Vasc Surg 2024;98:317-24.
62. Arsenescu T, Chifor R, Marita T, *et al.* 3D Ultrasound Reconstructions of the Carotid Artery and Thyroid Gland Using Artificial-Intelligence-Based Automatic Segmentation-Qualitative and Quantitative Evaluation of the Segmentation Results via Comparison with CT Angiography. Sensors (Basel) 2023;23:2806.
63. AbuRahma AF. The New 2023 European Society for Vascular Surgery (ESVS) Carotid Guidelines: The Transatlantic Perspective. Eur J Vasc Endovasc Surg 2023;65:5-6.
64. Naylor R, Rantner B, Ancetti S, *et al.* Editor's Choice - Eu-

ropean Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg 2023;65:7-111.
65. Chun-An C, Hung-Wen C. An artificial neural network model for the evaluation of carotid artery stenting prognosis using a national-wide database. Annu Int Conf IEEE Eng Med Biol Soc 2017:2017:2566-9.
66. Amritphale A, Chatterjee R, Chatterjee S, *et al.* Predictors of 30-day unplanned readmission after carotid artery stenting using artificial intelligence. Adv Ther 2021;38:2954-72.
67. Matsuo K, Fujita A, Hosoda K, *et al.* Potential of machine learning to predict early ischemic events after carotid endarterectomy or stenting: a comparison with surgeon predictions. Neurosurg Rev 2022;45:607-16.
68. Li B, Beaton D, Eisenberg N, *et al.* Using machine learning to predict outcomes following carotid endarterectomy. J Vasc Surg 2023;78:973-87.
69. Sakalihasan N, Michel J, Katsargyris A, *et al.* Abdominal aortic aneurysms. Nat Rev Dis Primers 2018;4:34.
70. van Disseldorp EMJ, Petterson NJ, Rutten MCC, *et al.* Patient specific wall stress analysis and mechanical characterization of abdominal aortic aneurysms using 4D ultrasound. Eur J Vasc Endovasc Surg 2016;52:635-42.
71. Maas EJ, Nievergeld AHM, Fonken JHC, *et al.* 3D-Ultrasound Based Mechanical and Geometrical Analysis of Abdominal Aortic Aneurysms and Relationship to Growth. Ann Biomed Eng 2023;51:2554-65.
72. Baek S, Arzani A. Current state-of-the-art and utilities of machine learning for detection, monitoring, growth prediction, rupture risk assessment, and post-surgical management of abdominal aortic aneurysms. Applications in Engineering Science 2022,10,100097.
73. Adam C, Fabre D, Mougin J, *et al.* Pre-surgical and Post-surgical Aortic Aneurysm Maximum Diameter Measurement: Full Automation by Artificial Intelligence. Eur J Vasc Endovasc Surg 2021;62:869-77.
74. Camara JR, Tomihama RT, Pop A, *et al.* Development of a convolutional neural network to detect abdominal aortic aneurysms. J Vasc Surg Cases Innov Tech 2022;8:305-11.
75. Kontopodis N, Klontzas M, Tzirakis K, *et al.* Prediction of abdominal aortic aneurysm growth by artificial intelligence taking into account clinical, biologic, morphologic, and biomechanical variables. Vascular 2023;31:409-16.
76. Forneris A, Beddoes R, Benovoy M, *et al.* AI-powered assessment of biomarkers for growth prediction of abdominal aortic aneurysms. JVS Vasc Sci 2023;4:100119.
77. Chung TK, Gueldner PH, Aloziem OU, *et al.* An artificial intelligence based abdominal aortic aneurysm prognosis classifier to predict patient outcomes. Sci Rep 2024;14:3390.
78. Li B, Aljabri B, Verma R, *et al.* Using machine learning to predict outcomes following open abdominal aortic aneurysm repair. J Vasc Surg 2023;78:1426-38.
79. Li B, Verma R, Beaton D, *et al.* Predicting Outcomes Following Endovascular Abdominal Aortic Aneurysm Repair Using Machine Learning. Ann Surg 2024;279:521-7.
80. Shu J, Santulli G. Update on peripheral artery disease: epidemiology and evidence- based facts. Atherosclerosis 2018;275:379-81.
81. McBane RD 2nd, Murphree DH, Liedl D, *et al.* Artificial intelligence for the evaluation of peripheral artery disease using arterial Doppler waveforms to predict abnormal ankle-brachial index. Vasc Med 2022;27:333-42.
82. McBane RD 2nd, Murphree DH, Liedl D, *et al.* Artificial intelligence of arterial Doppler waveforms to predict major adverse outcomes among patients with diabetes mellitus. J Vasc Surg 2024:S0741-5214(24)00401-4.
83. Li B, Warren BE, Eisenberg N, *et al.* Machine Learning to Predict Outcomes of Endovascular Intervention for Patients With PAD. JAMA Netw Open 2024;7:e242350.
84. Li B, Eisenberg N, Beaton D, Lee DS, *et al.* Using Machine Learning (XGBoost) to Predict Outcomes After Infrainguinal Bypass for Peripheral Artery Dis ease. Ann Surg 2024;279:705-13.
85. Brothers TE, Robison JG, Elliott BM. Prospective decision analysis for peripheral vascular disease predicts future quality of life. J Vasc Surg 2007;46:701-8.
86. Brothers TE, Baliga P. Artificial Intelligence to Predict Quality-of-Life Outcomes for Vascular Intervention of the Leg. J Am Coll Surg 2024;238:481-8.
87. Miceli G, Rizzo G, Basso MG, *et al.* Artificial Intelligence in Symptomatic Carotid Plaque Detection: A Narrative Review. Appl. Sci. 2023, 13, 4321.https://doi.org/10.3390/app13074321.
88. Lareyre F, Chaudhuri A, Behrendt CA, *et al.* Artificial intelligence-based predictive models in vascular diseases. Semin Vasc Surg 2023;36:440-7.
89. American Medical Association. Augmented intelligence in health care. Presented at the 2018 annual meeting. Available at: https:// www.ama-assn.org/system/files/2019-01/augmented-intelligence- policy-report.pdf. Accessed April 23, 2024.
90. Spanos K, Giannoukas AD, Kouvelos G, *et al.* Artificial intelligence application in vascular diseases. J Vasc Surg 2022;76:615-9.
91. Shaw J, Ali J, Atuire CA, Cheah PY, *et al.* Research ethics and artificial intelligence for global health: perspectives from the global forum on bioethics in research. BMC Med Ethics 2024;25:46.
92. The European Commission, AI Act, 13.03.2024. https://digitalstrategy.ec.europa.eu/en/policies/regulatory-framework-ai.

4.5 POWER IS NOTHING WITHOUT CONTROL: POTENTIAL DOWNSIDES OF AI-SUPPORTED CHATBOTS IN ADDRESSING PATIENT QUERIES ABOUT AORTIC DISEASE

Germano Melissano, Timo Söderlund, Giovanni Tinelli, Andrea Kahlberg

Nowadays, artificial intelligence (AI) powered chatbots are adopted ubiquitously, they are computer programs designed to simulate human-like conversations, particularly online. These chatbots represent an absolute game-changer as compared to previous "rule-based" ones (Figure 4.5.1). They are already accessible to the general public, experiencing rapid advancements due to very significant investments from various entities.

It is imperative to recognize both the positive and negative aspects of this technology. While many individuals view AI chatbots as reliable sources of information across various domains, including healthcare, where accuracy is paramount, users must remain vigilant regarding the potential diffusion of inaccurate information. The same innovative tool can prove detrimental if misused.

A community of individuals interested in aortic disease, led by a former patient (TS), is undertaking a project known as ChatAortaAI (Figure 4.5.2). This initiative aims to assess the accuracy of responses provided by two widely used chatbots, ChatGPT 3.0 and Bing, to common questions that patients and family members might pose. The project involves voluntary participation from individuals worldwide, including patients, caregivers, healthcare professionals, and others committed to advance the field of aortic disease.

The initial phase of the initiative involved a pilot study, where team members interrogated the chatbots with questions typically asked by individuals seeking information on aortic disease. The pilot study included 42 questions that were categorized into three levels: non-medical (BASIC), aortic (AORTA), and complex aortic disease (ADVANCED). Each question was posed multiple times in different sessions and languages.

The accuracy of responses in English was assessed by expert academic professionals using a three-point Likert scale: accurate, partially accurate, and inaccurate. Additionally, the consistency of responses within the same language was evaluated. Surprisingly, identical questions elicited diverse responses. Furthermore, accuracy decreased notably when questions were posed in languages other than English, particularly in less commonly spoken languages.

The findings revealed that English yielded more accurate responses compared to other languages tested. Overall, a significant proportion of responses across all languages were found to be incorrect. Specifically, responses from ChatGPT were incorrect in 44% of English questions and 65% of questions in other languages, while responses from Bing were incorrect in 35% and 50% of English and other language questions, respectively.

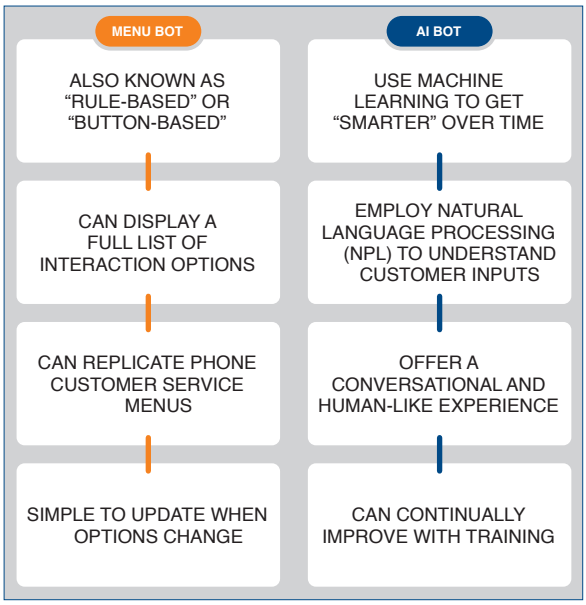


FIGURE 4.5.1 ● Main differences between "rule-based" and "AI-based" chatbots.

FIGURE 4.5.2 ● The cover of the promotional brochure of ChatAortaAI project (please read the full flyer on https://www.researchgate.net/publication/368817604_New_project_chatAortaAI_2023_by_Think_Tank_Aorta)

The functionality of AI chatbots holds promise but also carries risks, particularly in disseminating misleading or inaccurate information, raising concerns about medical misinformation. Therefore, the application of AI chatbots should be approached ethically and responsibly, considering potential risks. The team responsible for the study aims to monitor the development of language algorithms and conduct more structured studies in the future. In the meantime, the findings emphasize the need to caution both the medical community and the general public about the risks associated with seeking medical information on aortic diseases through AI chatbots.

AI chatbots are still in relatively early stages of their

development and unlike medical devices, which undergo rigorous testing before approval for human use, AI technologies, have been made available to the public without thorough scrutiny. These AI chatbots, positioned as free resources offering potentially "qualified" medical information, raise concerns about safety.

To address these concerns, our project focused specifically on the chatbots' ability to provide accurate medical information about aortic diseases. These chatbots can generate responses to queries they haven't been explicitly trained on, often producing varied responses. To assess their reliability, we repeatedly asked the same questions and observed a mix of correct and incorrect answers.

Furthermore, we observed significant language limitations, as the AI chatbots are primarily trained in English and a few other languages, leaving many of the world's languages underrepresented. In some cases, the chatbots couldn't even comprehend our questions accurately. This could be particularly harmful for individuals who primarily speak these underrepresented languages, as they may be exposed to incorrect and potentially harmful information from unreliable sources.

Our project's objective is not to endorse or validate AI chatbots for public use but rather to identify potential flaws in these widely accessible information sources when queried about aortic diseases. Users should be aware of these limitations when seeking medical information through AI tools, and developers could benefit from this feedback. This process is ongoing and must adapt to the rapid changes in technology. While oversight from regulatory agencies is desirable, individuals with expertise in aortic disease, an understanding of chatbots' mechanics and training, their propensity to offer varied responses, and the lack of training in underrepresented languages can continue evaluating these tools and informing their communities about potential drawbacks.

These results have been already published in surgical journals[1, 2] but would also require dissemination through the lay press in order to alert the general population on the potential risks involved.

REFERENCES

1. Melissano G, Tinelli G, Soderlund T. Current Artificial Intelligence Based Chatbots May Produce Inaccurate and Potentially Harmful Information for Patients With Aortic Disease. Eur J Vasc Endovasc Surg 2024;67:683-4.
2. Melissano G, Tinelli G, Soderlund T. Power is Nothing Without Control: Are Artificial Intelligence Chatbots in Vascular Diseases Tested and Verified? Eur J Vasc Endovasc Surg 2024;67:691-2.

5

BIOENGINEERING, BIOMATERIALS AND CELL-THERAPIES

5.1 CURRENT EVIDENCE ON VASCULAR BIOMATERIALS AND FUTURE PERSPECTIVES

Vincenzo Vento, Salomé Kuntz, Anne Lejay, Nabil Chakfe

INTRODUCTION

In last decades, vascular surgery has greatly benefited from technological advances. In some cases, these new technological tools have revolutionized its traditional practice. The advent of cutting-edge technologies has opened new perspectives in the diagnosis, treatment, and management of vascular pathologies, enabling surgeons to achieve increasingly precise and effective outcomes for patients.[1]

The evolution of medical imaging has been one of the most significant transformations. High-resolution imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have provided detailed views of vascular anatomy, facilitating early diagnosis of pathologies and optimal procedure planning. Progress in robotics and automation has introduced new possibilities for more precise and minimally invasive surgical interventions, simultaneously reducing the risk of post-operative complications.

Innovative materials, such as advanced polymers and special metal alloys, have revolutionized the design and production of vascular devices like stents and grafts. These materials have been selected to maximize biocompatibility and durability, ensuring superior long-term outcomes for patients.

Minimally invasive therapies have replaced traditional surgical procedures in many cases, offering shorter recovery times and reducing the impact on patients' quality of life. Additionally, the integration of artificial intelligence (AI) and machine learning (ML) has enabled the analysis of large volumes of clinical and radiological data to support personalized therapeutic decisions and predict potential complications.

These technological innovations are just a glimpse of what the future holds for vascular surgery.

ADVANCED IMAGING

Advanced imaging techniques, such as high-definition CT (HDCT) and multiparametric MRI (mpMRI), are driving innovation in vascular surgery by providing detailed views of patients' vascular anatomy.[2, 3] HDCT applies advanced computational algorithms to generate high-resolution images, aiding in the identification of lesions crucial for surgical planning. Recent studies have highlighted its effectiveness in diagnosing complex vascular pathologies like aortic dissections, minimizing patient discomfort and reducing the need for contrast agents. On the other hand, mpMRI integrates multiple imaging sequences to capture diverse tissue characteristics, offering comprehensive anatomical and functional information. It has proven efficacy in evaluating peripheral arterial disease (PAD) and assessing collateral circulation in patients with critical limb ischemia (CLI), aiding in treatment response prediction and postoperative outcome assessment.[4]

These advancements in imaging technologies are complemented by digital simulation platforms, like FFR-CT, HEARTguide (FEops, Ghent, Belgium), and PrediSurge (Saint-Etienne, France), which integrate real-time imaging capabilities with advanced computational modeling.[5, 6] These platforms enable healthcare professionals to explore procedural strategies, predict patient outcomes, and optimize treatments safely and effectively. Furthermore, four-dimensional (4D) MRI and other imaging technologies, such as iterative reconstruction CT and multidetector CT, are able to provide dynamic and detailed insights into changes in vascular anatomy over time, facilitating accurate diagnosis. Advanced analytics - like fractional flow reserve and wall shear stress – may further enrich the evaluation of cardiovascular diseases.

The integration of these advanced imaging modalities and digital simulation platforms into routine clinical practice has revolutionized vascular surgery by enhancing diagnostic accuracy, procedural planning, and treatment decision. Ongoing research focuses on refining imaging protocols, developing AI-assisted image analysis tools for automated segmentation, and quantification of vascular structures. Additionally, emerging techniques like functional imaging and molecular imaging hold promise for elucidating pathophysiological processes at a molecular level, paving the way for targeted therapies and precision medicine in vascular surgery.[7] In conclusion, these advancements play a central role in modern vascular surgery, enabling surgeons to navigate complex anatomical challenges with greater confidence and precision, ultimately optimizing patient outcomes and reshaping the landscape of vascular surgical care.

AUGMENTED REALITY

Augmented reality (AR) headsets represent a significant advancement in the field of vascular surgery, offering surgeons valuable tools for navigation and visualization during procedures. These headsets allow surgeons to overlay essential information directly onto the surgical field, improving their understanding of patient anatomy and facilitating navigation through complex structures.[8] In vascular interventions, surgeons can access real-time vital data, diagnostic images, and anatomical information, enhancing precision and reducing the risk of errors. AR technology also enables surgeons to access detailed three-dimensional (3D) maps of the cardiovascular system, facilitating more comprehensive pre-operative planning and a better understanding of anatomical relationships.[9] Among the standout augmented reality headsets, the Microsoft HoloLens (Microsoft, Redford, USA) stands out

as a pioneering device, immersing surgeons in a 3D holographic environment within the operating room. Surgeons equipped with Microsoft HoloLens can overlay vital diagnostic images onto specific areas of the patient they are operating on, revolutionizing precision and awareness throughout the procedure (10). Additionally, Magic Leap glasses (Magic Leap Inc., Plantation, FL, USA) provides surgeons with a 3D perspective on crucial data and images, improving their understanding of complex anatomical structures and translating into improved surgical outcomes.[11] The Epson Moverio BT-300 (Epson Inc, Suwa, Japan) offers lightweight and compact AR glasses with a transparent display, overlaying essential data directly onto the surgical field and enhancing surgical precision.[12] These examples illustrate how AR devices are reshaping the surgical landscape, providing a more intuitive and informed experience for surgeons and ultimately leading to positive outcomes for patients. However, it's essential to acknowledge and address the limitations and challenges associated with AR technology, including potential technical glitches, the learning curve for surgeons, and integration into existing surgical workflows.

3D PRINTING

The introduction of 3D printing in the cardiovascular field signifies a significant advancement in personalized medicine and interventional therapies.[13] This cutting-edge technology enables the creation of precise anatomical models tailored specifically to individual patients,[14] providing healthcare professionals with essential tools for preoperative planning, medical education, and patient communication. However, it's crucial to consider the current challenges and limitations associated with 3D printing technology in the cardiovascular domain.

Bioprinting, for instance, has yet to gain widespread adoption in the cardiovascular sector due to various reasons. Currently, this technology is primarily employed for building complex tissue structures such as stents, prosthetic valves, and customized vascular grafts.[15] Nonetheless, numerous hurdles exist that hinder the clinical application of these implants, and cardiac tissue engineering remains an area of ongoing research, with many unresolved issues.

Despite this, the primary application of 3D printing in the cardiovascular field currently lies in training and pre-intervention planning. Although anatomical models created with 3D printing offer valuable insights, it's worth noting that most of them are static and may not fully capture the dynamic nature of pathological or normal tissues.

Nevertheless, with the continuous advancement of 3D printing technology, there are high expectations for its impact in the cardiovascular field, with the potential to improve patient outcomes through personalized and precision medicine approaches. Additionally, 3D printing has paved the way for "bio fabrication", enabling the creation of tissue structures with biomimetic properties, for potential use in regenerative medicine.[16, 17]

MINIMIZING IONIZING RADIATION EXPOSURE

A critical aspect driving the evolution of vascular procedures is the concerted effort to minimize the exposure of both patients and healthcare providers to ionizing radiation.[18] This objective is being achieved through the advancement of imaging technologies, and the refinement of existing methodologies. Cutting-edge imaging modalities like fluoroscopy and angiography now allow clinicians to visualize the cardiovascular system in real-time with exceptional clarity while significantly reducing radiation doses.[19]

Furthermore, the implementation of innovative shielding techniques and radiation-reduction protocols has been instrumental in decreasing radiation exposure. Techniques such as lead shielding and advanced collimation systems, coupled with optimized imaging protocols, enable a more precise and controlled delivery of radiation during procedures.[20] These advancements not only protect the health of patients and healthcare professionals, but also align with broader initiatives aimed at enhancing the safety and sustainability of cardiovascular interventions.

To ensure the effective adoption of these techniques, comprehensive training and simulation programs are essential. Educating healthcare professionals on the proper use of radiation-reduction technologies, and ensuring proficiency in alternative imaging methods through simulation, can substantially enhance safety measures and optimize patient care within the realm of cardiovascular interventions.[21, 22]

In addition to conventional techniques like fluoroscopy and angiography, promising alternatives have emerged to minimize radiation exposure during endovascular procedures. These alternatives offer advanced imaging modalities that provide precise guidance during procedures while minimizing exposure to ionizing radiation.

One such alternative increasingly used is intravascular ultrasound (IVUS), which utilizes ultrasound to generate high-resolution images of vascular structures from within blood vessels.[23] IVUS offers a detailed view of vascular walls and atherosclerotic plaques, enabling physicians to accurately assess pathology and guide procedures more safely.

Another promising alternative is magnetic resonance angiography (MRA), which employs magnetic fields and radio waves to produce detailed images of blood vessels without ionizing radiation.[24] MRA allows clear visualization of vascular structures and accurate assessment of blood flow, aiding in the safe planning and execution of endovascular procedures.

Finally, Fiber Optic RealShape (FORS) technology presents another innovative alternative to reduce radiation exposure during cardiovascular procedures. FORS utilizes fiber optics to create three-dimensional images of vascular structures, enabling surgeons to visualize vessel morphology and positioning in real-time without

the use of ionizing X-rays. This approach offers precise guidance during procedures, minimizing the risk of radiation exposure for both patients and healthcare providers.[25]

In essence, these promising alternatives represent a significant leap forward in reducing radiation exposure during cardiovascular procedures while providing precise guidance to enhance safety and clinical outcomes for patients.

INNOVATIVE MATERIALS

The field of vascular surgery has experienced remarkable advancements in material science, leading to the creation of groundbreaking materials that have transformed the design and manufacturing of vascular devices, particularly stents and grafts. These materials have been carefully selected to prioritize biocompatibility, durability, and long-term performance, resulting in significant improvements in patient outcomes.

Advanced polymers have emerged as a fundamental element in the evolution of materials for vascular devices. Polymeric materials, including biodegradable polymers and polymer composites, offer unique properties such as flexibility, mechanical strength, and customized degradation profiles. These attributes are especially beneficial in the production of drug-eluting stents (DES) and bioresorbable vascular scaffolds (BVS).[26]

Recent research has emphasized the critical role of polymer selection in optimizing stent performance and biocompatibility. For example, a study by Zheng *et al.* showcased how novel biodegradable polymers with controlled degradation kinetics can enhance vascular healing and decrease late-stage complications associated with stent thrombosis and restenosis.[27]

Special metal alloys, such as cobalt-chromium (CoCr), nickel-titanium (NiTi) shape memory alloys, and bioabsorbable metals, have revolutionized the mechanical properties and lifespan of vascular implants.[28,29] These alloys exhibit outstanding biocompatibility and corrosion resistance, making them excellent candidates for stent fabrication. Recent advancements in alloy design have focused on improving radial strength, flexibility, and radiopacity while minimizing the risk of thrombosis and in-stent restenosis.

The paramount importance of biocompatibility and durability in vascular device materials cannot be overstated. Modern materials undergo rigorous testing to ensure minimal inflammatory response, thrombogenicity, and endothelial disruption upon implantation. Additionally, durability assessments encompass mechanical integrity under cyclic loading conditions and resistance to fatigue failure over extended periods.

Recent literature underscores the critical role of surface modifications and coatings in enhancing biocompatibility and reducing adverse reactions. For instance, biofunctionalized polymer coatings loaded with anti-restenosis drugs have shown promising results in preclinical studies for improving long-term patency rates of vascular grafts and stents.[30]

Looking ahead, ongoing research in material science focuses on leveraging nanotechnology, additive manufacturing (3D printing), and biomimetic approaches to develop next-generation vascular devices with unparalleled performance and functionality. The integration of smart materials capable of sensing physiological parameters and dynamically responding to vascular dynamics holds immense potential for personalized and adaptive therapies in vascular medicine.

Innovative materials have significantly propelled the field of vascular device design forward, enabling the development of safer, more effective, and durable implants for treating cardiovascular pathologies. Continued interdisciplinary collaborations among material scientists, biomedical engineers, and clinicians are poised to drive further innovations, ultimately enhancing patient care and outcomes in vascular surgery.

ROBOTIC TECHNOLOGIES

The advent of innovative materials has facilitated the development of smaller and more precise instruments, enabling procedures that are less invasive and characterized by expedited recovery times. These materials contribute to the creation of sophisticated robotic systems and minimally invasive techniques that redefine the landscape of vascular surgery.

Robotic technologies have further amplified the capabilities of vascular interventions, offering enhanced precision and dexterity to healthcare professionals. By leveraging robotic assistance, procedures can be performed with greater accuracy, allowing for intricate maneuvers that were once challenging with traditional approaches. The amalgamation of minimally invasive techniques and robotic technologies not only minimizes the physical impact on patients, but also contributes to improved procedural outcomes and safety for healthcare workers.

In the rapidly advancing field of cardiovascular interventions, the integration of robotic technologies has given rise to innovative solutions, particularly in endovascular procedures. The development of current endovascular robotic systems represents a significant stride forward, providing healthcare professionals with advanced tools for precise and controlled interventions. For example, the Hansen Sensei Robotic Catheter System (Hansen Medical, Inc., Mountain View, CA, USA) allows for highly accurate and controlled movements during endovascular procedures, reducing the margin of error and improving patient outcomes.[31]

Similarly, the CorPath GRX Robotic System (Cordinus Vascular Robotics, Natick, MA, USA), enables remote robotic-assisted control of guidewires and catheters in endovascular procedures, allowing for intricate movements with heightened precision.[32] The Magellan Robotic System (Hansen, Mountain View, CA, USA) offers advanced robotic assistance in navigating complex

vascular anatomy during endovascular procedures. With its robotic catheter and guide wire control, the Magellan System provides enhanced precision and control, particularly in challenging vascular territories.[33]

While the progress of endovascular robotics may be slow, these systems hold the promise of further optimizing procedural accuracy, minimizing invasiveness, and ultimately contributing to advancements in patient care within the realm of cardiovascular interventions. However, it's essential to address the limitations and challenges associated with the integration of robotic technologies in vascular surgery to ensure their safe and effective use in clinical practice. Continued research and development in this field are crucial to unlocking the full potential of robotic-assisted vascular interventions and improving outcomes for patients.

INNOVATIVE THERAPEUTIC ADVANCES IN PERIPHERAL ARTERIAL DISEASE

Balloon angioplasty

Over the years, advancements in balloon angioplasty technology have significantly improved patient outcomes. For instance, the introduction of drug-coated balloons (DCB) has revolutionized the field by incorporating medications directly onto the balloon's surface. Studies have shown that DCB angioplasty has led to notable improvements in long-term patency rates, particularly in patients with PAD (34). There has been a discussion around different types of DCBs, notably paclitaxel-coated and sirolimus-coated balloons.[35-37] Paclitaxel-coated balloons use a chemotherapy cytotoxic agent, that kills highly proliferating cells to reduce intimal hyperplasia and subsequent restenosis. Sirolimus-coated balloons instead release an immunosuppressant, cytostatic drug, which has similar effects in inhibiting cell growth by blocking the mitotic cycle. Both types of DCBs have shown effectiveness in improving long-term outcomes for patients undergoing balloon angioplasty, with ongoing research aiming to further refine their use and optimize patient care.

Another notable innovation in balloon angioplasty is the development of intravascular lithotripsy (IVL).[38] This approach involves delivering focused shock waves to the target area within the artery using specific equipment. IVL holds promise in treating heavily calcified lesions, which are traditionally challenging to manage with standard balloon angioplasty alone. By breaking up calcified or hardened plaque, IVL facilitates the distention of the artery with conventional balloon angioplasty, ultimately improving blood flow and clinical outcomes. This technique offers a less invasive alternative for addressing calcified lesions, potentially reducing the need for more invasive procedures such as atherectomy. Ongoing research keeps exploring the full potential of IVL shock-wave angioplasty, and its role in optimizing treatment strategies for patients with complex highly-calcified arterial disease.

Stents

The latest generation of stents incorporates innovative features such as drug-eluting coatings, bioresorbable scaffolds, and improved radial strength, all tailored to enhance patency rates and reduce the risk of complications in patients with PAD. By precisely scaffolding the artery while delivering therapeutic agents, these advanced stents hold promise in improving long-term outcomes and reshaping the management of PAD.[39]

For example, one notable advancement in stent technology is the development of new DES specifically designed for peripheral applications. Devices like the Esprit™ BTK Everolimus Eluting Resorbable Scaffold System (Abbott Vascular, Abbott Park, IL, USA) may represent a useful tool in the fight against below-the-knee PAD. This DES releases Everolimus to inhibit cell proliferation, offering improved long-term patency compared to bare-metal stents.

Additionally, bioresorbable vascular scaffolds (BVS) represent another innovative concept within stent technology. Devices like the Absorb Bioresorbable Vascular Scaffold (Abbott Vascular, Abbott Park, IL, USA) offer temporary mechanical support to the artery, while gradually dissolving over time. This technology allows for vessel healing and remodeling, without the drawbacks related to the long-term presence of a metallic device, potentially reducing the risk of late complications.

Atherectomy

Vascular surgeons may so far count on a range of advanced atherectomy devices, designed to address some unsolved challenges posed by PAD. Among these, the Auryon System (AngioDynamics, Inc., Latham, New York, NY, USA) combines a catheter using 355 nm Nd:YAG laser technology with a short pulse between 10 and 25 ns, with a blunt blade enabling safe and efficient atherectomy. It aims to reduce the risk of thermal injury to the target artery. The 2.0- and 2.35-mm catheters can also be used to aspirate thrombus within occlusive, native, and stented femoro-popliteal vessels. the pulsed-wave 355-nm UV-laser atherectomy has emerged as a promising "debulking" approach in the treatment of infrainguinal PAD.[40]

These devices represent only a portion of the wide range of novel tools available for PAD endovascular therapy. With their unique features and specific mechanisms of action, physicians can customize treatment based on the specific needs of each patient, ensuring optimal outcomes and rapid recovery.

INNOVATIVE THERAPEUTIC ADVANCES IN THE TREATMENT OF AORTIC DISEASE

In recent years, significant advancements have been made in the development of novel devices for treating different segments of the aorta, including the abdominal aorta, descending thoracic aorta, aortic arch, ascending aorta, and thoracoabdominal aorta. They try to offer minimal-

ly invasive solutions for aortic pathologies, reducing the need for open surgical procedures and improving patient outcomes.

One such innovation is the Nectero EAST System (Nectero Medical, Tempe, AZ, USA), an innovative endovascular device designed to treat abdominal aortic aneurysms (AAA). This system is mainly represented by a balloon-catheter able to deliver therapeutic agents directly to the aneurysm site.[41] These agents are intended to stabilize the aneurysm wall, by reducing inflammation and extracellular matrix degradation, meant as key factors for aneurysm progression. Early clinical studies have shown promising results, suggesting that it might reduce aneurysm growth, and potentially delay or prevent the need for more invasive surgical interventions. This less invasive approach may offer in the future a new option for patients who are unsuitable for conventional surgery.

As regards the evolution of aortic endoprostheses, the most recent off-the-shelf multi-branched aortic stent-graft, named TAMBE (W. L. Gore & Associates, Flagstaff, AZ, USA), is thought to become commercially available in Europe in the near future, as a novel alternative solution for complex pararenal and thoracoabdominal aortic aneurysm endovascular exclusion.[42]

Similarly, the recently released Thoracic Branch Endoprosthesis TAG "TBE" stent-graft (W. L. Gore & Associates), is intended as a new tool for the treatment of aortic arch pathologies, including aneurysms and dissections.[43] This preloaded-single-branch endoprosthesis allows to treat distal aortic arch and proximal descending aortic disease, while maintaining flow into the left subclavian artery, without the need of associated open surgical procedures.

Finally, in the field of aortic therapy, it is certainly worth mentioning the novel "hybrid" ThoracoFlo system (Terumo Aortic, Glasgow, UK).[44] This innovative device is designed to provide effective and potentially less invasive treatment for various thoracic aortic pathologies, including aneurysms and dissections. It is based on the groundbreaking idea to combine a stent-graft with an integrated delivery system, facilitating precise placement and deployment in the thoracic aorta. One of the key features of ThoracoFlo is flexibility, allowing for customized treatment options tailored on each patient's anatomy. The device's advanced design enables optimal conformability to the aortic wall, ensuring secure sealing and long-term durability. Overall, it might represent a significant step forward in the treatment of thoracic aortic disease.

These advancements collectively highlight the continuous progress in aortic field, offering new hope and improved outcomes for patients affected by these dramatic pathologies.

INNOVATIVE THERAPEUTIC ADVANCES IN CAROTID STENOSIS

Carotid stenosis is a significant predictor of stroke and transient ischemic attack (TIA). Advances in therapeutic strategies aim to reduce the risk of cerebrovascular events, while minimizing procedural risks and optimizing long-term outcomes.

In this context, a recent innovative endovascular tool is the Neuroguard IEP System (Contego Medical, Inc, Raleigh, NC, USA) This device is thought to offer a cutting-edge solution for embolic protection during carotid stenting procedures.[45] It integrates a range of advanced features, most importantly a dual-mesh embolic filter designed to capture and retain emboli during stent placement. Additionally, the system features a dual-lumen guide that allows for precise navigation through the carotid artery, ensuring accurate stent placement without compromising cerebral blood flow.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Artificial intelligence (AI) and machine learning (ML) have emerged as transformative forces in the landscape of cardiovascular interventions, including vascular surgery. The integration of AI/ML technologies has ushered in a new era of precision and effectiveness, revolutionizing not only early diagnosis and procedural planning but also intraoperative guidance and postoperative outcomes prediction.

In vascular surgery, AI/ML systems leverage vast datasets including radiological images, clinical parameters, and patient records, in order to analyze complex patterns and predict complications. For example, already mentioned AI algorithms can analyze CT scans, MRI scans, and angiograms to automatically detect and quantify features like stenosis, aneurysms, or plaque burden. Studies have demonstrated the efficacy of AI-based image analysis in improving diagnostic accuracy, reducing interpretation variability among radiologists.[46] Moreover, AI can contribute significantly to clinical decision support by integrating various data sources, to create predictive models for procedural planning. For instance, AI-driven risk stratification models can optimize patient selection for endovascular interventions, resulting in improved clinical outcomes and resource utilization. Such models can identify patients at higher risk of adverse events or treatment failure, enabling proactive interventions and personalized care pathways.

Predictive analytics powered by ML algorithms may facilitate the prediction of postoperative outcomes and complications, based on individual patient characteristics and procedural variables. For example, AI algorithms can analyze historical data to forecast the likelihood of adverse events such as restenosis, thrombosis, or device failure, guiding informed decision-making and patient counseling.[47, 48]

In addition to preoperative planning, AI plays a crucial role in real-time surgical assistance during vascular procedures. AI-powered intraoperative guidance systems provide surgeons with real-time feedback and decision support, analyzing intraoperative data streams and offe-

ring procedural recommendations to optimize surgical workflow and mitigate intraoperative risks. Just citing the most renowned, the Cydar imaging guidance system (CYDAR Medical, Cambridge, UK), applies AI algorithms to enhance intra-operative decision-making, providing surgeons with detailed insights and guidance for optimal navigation within the patient's cardiovascular system.[49]

However, the widespread adoption of AI/ML in vascular surgery raises ethical and regulatory considerations, mainly regarding data privacy, algorithm transparency, and clinical validation. Regulatory bodies and professional societies are actively developing guidelines and standards to ensure the safe and responsible implementation of AI-driven technologies in clinical practice.

In conclusion, the integration of AI and ML holds tremendous promise for transforming vascular surgery by enhancing diagnostic accuracy, optimizing treatment planning, and improving patient outcomes. Continued research, interdisciplinary collaboration, and ethical considerations will be essential in gathering the full potential of AI-driven technologies.

CONCLUSIONS

The integration of cutting-edge technologies such as advanced imaging, robotics and automation, innovative materials, minimally invasive therapies, and AI and ML is radically transforming the field of vascular surgery. These innovations offer significant advantages in terms of precision, safety, and clinical outcomes for patients with vascular pathologies.

However, widespread adoption of these technologies requires rigorous ethical and regulatory evaluation to ensure patient safety and data transparency. Continued commitment to research and development of these technologies is essential to improve the performance of vascular surgery and promote an increasingly personalized and patient-centered approach.

REFERENCES

1. Vento V, Kuntz S, Lejay A, *et al.* Evolutionary trends and innovations in cardiovascular intervention. Front Med Technol 2024;6:1384008.
2. Schuijf JD, Lima JAC, Boedeker KL, *et al.* CT imaging with ultra-high-resolution: Opportunities for cardiovascular imaging in clinical practice. J Cardiovasc Comput Tomogr 2022;16:388–96.
3. Bissell MM, Raimondi F, Ait Ali L, *et al.* 4D Flow cardiovascular magnetic resonance consensus statement: 2023 update. J Cardiovasc Magnet Res 2023;25:40.
4. Galanakis N, Maris TG, Kontopodis N, *et al.* The role of dynamic contrast-enhanced MRI in evaluation of percutaneous transluminal angioplasty outcome in patients with critical limb ischemia. Eur J Radiol 2020;129:109081.
5. Derycke L, Sénémaud J, Perrin D, *et al.* Patient Specific Computer Modelling for Automated Sizing of Fenestrated Stent Grafts. Eur J Vasc Endovasc Surg 2020;59:237–46.
6. Liu H, Crespo RG, Martínez OS. Enhancing Privacy and Data Security across Healthcare Applications Using Blockchain and Distributed Ledger Concepts. Healthcare (Basel) 2020;8:243.
7. Floridi C, Cacioppa LM, Valeri T, *et al.* The Clinical Utility of Lower Extremity Dual-Energy CT Angiography in the Detection of Bone Marrow Edema in Diabetic Patients with Peripheral Artery Disease. JCM 2024;13:1536.
8. Eves J, Sudarsanam A, Shalhoub J, *et al.* Augmented Reality in Vascular and Endovascular Surgery: Scoping Review. JMIR Serious Games 2022;10:e34501.
9. Hussain AK, Kakakhel MM, Ashraf MF, *et al.* Innovative Approaches to Safe Surgery: A Narrative Synthesis of Best Practices. Cureus 2023;15:e49723.
10. Palumbo A. Microsoft HoloLens 2 in Medical and Healthcare Context: State of the Art and Future Prospects. Sensors (Basel) 2022;22:7709.
11. Zari G, Condino S, Cutolo F, *et al.* Magic Leap 1 versus Microsoft HoloLens 2 for the Visualization of 3D Content Obtained from Radiological Images. Sensors (Basel) 2023;23:3040.
12. Kosieradzki M, Lisik W, Gierwiało R, *et al.* Applicability of Augmented Reality in an Organ Transplantation. Ann Transplant 2020;25:e923597.
13. Tam CHA, Chan YC, Law Y, *et al.* The Role of Three-Dimensional Printing in Contemporary Vascular and Endovascular Surgery: A Systematic Review. Ann Vasc Surg 2018;53:243–54.
14. Giannopoulos AA, Mitsouras D, Yoo SJ, *et al.* Applications of 3D printing in cardiovascular diseases. Nat Rev Cardiol 2016;13:701–18.
15. Bartel T, Rivard A, Jimenez A, *et al.* Medical three-dimensional printing opens up new opportunities in cardiology and cardiac surgery. Eur Heart J 2018;39:1246–54.
16. Liu N, Ye X, Yao B, *et al.* Advances in 3D bioprinting technology for cardiac tissue engineering and regeneration. Bioact Mater 2021;6:1388–401.
17. Fazal F, Raghav S, Callanan A, *et al.* Recent advancements in the bioprinting of vascular grafts. Biofabrication 2021;13:032003.
18. Vento V, Soler R, Fabre D, *et al.* Optimizing imaging and reducing radiation exposure during complex aortic endovascular procedures. J Cardiovasc Surg (Torino) 2019;60:41-53.
19. Keshavarz-Motamed Z, Del Alamo JC, Bluestein D, *et al.* Editorial: Novel methods to advance diagnostic and treatment value of medical imaging for cardiovascular disease. Front Bioeng Biotechnol 2022;10:987326.
20. Dixon SR, Rabah M, Emerson S, *et al.* A Novel Catheterization Laboratory Radiation Shielding System: Results of Pre-Clinical Testing. Cardiovasc Revasc Med 2022;36:51–5.
21. Vento V, Cercenelli L, Mascoli C, *et al.* The Role of Simulation in Boosting the Learning Curve in EVAR Procedures. J Surg Educ 2018;75:534–40.
22. Debucquois A, Vento V, Neumann N, *et al.*; Collaborators. Xray Exposure Time in Dedicated Academic Simulation Programs Is Realistic of Patient Procedures. EJVES Vasc Forum 2022;55:5-8.
23. Mukherjee D, White CJ. Role of IVUS Imaging During Arterial and Venous Lower Extremity Interventions. JACC: Cardiovascular Interventions 2022;15:1579–81.
24. Abdelaziz M, Tian L, Hamady M, *et al.* X-ray to MR: the progress of flexible instruments for endovascular navigation. Prog Biomed Eng 2021;3:032004.
25. Modarai B, Haulon S, Ainsbury E, *et al.* Editor's Choice – European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Radiation Safety. Eur J Vasc Endovasc Surg 2023;65:171–222.
26. Toh HW, Toong DWY, Ng JCK, *et al.* Polymer blends and polymer composites for cardiovascular implants. Eur Polym J 2021;146:110249.
27. Zheng B, Liu Y, Zhang R, *et al.* A novel biodegradable polymer-coated sirolimus-eluting stent: 1-year results of the HELIOS registry. Chin Med J 2023;136:1848–54.
28. Safdel A, Torbati-Sarraf H, Elbestawi MA. Laser powder bed fusion of differently designed NiTi stent structures having enhanced recoverability and superelasticity. Journal of Alloys and Compounds 2023;954:170196.

29. Lushchik PE, Botirov MT, Rafalski IV, *et al.* Co-Cr alloys for biocompatible medical products. Yekimov S, Sazonets I, editors. E3S Web of Conf 2023;452:05015.
30. Shen Y, Yu X, Cui J, *et al.* Development of Biodegradable Polymeric Stents for the Treatment of Cardiovascular Diseases. Biomolecules 2022;12:1245.
31. Song C, Xia S, Zhang H, *et al.* Novel Endovascular Interventional Surgical Robotic System Based on Biomimetic Manipulation. Micromachines 2022;13:1587.
32. Legeza P, Britz GW, Loh T, *et al.* Current utilization and future directions of robotic-assisted endovascular surgery. Expert Rev Med Devices 2020;17:919–27.
33. Najafi G, Kreiser K, Abdelaziz M, *et al.* Current State of Robotics in Interventional Radiology. Cardiovasc Intervent Radiol 2023;46:549–61.
34. Beckman JA, Schneider PA, Conte MS. Advances in Revascularization for Peripheral Artery Disease: Revascularization in PAD. Circulation Res 2021;128:1885–912.
35. Linn YL, Choke ETC, Yap CJQ, *et al.* Utility of sirolimus coated balloons in the peripheral vasculature – a review of the current literature. CVIR Endovasc 2022;5:29.
36. Bair EC, McCarver BC, Cooper NT, *et al.* The Use of Paclitaxel-Coated Devices in the Treatment of Peripheral Arterial Disease is Not Associated With Increased Mortality or Amputations. Ann Vasc Surg 2022;87:64–70.
37. Caradu C, Lakhlifi E, Colacchio EC, *et al.* Systematic review and updated meta-analysis of the use of drug-coated balloon angioplasty versus plain old balloon angioplasty for femoropopliteal arterial disease. J Vasc Surg 2019;70:981-95.e10.
38. Kereiakes DJ, Virmani R, Hokama JY, *et al.* Principles of Intravascular Lithotripsy for Calcific Plaque Modification. JACC: Cardiovasc Interv 2021;14:1275–92.
39. Varcoe RL, DeRubertis BG, Kolluri R, *et al.* Drug-Eluting Resorbable Scaffold versus Angioplasty for Infrapopliteal Artery Disease. N Engl J Med 2024;390:9–19.
40. Das TS, Shammas NW, Yoho JA, *et al.* Solid state, pulsed-wave 355 nm UV laser atherectomy debulking in the treatment of infrainguinal peripheral arterial disease: The Pathfinder Registry. Cathet Cardio Intervent 2024;103:949–62.
41. Cheng SWK, Eagleton M, Echeverri S, *et al.* A pilot study to evaluate a novel localized treatment to stabilize small- to medium-sized infrarenal abdominal aortic aneurysms. J Vasc Surg 2023;78:929-35.e1.
42. Cambiaghi T, Grandi A, Bilman V, *et al.* Anatomic feasibility of the investigational GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis (TAMBE), off-the-shelf multibranched endograft for the treatment of pararenal and thoracoabdominal aortic aneurysms. J Vasc Surg 2021;73:22–30.
43. DiLosa K, Pozolo C, Heafner T, *et al.* Early experience with the Gore TAG thoracic branch endoprosthesis for treatment of acute aortic pathology. J Vasc Surg Cases Innov Tech 2024;10:101363.
44. Debus ES, Malik K, Kölbel T, *et al.* First in Human Implantation of the Thoracoflo Graft: A New Hybrid Device for Thoraco-Abdominal Aortic Repair. EJVES Vasc Forum 2023;58:28–31.
45. Langhoff R, Petrov I, Kedev S, *et al.* PERFORMANCE 1 study: Novel carotid stent system with integrated post-dilation balloon and embolic protection device. Cathet Cardio Intervent 2022;100:1090–9.
46. Jonas R, Earls J, Marques H, *et al.* Relationship of age, atherosclerosis and angiographic stenosis using artificial intelligence. Open Heart 2021;8:e001832.
47. Li B, Warren BE, Eisenberg N, *et al.* Machine Learning to Predict Outcomes of Endovascular Intervention for Patients With PAD. JAMA Netw Open 2024;7:e242350.
48. Li B, Eisenberg N, Beaton D, *et al.* Using machine learning to predict outcomes following suprainguinal bypass. J Vasc Surg 2024;79:593-608.e8.
49. Bailey CJ, Edwards JB, Giarelli M, *et al.* Cloud-based fusion imaging improves operative metrics during fenestrated endovascular aneurysm repair. J Vasc Surg 2023;77:366–73.

5.2 NEW METHODOLOGICAL APPROACHES IN MED-TECH RESEARCH AND INNOVATION

Stefano Bonvini, Sara Allievi, Nicola Doppio

INTRODUCTION

In the realm of technological advancements across various human activities in recent decades, the field of medicine undeniably stands out for its significant challenges. Comparing the progress seen in areas like telecommunications, information technology, automotive engineering, and other consumer sectors to the tools and innovations available just three decades ago, the stark leap forward is strikingly evident. In the medical domain, such advancements have not been as conspicuous. One contributing factor is probably represented by the nature of medical challenges, that often require solutions beyond traditional medical approaches, therefore demanding innovations in technology, software, and materials. In today's knowledge-driven world, specialization often prevails, making it improbable for a cardiac surgeon - specialized in coronary artery bypass procedures - to possess the expertise in materials science necessary for devising new surgical instruments. Similarly, it's unlikely for an engineer or chemist - specialized in materials - to possess the knowledge of atherosclerosis pathophysiology and its surgical implications, required for conceiving medically relevant solutions for arteriopathies.

Another relevant aspect, when it comes to technologies in the medical field, concerns the weight of the physician's role in the patient's care course. For example, advancements in the endovascular field, such as the development of increasingly high-performance products like endoprostheses, have guaranteed favorable outcomes for patients regardless of the operator. The reduced weight of the surgeon's role within this process is attributed to more routine and standardized gestures, such as tightening a screw. Physicians, with the exception of a few rare cases, are hardly involved in product development, and their activity consists of applying technologies developed by others into their own practice. The transition from open to endovascular surgery shows this concept effectively. While the open treatment of abdominal aortic aneurysms involves suturing an anastomosis, which is a personal and somewhat unrepeatable gesture, deploying an endoprosthesis represents a standardized and depersonalized procedure, where the differentiating factor increasingly lies in the characteristics of the prosthesis itself rather than the surgeon's individual skill or technique.

The medical landscape is currently undergoing a transformative wave of technological integration. As a result, even in the realm of research, surgeons often find themselves primarily analyzing outcomes stemming from the application of technologies developed by private company research and development (R&D) efforts. To remain pivotal in the patient care process in the future, surgeons must adapt by delving into the realm of technological development, acquiring knowledge beyond their traditional medical expertise. However, expecting surgeons to acquire adequate expertise in engineering or computer science to lead research projects aimed at developing new technologies is unrealistic. Instead, they should foster new modes of interdisciplinary collaboration, engaging in constructive dialogue across diverse fields while retaining the depth of their medical knowledge. This multidisciplinary approach is essential for ensuring that surgeons take the lead in future healthcare innovation while upholding the integrity of their specialized expertise.

One of the most pressing challenges in research today lies in the ability to bring together professionals from diverse fields, fostering collaboration to propel innovation in healthcare. This endeavor holds significant ethical and professional implications, promising exciting advancements. It entails not only fostering dialogue and understanding the language of other professionals but also adopting a novel approach to research. This approach, distinct from the traditional medical research paradigm, aligns more closely with the rapid pace characteristic of the industrial world. Indeed, it is a common experience that technological advancements in everyday life progress at a markedly faster rate than what is typically observed in the medical field.

An essential component of thriving in this innovative approach is the involvement of young professionals. Their age often correlates with a greater affinity for navigating new technologies and possessing the capacity for "out-of-the-box" thinking. Unlike their more seasoned counterparts, young professionals have yet to accrue extensive professional experience, a process that typically transpires later in life in surgical fields. Consequently, they are better positioned to conceive ideas in unconventional and, thus, original ways.

Therefore, recognizing the need for advancements in the realm of medicine, we have explored a novel method for conducting research, innovation, and training in vascular surgery. This innovative methodology represents a bold exit from conventional practices, marking our commitment in pushing the boundaries in vascular surgery.

OPEN INNOVATION AND VASCULAR SURGERY

The innovative methodology that we present in this chapter is represented by three main methods and approaches, recently adopted in the fields of R&D, product development, and, in general, innovation management.

First of all, it embraces the concept of Open Innovation,[1] which was introduced in the early 2000s by Prof. Henry Chesborough. Open Innovation refers to factual evidence that effective innovation processes often involve not only organization's internal R&D structures and competencies but also external contributors, such as cu-

stomers, end users, business partners and suppliers, all across the value chain. This relates to the fact that these actors retain knowledge and insight, often based on direct and personal experience, that can significantly contribute to improve the value products and services, and, with that, their market viability and competitiveness. Open innovation has been initially experienced by companies via online platforms and businesses, able to match the demand and offer of technological solutions to scientific and engineering innovation problems (or "challenges") worldwide. Differently, at a more national, regional or even local scale, open innovation can take place by involving startups or young talents, such as hackathons or innovation prizes.[2]

Second, the methodology we present embed Agile and Lean product development tenets, which implies breaking down the R&D and innovation process into smaller (shorter) iteration cycles (often called "sprints") during which developing, testing and delivering more refined and value-adding versions of the intended product or solutions, in an incremental way. This approach, which is derived from the Japanese Lean Manufacturing philosophy pioneered by Toyota in the 1950s and 60s, mainly serves the purpose of decreasing the risks of unsuccessful outcomes of longer and cumbersome product development projects. Building on such paradigm, the more recently diffused "Lean Startup" approach[3] suggests that early stages ventures perform quick and iterative market tests and experiments of "minimum viable versions" of products or services (so-called "MVP" – Minimum Viable Product) with end users and potential customers, to assess the robustness of the many business and technological assumptions that underpin the earlier phases of a product development endeavor, before investing in its actual prototyping or development.

Third, this methodology embeds principles from Design Thinking,[4] as it involves participants to perform activities and deploy competences normally featured by designers: analyzing a given industrial or business context; identifying and investigating a problem or opportunity ("challenge"); engaging in creative production of ideas of solutions adopting a divergent standpoint; addressing decision making to select the best idea of solution, adopting a convergent stance; building low-cost prototypes allowing for early user testing and co-design session.

Such theoretical and methodological references have been chosen to inform the approach we propose in the light of the fact that Open innovation, in particular, has become a catalyst for transformative change within the healthcare sector. It has played a pivotal role in the rapid response to the COVID-19 pandemic, including the design and production of medical supplies and personal protective equipment, vaccine development, and efforts to contain the spread of the virus and mitigate the impact on global health systems.[5] Collaborative efforts has also been made in pharmaceutical research,[6] the development of digital health technologies (such as artificial intelligence, internet of medical things [IoMT]),[7] implants, and personalized medicine.[8] Open innovation approaches have demonstrated their potential to address critical challenges and improve healthcare delivery,[9] disease prevention, and health promotion.

However, it is worth noting that - despite the potential benefits - adopting open innovation approaches in healthcare comes with challenges. Health innovation systems possess distinctive characteristics compared to other sectors' innovation systems. Firstly, state health systems serve as major customers for innovations, but they are complex and fragmented. Secondly, health innovation systems separate major customers (health systems) from major users (patients/citizens). Despite producing numerous innovations, health innovation faces inefficiencies, including slowness, high costs, and poor targeting and adoption.[10] Additionally, cultural barriers, regulatory and reimbursement processes, ethics, and data privacy concerns, and interoperability issues pose significant obstacles to the widespread implementation of open innovation strategies. The development of new patient roles, complementary technologies, revised processes, innovative business models, and policy changes will be essential to foster collaboration and user-centric innovation, ultimately enhancing the quality and accessibility of healthcare for everybody.

THE MEDITECH CHALLENGE - VASCULAR SURGERY METHODOLOGY

The methodology we propose is a new format of open innovation contest (or "innovation challenge), that we have called "MediTech Challenge – Vascular Surgery". This initiative was launched by the University of Trento and the Provincial Agency for Health Services of the Autonomous Province of Trento (APSS), in collaboration with Hub Innovazione Trentino (HIT) – a foundation knowledge and technology transfer –, with the aim of providing a unique experiential learning opportunity to resident doctors specializing in vascular surgery and PhD and Master.

The Initiative lasts four months and blends classic face-to-face training with coaching sessions, problem-solving, and practical hands-on activities aimed at ideating new solutions to technical problems (challenges) in the field of vascular surgery by leveraging scientific and technological expertise in various disciplines. The methodology is based on a structured collaboration between engineering students, young researchers and resident doctors (called "solvers"), who form multidisciplinary teams to devise solutions to the challenges.

Overall, the initiative seeks to have educational purposes: the main learning outcome for resident doctors is understanding how advanced technologies, engineering disciplines and innovation management approaches can be utilized to develop innovations impacting the vascular surgery practice.

To participate, candidates must submit an application individually to an open call published by the University

of Trento. Selected applicants are assigned to a team that includes both residents and young engineers; each team is supported by university professors and senior vascular surgeons and addresses one challenge topic that is identified upfront. Six topics were identified in the first edition of the Meditech Challenge (Table 5.2.I). The topics were identified during a series of meetings between surgeons and university professors (first at a group level, then bilaterally) which lasted roughly 12 months, and produced one-page technical documents specifying the challenges (so-called "challenge briefs").

Once a challenge is assigned, each team applies the innovation methods mentioned above, which normally entail the following practical activities: performing literature review; performing early patent search; acquiring data and information; performing field observation and interviews; performing data analysis with advanced software; modeling of phenomena and processes; accessing university laboratories for the use of machinery; engaging in ideation sessions; designing and engineering prototypes (including mechanical design, coding, materials characterization, mathematical and physical modeling); performing tests and experiments; reporting; presenting results in a public setting.

The Meditech Challenge lasts almost 4 months, during which teams are provided with methodological training by technology transfer and innovation managers, as well as with dedicated webinars on vertical topics by surgeons or representatives of MedTech companies. Indeed, the initiative is co-financed (sponsored) by a number of companies that are identified via a second public call for selection. Sponsoring companies, which participate under a NDA - Non Disclosure Agreement, are invited to take part to ongoing discussions with teams, provide feedback and possible guidance to improve the market viability of solutions under scrutiny.

Each team is asked to produce a final report containing the description of the problem addressed, the idea of solution, its novelty, its target market and expected impact, as well as a technology maturation / validation plan (including milestones, activities and resources for a follow-up project), which aims to attract partners and investors. A common template for this report is provided; specific concepts and metrics from new product development and innovation processes are used, such as the TRL – Technology Readiness Level, a 9-step scale initially developed and utilized by NASA to manage the advancement of the many projects in the Apollo program, and nowadays widely utilized by companies and research institutions to shortly assess the maturity of a technological solution under development. In Table 5.2.II we provide a snapshot of the structure and main of the report that each team of the Challenge is asked to present by the end of the initiative.

At the end of the Challenge, teams present their ideas of solutions during a public event (Figure 5.2.1). Results are evaluated by a jury including vascular surgeons, biomedical engineers, and innovation management experts.

Table 5.2.I ● The six topics of the Meditech Challenge.

Team 1	New stent designs capable of minimizing or preventing the occurrence of type 1 endoleaks.
Team 2	Use of advanced biocompatible functional materials (hydrogels; aerogels; 3D foldable materials) to prevent type 2 endoleaks.
Team 3	New concepts of robots for remote vascular surgery operations.
Team 4	Artificial intelligence-based decision support systems for optimizing the planning and execution of surgical interventions.
Team 5	Solutions for CT-ultrasound data fusion to limit the use of CT after procedure.
Team 6	Computational fluid-dynamic models for endoleaks detection from PPG.

Four criteria are used for evaluating the results: maturity of results, scientific robustness, potential business impact, quality of the final presentation. The final event is preceded by private one-on-one meetings between teams and sponsoring companies interested in gaining a deeper understanding of specific solutions for potential follow-up (again, upon signing an NDA - Non Disclosure Agreements).

It is worth noting that the Intellectual Property (IP) of the developed ideas of solutions is owned by the University of Trento, not by the single participants, nor by their institutions (*e.g.* polyclinics or hospitals, in case of residents). Albeit this might seem unfair or counterintuitive, this policy makes it easier for any legal entity (a large MedTech corporate or a startup company possibly launched by team members) to enter discussions with another legal entity (the University of Trento) to acquire the IP and pursue further technology maturation / validation and industrialization. A different IP policy, such as, for instance, having the foreground (newly developed) IP "jointly owned" by the team participants, would in fact hinder the capability to exploit is, as anybody in the team could pose a prohibition.

EARLY FINDINGS FROM THE FIRST EDITION

The first edition of the Meditech Challenge - Vascular Surgery was kicked off on February 7, 2024, after a partnership agreement was set out between the three partners. A call for selections of solvers and sponsoring companies was prepared and published by the University of Trento in the previous months, between October and December 2023. Seventy-four solvers applied, and forty-eight were selected (fifteen residents and thirty-three PhD and Master students).

Six companies responded to the call for selection of sponsors, plus one company granted a direct contribution following own policies: this allowed to raise 35 K€ to cover direct costs if the initiative (event catering, travel and accommodation for residents, promotional, communication and dissemination material, prizes, gadgets).

Table 5.2.II ● Template of the maturation plan.

PART 1: solution description	
1. PROJECT NAME AND ACRONYM	Specify project name and acronym.
2. ABSTRACT	Provide a summary of the project, describing the main gist of your idea, its value proposition, and why it should be funded (max 750 characters).
3. TEAM	List the current members of the team, affiliation and contacts (emails), including involved professors acting as mentors, and, among them, one Principal Investigator (PI). Please use a table.
4. PROBLEM	Describe the problem, its context, the involved processes, technologies, methods, end users. Why is this a problem? Provide problem metrics if possible (cost, time, quality). Success criteria: how would an appropriate solution look like? What are the requirements and constraints for an appropriate solution? (scientific, technological, business). Provide references to current literature or other evidence (max 3000 characters).
5. SOLUTION	Describe your idea of solutions: what it is (design, software, product, material, method, process); how it works (why and how it solves the problem); its key benefits to users; to what degrees it matches the success criteria and requirements. Feel free to include schemes, sketches, pictures, charts (max 3000 characters).
6. NOVELTY	Clarify the advantages of your solution with respect to current state of clinical practice, methods, market products, technologies by referring to product benchmarks, literature and patents references (max 1500 characters).
7. CURRENT MATURATION	What is the maturation stage of your solution? Is it an idea, is it a concept, do you have a working prototype? Please try to refer to the Technology Readiness Level (TRL) scale; what evidence do you have that your solution works/might work? Please include results from tests/experiments, as well as working hypotheses and underpinning assumptions (max 1500 characters).
8. MARKET	Demonstrate that there may be a market demand for your solution: what kind of companies or entity may be interested in acquiring or exploiting this solution? In what sector? How much do they currently spend every year in competitive or substitutive solutions? How are these companies connected with the end users having the problem? (Max 1500 characters).
9. IMPACT	What is the potential impact of this idea, in case it is widely adopted in the long term? Please clarify the potential economic, scientific, social and environmental impacts (max 1500 characters).
PART 2: validation/maturation plan description	
10. TARGET MATURATION	Why is this maturation needed (*e.g.* what do you want to validate/demonstrate)? What is the maturation stage that you want to achieve with this project? (Refer to the Technology Readiness Level, TRL scale); what data and evidence will you collect to prove that your solution works/might work? Please clarify advancement with respect to section 7 (max 1500 characters).
11. WORKPLAN	What will you do to achieve the above-mentioned results? Please provide a list of tasks/actions, specific objectives and Key Performance Indicators (KPIs) deliverables, a timeline, including milestones, and the methods/processes you will use. Feel free to include a Gantt chart (max 3000 characters + Gantt chart – picture or summary table).
12. RESOURCES	What resources will you need to carry out the workplan? Please clarify the human resources involved (people and competences, and their effort in Person Month, PM), their affiliation (within and beyond UniTrento) infrastructures/labs, machinery, consumables, and other costs; provide a full budget table (max 1500 characters + summary budget table or picture).
13. INTELLECTUAL PROPERTY	Who owns the proposed idea? Who contributed to developing the idea? Was this idea (or parts of it) funded by any entity in the past? Was there any public disclosure of your idea? What is the IP protection strategy? (Max 1500 characters).
14. EXPLOITATION STRATEGY	How do you expect to exploit / valorize the results? Are you (as a team) going to further invest in this technology idea (*e.g.*, by means of launching a startup/spinoff, or by further researching on the topic)? Or: do you think some companies or other entity may be interested in further investing in this solution (collaborations, funding, acquiring or licensing the IP)? What is the overall IP valorization/exploitation strategy? What will you do to reach these entities (*e.g.* dissemination actions) (max 1500 characters).
15. RISKS	Please identify the risks related with your project: provide a risk assessment table (probability x severity) and mitigation actions (max 1500 characters within the table).

FIGURE 5.2.1 ● Participants of the Meditech Challenge at the final event, showcasing innovation and collaboration in healthcare technology.

Personnel costs and indirect costs were not budgeted, as considered part of the in-kind contributions of the three partners.

Six teams were formed by the organizers, balancing multidisciplinary, seniority, and fitting the purpose of addressing the six above-mentioned challenge topics. We hereby provide a more detailed description of the six topics, along with some early evidence of the team's operation and work in progress.

Topic 1: Design of new conformable geometries for stent-grafts. Current stents and prostheses often fail to conform adequately to patients' anatomy, leading to potential complications such as type 1 endoleaks and migration. Lack of optimal proximal and distal sealing on artery walls might contribute to long-term issues that require reinterventions. The objective of this challenge was to conceive a new stent-graft design that enhances overall prosthetic conformability, particularly in terms of high radial force and minimal axial movement, while ensuring optimal interaction with the artery wall. One promising approach involves integrating an active seal within the tissue to enhance adherence. This innovation aims to improve patient outcomes and reduce the need for long-term reinterventions. The team focused on CAD (Computer-Aided Design) design and prototyping (with additive manufacturing techniques) of a new fixation and sealing mechanism for an abdominal stent.

Topic 2: Use of biocompatible functional materials to prevent type II endoleak. Type II endoleak remains a challenging complication after EVAR. Current solutions, including embolization and specialized prosthetics, are limited by efficacy and practicality. This challenge aimed to explore the use of biocompatible functional materials to prevent type II endoleak. Various options have been considered by the team, including hydrogels, polymers, and coil-shaped peptides. Specific focus has been driven in developing a concept of a self-expanding and biodegradable barbed filament. An alternative option under scrutiny is a novel degradable and biocompatible solution in the form of millimetric beads to be inserted in the aneurysmal sac. Both the solutions under consideration are non-permanent, to enable the shrinkage of the sac, and radiopaque, to permit the visualization upon medical imaging, two characteristics non-available simultaneously in the devices currently on the market.

Topic 3: New concept of robots for vascular surgery. This challenge addressed the need for remote-operated robots in vascular surgery, aiming at simplifying stent-graft deployment and minimizing surgeons' exposure to radiation. The challenge involves adapting microsurgery robots or those used in other surgical contexts to vascular surgery. The proposed solution is a robot concept that seeks to replicate surgeons' movements to allow a remote insertion of a catheter and a guide wire. The provision of accurate and instant haptic feedback appears to be the main challenge to engineer the conceived system. Future steps include prototyping and testing within simulated and 3D-printed aortic structures.

Topic 4: Artificial intelligence solutions to support procedure planning. This challenge aimed to develop an AI-based software capable of assisting a surgeon while planning an EVAR. This software is supposed to extract the morphological features of different aortic segments from CT scans and based on those, provide the surgeon with the best stent-graft-IFU matches. This would improve time efficiency and augment the successful treatment rate. The team has been working on teaching the model to segment the aorta based on CT scans provided by 3 independent medical centers.

Topic 5: TC-ultrasound data fusion. This challenge explored the feasibility of replacing CT scans with ultrasound imaging for follow-up after EVAR. The task involved developing a method to fuse ultrasound images with pre-existing CT data, enhancing the evaluation of surgical outcomes and minimizing radiation exposure. This promises more accuracy and less invasiveness, but also would represents an advantage for radiologists and surgeons, as healthcare professionals can achieve a comprehensive view, facilitating precise diagnosis and monitoring.

Topic 6: Hemodynamic computational models for vascular surgery. Elevated pulse-wave velocity (PWV) indicates increased arterial stiffness and is associated with adverse cardiovascular outcomes. Previous studies indicate that the deployment of stent grafts might increase such cardiovascular risk markers. This challenge proposed to employ computational wave propagation models as a virtual lab to quantify the impact of EVAR on aortic stiffness. This approach aims to identify graft properties that reduce cardiovascular risk indicators, potentially informing prosthesis design. Furthermore, the team has assessed the detectability of endoleaks in peripheral sites using non-invasive signals, such as wearable-acquired PPG.

At the time this chapter is being written the initiative is still ongoing; although at this stage we cannot evaluate the overall results and the capability of the initiative to reach its strategic goals, by reflecting on the ongoing experience we can already draw some preliminary observation that are worth sharing.

First, the multidisciplinary profile of the teams - connecting resident doctors with PhD and MSc students from engineering, mathematics, physics, economics, and management disciplines - has been proving successful. We have collected numerous positive informal feedback from both residents and university students about the mutual benefits related to the exchange of knowledge taking place between the two types of solvers at a team level. Of course, many concepts taken for granted by one of the parties (especially medical concepts, such as "endoleak", or "EVAR") were obscure for the other; for that reason, organizers instructed teams to allocate enough time during the initial meetings to build a common ground of understanding on basic concepts. Also, an ice-breaking and team building session was organized online before the kickoff meeting, which allowed participants to get acquainted with each other. Face-to-face networking sessions and meetings were also organized in the first period.

Second, it proved crucial to provide teams with methodological training and support on the innovation management approaches illustrated in section 2. Overall, teams were equipped with a process-model blueprint to follow to get from the assigned problem to a solution (upfront online training was provided to all participants before the kickoff meeting). Furthermore, it is worth noting that teams' operations were closely monitored by organizers, who have set up progress report meetings and support and troubleshooting sessions over the course of the four months. For similar purposes, an in-situ interim meeting was organized halfway through the duration of the Challenge where teams were asked to present ongoing results: this had the effect of creating peer pressure and mutual expectations with the results. Overall, it is worth noting that the whole process must be methodologically informed and closely supported during its implementation in order to avoid unclarity and roadblocks, which proven to be considerably time consuming and requiring specific innovation management and knowledge and technology transfer expertise.

Finally, the involvement of companies must be carefully planned, especially in case organizers have is an explicit will to pursue actual product innovation - besides the educational goals of the initiative. Indeed, companies may be genuinely interested in funding further work and, in perspective, acquiring the IP resulting from the Challenge. Under this light, it is be beneficial to involve companies' representatives during the Challenge, for instance allowing them to provide early feedback to teams, therefore ensuring that devised solutions are aligned with state of the art of R&D and market needs. However, MedTech companies have very strict policies with regards to engagement with public entities (including universities, not only clinical structures) which may hinder their capability to take an active part in the process.

In conclusion, despite the many merits, teams recognized that the application of these approaches in medicine, and particularly in vascular surgery, may face some limitations. First, vascular surgery heavily relies on advanced imaging modalities and specialized equipment, which innovation can be resource-consuming, posing logistical hurdles. Secondly, prioritizing product or technology-related research and innovation it might fail to capture the full complexity of vascular pathology and patient care dynamics in real-world clinical scenarios (patient-physician interaction, diagnosis uncertainties, intraoperative and postoperative complications, procedural errors, and adverse patient outcomes). While fostering innovation and experimentation, patient safety, and minimize the risk of harm should be prioritized. Additionally, despite promoting education and innovation, this approach may struggle to fit in with the time-intensive nature of vascular surgery training and daily practice. Lastly, since communication is crucial for effective collaboration, the diverse educational backgrounds and expertise of the people involved can hinder effective interaction and the development of products or solutions.

CONCLUSIONS

The Meditech Challenge - Vascular Surgery is an experimental professional education and open innovation initiative that has been lunched in the Trentino province (Italy) in 2024 with the scope of fostering multidisciplinary exchange and open innovation between resident vascular surgeons and university and PhD students with a technological and scientific background. The launch of the Challenge was made possible by a partnership between the regional public health agency (APSS), the local university (University of Trento), and the regional hub for innovation (Fondazione Hub Innovazione Trentino).

The outcomes of the first edition of the Challenge will be evaluated during 2024: this will allow to extract evidence of its effectiveness, as well as additional scientific and managerial insights and implications for practi-

tioners possibly interested in replicating the format elsewhere.

From the ongoing experience we can already draw some encouraging – though preliminary – evidence: organizers were able to rollout the initiative following the plan and regulations (call for selection), respecting the devised timeline and involving a viable number of participants (residents, university students, senior surgeons and technology experts, sponsoring companies). Operations followed the plan, and the teams went through all the planned activities, and managed to send a report with the description of the solutions, to be evaluated by a jury, and presented during a final event.

Despite the disparities between research in the tech realm and medical research, these preliminary findings hint at the remarkable potential for these approaches to revolutionize vascular surgery in the near future.

REFERENCES

1. Chesbrough HW. Open Innovation: The New Imperative for Creating and Profiting from Technology. Harvard Business School Press; 2003.
2. Franzò Si Doppio N, Natalicchio A, *et al.* Designing innovation contests to support external knowledge search in small and medium-sized enterprises. Technovation 2023;121(C).
3. Ries E. The Lean Startup: How Today's Entrepreneurs Use Continuous Innovation to Create Radically Successful Businesses. Currency; 2017.
4. Brown T. Design Thinking. Harv Bus Rev 2008.
5. Liu Z, Shi Y, Yang B. Open Innovation in Times of Crisis: An Overview of the Healthcare Sector in Response to the COVID-19 Pandemic. J Open Innov Technol Mark Complex 2022;8(1).
6. Yeung AWK, Atanasov AG, Sheridan H, *et al.* Open Innovation in Medical and Pharmaceutical Research: A Literature Landscape Analysis. Front Pharmacol 2020;11:587526.
7. Cesario A, D'Oria M, Simone I, *et al.* Open Innovation as the Catalyst in the Personalized Medicine to Personalized Digital Medicine Transition. J Pers Med 2022;12:1500.
8. Flessa S, Huebner C. Innovations in Health Care-A Conceptual Framework. Int J Environ Res Public Health. 2021;18:10026.
9. Šlapáková Losová V, Dvouletý O. The role of open innovation in addressing resource constraints in healthcare: a systematic literature review. J Health Organ Manag 2024 25;ahead-of-print(ahead-of-print).
10. M. Gabriel, I. Stanley TS. Open Innovation In Health: A Guide To Transforming Healthcare Through Collaboration.; 2017; download at: https://media.nesta.org.uk/documents/open_innovation_in_health_0.pdf

5.3 ACTUAL STATE AND PROMISES OF REGENERATIVE MEDICINE IN VASCULAR AND ENDOVASCULAR SURGERY

Eugenio Caradonna, Flavio Peinetti, Francesco Setacci, Fulvio Ferrara, Carlo Setacci

INTRODUCTION

Peripheral artery disease (PAD)represents the set of several occlusive arterial syndromes that range from asymptomatic clinical pictures to dramatic disease requiring amputation. This spectrum becomes more progressive and symptomatic with time, often transforming into chronic limb threatening ischemia (CLTI).

Patients with CLTI experience a rapid functional impairment, that affects dramatically the quality of life and social lifestyle.

The goals and pillars of CLTI therapy are:

a. medical treatment: pain control, reduction of major adverse cardiovascular events and improvement in quality of life.

b. interventional treatment: limb salvage, wound healing, maintenance of ambulatory status (fostering independence and psychological well-being).

c. surveillance: close follow-up and monitoring after delivery of treatment and even after healing.

Treatment efforts employing medical, endovascular, and surgical techniques have focused largely on reestablishing blood perfusion to distal blood vessels and risk factors modification to relieve pain, heal ulcers and preserve limbs.

OVERVIEW ON REGENERATIVE MEDICINE AND HOW IT CAN TRANSFORM VASCULAR SURGERY

Many patients with CLTI are not suitable for revascularization based on their vessel anatomy, or because the procedure is often unsuccessful due to graft failure and/or stent thrombosis or restenosis. Currently there is no specific medical treatment directed at improving blood flow distal to vessel occlusion. To address this relative lack of specific medical therapy, current investigational approaches involve promotion of therapeutic angiogenesis in the limb, distally to the occlusion site.

In this context, a formidable aid to Vascular Surgery comes from regenerative medicine.

The process of neovascularization can involve some or all the process of angiogenesis, arteriogenesis and vasculogenesis. Angiogenesis means growth of new capillaries from pre-existing blood vessels induced by the proliferation, differentiation, and migration of endothelial cells in response to *stimuli* such as hypoxia, ischemia, mechanical stretch, and inflammation. This process is regulated by a complex interaction of pro and antiangiogenic growth factors, local tissue environment and genetic factors. Harnessing this physiological process using pharmacological and/or genetic modulation to enhance formation of new blood vessels distal to an arterial occlusion is known as therapeutic angiogenesis.

The clinical approach of CLTI has recently moved from surgical to endovascular repair.

In particular, since diabetic foot shows a large involvement of below-the-knee (BTK) and below-the-ankle (BTA) arteries, the peripheral endoluminal approach (PTA) has become the first choice in diabetic patients, even considering cardiovascular and renal typical comorbidities. Despite the high success of PTA, clinical restenosis still represents a huge problem reaching around 70% at one year follow-up. Of note, the risk for major amputation is correlated with the involvement of BTA arteries in CLTI patients with foot gangrene. In addition, although early revascularization procedures of diabetic foot ulcers can lead to a high rate of limb salvage, nevertheless several PTA fails, and the obstructive patterns are considered as NO-OPTION CLTI representing approximately 25% of patients. The high risk of PTA failure in NO-CLTI patients is mainly due to very distal BTK disease with involvement of pedal and plantar arteries. This clinical condition is a predictor of non-healing ulcers this, failure of surgical approaches, with a final tremendous risk of major amputation. Thus, this still unmet clinical need provides the rationale for exploring advanced alternative therapies against limb ischemia.

CELL-BASED THERAPIES FOR VASCULAR DISEASES

The field of cell-based therapies is assuming an important role within various vascular diseases, offering innovative approaches to promote angiogenesis, vascular repair, and tissue regeneration. The core processes of stem cell vascular medicine, angiogenesis, arteriogenesis, and vasculogenesis are interrelated, but distinct.

Vasculogenesis is the process of blood vessel formation that occurs through the *in situ* differentiation of precursor cells known as angioblasts, which aggregate and form blood vessels.

It is a critical mechanism not only during embryonic development but also in adults, where it contributes to the reparative effects of progenitor cell therapy in ischemic diseases.

This process is different from angiogenesis, and arteriogenesis.[1]

Angiogenesis refers to the process of creating new blood vessels from pre-existing ones, which is vital for various physiological functions, including embryonic development, wound healing, and the regulation of the menstrual cycle. This process can occur through different mechanisms, such as the sprouting of new vessels from existing ones, the splitting of existing vessels, and the recruitment of endothelial progenitor cells.[2] The regula-

tion of angiogenesis is under cytokines, such as vascular endothelial growth factors (VEGF) and stromal derived factor- 1α (SDF-1α) essential for the recruitment and homing of circulating angiogenic cells.[3-5]

Arteriogenesis is the process of remodeling and enlarging pre-existing arterioles into larger arteries, and it's critical for restoring blood flow to tissues with occluded or stenosed arteries, such as in cases of ischemic heart disease or PAD. It is initiated by an increase in fluid shear stress on the endothelial cells that line the arterioles, leading to the activation of various signaling pathways and the recruitment of cells involved in vascular remodeling.[6]

Postnatal angiogenesis, also referred as neoangiogenesis, refers to the development of new blood vessels in adult tissues. This phenomenon occurs in a variety of physiological and pathological conditions, including wound healing, the development of exercise-induced muscle growth, and the progression of cancer and age-related macular degeneration. The formation of new blood vessels is a tightly regulated process that involves the interplay of pro-angiogenic and anti-angiogenic factors, as well as the recruitment and proliferation of endothelial cells, supporting cells, and stem cell with angiogenic potential which are mobilized from the bone marrow.

While angiogenesis and vasculogenesis involve the formation of new blood vessels, arteriogenesis is focused on the remodeling and enlargement of existing arterioles.

Stem cells own remarkable self-renewal and differentiation capabilities, making them attractive candidates for regenerative medicine. Several types of stem cells have been explored for their potential in treating vascular diseases.

Embryonic stem cells

Embryonic stem cells (ESCs), derived from the inner cell mass of blastocysts, are pluripotent, and they can differentiate into virtually any cell type in the body, including vascular cells. However, their use raises ethical concerns and carries a risk of teratoma formation.[7]

Adult stem cells

Adult stem cells, such as mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs), can be obtained from various sources, including bone marrow, adipose tissue, and peripheral blood. These cells have demonstrated potential for promoting angiogenesis, vascular repair, and tissue regeneration.

According to Asahara *et al.*, a subset of bone marrow-derived cells, specifically $CD34^+$ cells, contribute to the formation of new blood vessels.[8] These cells, known as EPCs, play a crucial role in the physiological processes that result in the development of new blood vessels.[9-11]

The CD34 surface marker is a transmembrane protein, present on vascular endothelial cells (ECs), EPCs and HPC.[12] $CD34^+$ populations possess unique regenerative capabilities, which have attracted considerable attention in the field of vascular medicine.[13-15]

Since the seminal work of Asahara, the extensive research performed have contributed to characterize the population of progenitor cells particularly hematopoietic stem cells (HPS) and EPC.

CD133, also known as prominin-1 and a transmembrane glycoprotein, is typically expressed on undifferentiated cells such as endothelial progenitor cells, hematopoietic stem cells, fetal brainstem cells, and prostate epithelial cells.[16] Several other cell populations are important in angiogenesis: endothelial colony forming cell (ECFC), C-Kit cells, very small embryonic like cells (VSELc) and mesenchymal stem cells.[17, 18]

Notwithstanding the fundamental role of platelets.[19]

ECFCs ($CD45^-$, 34^+) which emerge as a population of late outgrowths from EPC in culture medium, have been found to circulate and exhibit highly proliferative characteristics. Additionally, these cells possess the capacity to form tube-like structures.[20]

C-kit cells, also known as CD117-positive stem cells, are a specific type of stem cell that expresses the c-kit receptor. These cells play a crucial role in several physiological processes, including the formation of various blood cells and tissues.

Adult tissue contains a rare very small population of stem cell with characteristic resembling embryonic cells (VSElc)[21, 22] that seems to play a supportive role in angiogenesis.[18]

The function of EPCs is pivotal in maintaining the balance of endothelial cells and plays a crucial role in repairing ischemic damage. EPCs, ECFCs, C-kit, VSELc, and MSCs produce cytokines such as VEGF-A, FGF, IGF-1, PDGR, and TGFβ, which stimulate vasculogenesis.[23-26] The aforementioned cells, and platelets are responsible for the production of exosomes and microvesicles, which are crucial for facilitating cell-to-cell communication and the activation of genes necessary for angiogenesis.[27-29] These exosomes and microvesicles contain cytokines and microRNAs (miRNAs), both of which play a vital role in this process. BMCs and peripheral blood mononuclear cells (PBMNc) differ in cytokines expression. VEGF is mainly expressed in BMCs.[30]

Ischemic events cause a complex pathophysiological process that aims to repair the damage. Cytokines released during ischemia interact with the cell niches of the bone marrow, resulting in the migration of endothelial progenitor cells into the ischemic tissue through processes of adhesion, proliferation, differentiation, and the release of cytokines. Of notice, in chronic limb ischemia the expression of genes of vascular endothelial growth factor (VEGF) and stromal derived factor 1α (SDF-1α) is reduced in the tissue.[31]

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are generated by reprogramming somatic cells back to a pluripotent state, offering an alternative source of patient-specific stem cells without the ethical concerns associated with ESCs. iPSCs can be differentiated into vascular cells for therapeutic applications.

Bootsakhorn *et al.* designed an innovative strategy for generating functional endothelial cells within a short time frame of 5 days from PBMNc in patients with critical limb ischemia.

This groundbreaking approach provides a renewable and potentially autologous source of endothelial cells for regenerative therapy in peripheral artery disease, representing a major advancement towards personalized treatment strategies in the field of regenerative medicine for PAD.[32]

In a study conducted by Bin Jang *et al.*, patient-specific endothelial cells were generated using iPSC technology for individuals with PAD. The research aimed to assess the functionality and variability of these iPSC-derived endothelial cells in PAD patients. The study found that there was patient-dependent variability in tubular network formation, low platelet binding in most iPSC-ECs, uptake of acetylated low-density lipoprotein, and production of nitric oxide. Furthermore, the study highlighted the challenges of obtaining an adequate quantity and quality of patient-derived endothelial progenitor cells (EPCs) from PAD patients. The study emphasized the potential of autologous iPSC-ECs as a novel cell source for vascular regeneration in PAD, offering personalized and effective regenerative treatments.[33]

Induced pluripotent stem cells (iPSCs) in the field of cardiovascular medicine hold significant potential for advancing the treatment of peripheral artery disease (PAD). This area of research offers promising perspectives and innovative strategies for managing PAD.

Other stem cells therapy

Martha L. Arango Rodríguez *et al.* conducted a randomized, double-blind, controlled investigation to compare the therapeutic effects of autologous bone marrow mononuclear cells (auto-BM-MNC) and allogenic Wharton jelly-derived mesenchymal stem cells (allo-WJ-MSCs) in diabetic patients with chronic limb-threatening ischemia (CLTI). The results indicated that both auto-BM-MNC and allo-WJ-MSCs displayed potential therapeutic benefits for CLTI in diabetic patients.[34]

PRECLINICAL STUDIES AND CLINICAL TRIALS

Preclinical research

Numerous preclinical studies have been conducted to evaluate the safety and efficacy of stem cell therapies for vascular diseases. Animal models of ischemic cardiovascular diseases, peripheral artery disease, and other vascular conditions have been utilized to investigate the potential of stem cells in promoting angiogenesis, reducing inflammation, and improving tissue perfusion.

Early-stage clinical trials have also been initiated to assess the safety and feasibility of stem cell therapies in patients with various vascular diseases. These studies have involved the administration of autologous or allogeneic stem cells via different routes, such as intravenous, intramuscular, or intra-arterial injections.

In a systematic review and meta-analysis conducted by Van Rhijn-Brouwer *et al.*, the efficacy of bone marrow derived cell therapies in enhancing hind limb perfusion in animal models was examined. The review included a total of 85 studies involving 1053 animals. The analysis revealed a significant increase in perfusion in the affected limb following the administration of bone marrow cells as compared to control groups. However, a significant level of heterogeneity among the included studies was observed, indicating variability in outcomes that could not be explained by factors such as dose, species, cell type, or administration route.

Although the results demonstrated a positive impact on perfusion, the overall quality of preclinical research in this area was deemed insufficient to pinpoint specific factors that could enhance the outcomes of human clinical trials. According to the GRADE assessment (Grading of Recommendations, Assessment, Development, and Evaluations), the certainty of evidence was rated as low, underscoring the need for further research to better understand the factors influencing the efficacy of bone marrow derived cell therapies in enhancing hind limb perfusion.

The current animal models for predicting the clinical translation of stem cells therapy for PAD have certain limitations. For instance, they do not typically have relevant comorbidities such as advanced age and atherosclerosis, and they may not fully replicate the progressive atherosclerotic narrowing that is observed in clinical PAD. Developing animal models that incorporate these key comorbidities can address the aforementioned limitations, enhance the predictive value of preclinical studies, and increase the likelihood of successfully translating regenerative therapies for PAD into clinical applications.

Clinical studies

A meta-analysis conducted by Rigato *et al.* pooled studies on autologous cell therapy for PAD with a focus on CLTI. It included 19 randomized clinical trials involving 837 patients. The analysis concluded that cell therapy may improve amputation-free survival and surrogate endpoints related to limb perfusion and functional capacity, but the evidence is mixed across different types of studies. The authors emphasized the need for high-quality trials to better understand the potential benefits of cell therapy in PAD/CLTI.[35]

The meta-analysis conducted by Wei Gao *et al.* encompassed 27 randomized controlled trials and a total of 1,186 patients diagnosed with PAD. The results indicated that patients who received autologous stem cell therapy and were not offered any other treatment options demonstrated superior rates of ulcer healing when compared to those who received conventional therapy. However, no significant differences were observed in major limb salvage rates. These findings highlight again the need for further high-quality research to provide clearer insights. Additionally, the authors emphasized the importance of standardizing transplantation methods, stem cell type, and quantity to enhance the safety and

efficacy of stem cell therapy for PAD. While autologous stem cell therapy holds potential benefits for PAD patients, additional well-designed studies are necessary to definitively establish its safety and efficacy.[36]

Meta-analysis conducted by Pu *et al.* comprised 12 randomized controlled trials with 630 patients with CLTI and no-option to investigate the safety and efficacy of autologous stem cell therapy. The study utilized stem cells sourced from bone marrow and peripheral blood following G-CSF. The results demonstrated that autologous cell therapy exhibited significant improvements in total amputation rates, major amputation rates, ankle-brachial index, transcutaneous oxygen tension, and rest pain score when compared to placebo or standard care.[37]

Overall, the above-mentioned findings showed a possible trend of efficacy of autologous stem cell therapy, highlighting the need of further (more robust) research aimed to validate its role for as an alternative and promising treatment option for CLTI patients.

CHALLENGES AND FUTURE DIRECTIONS

Gene therapy

Gene therapy for PAD primarily targets therapeutic angiogenesis in patients with CLTI.

Gene therapy exhibits promising potential for improving blood flow and diminishing the probability of amputation in individuals afflicted with PAD. Through the utilization of diverse mechanisms, gene therapy may foster the growth of new blood vessels and the enlargement of existing ones, thereby facilitating improved blood circulation in ischemic limbs. Vectors, particularly nonviral plasmid DNA and modified viruses are widely utilized in gene therapy applications. The employment of advanced delivery systems, for example, Adeno-Associated Virus (AAV) vectors, enables gene therapy to achieve sustained expression of therapeutic genes, resulting in enduring advantages. Study relating gene therapy in animal model present the same inherent problem as described for stem cells therapy. In a 1996 case report, Isner *et al.* administered a plasmid encoding vascular endothelial growth factor (VEGF) applied to a hydrogel polymer-coated angioplasty balloon to the right leg of a CLTI patient. Four weeks after gene therapy, digital subtraction angiography revealed increased collateral vessels at the knee, mid-tibial, and ankle levels.[38] Given the Isner case, considerable progress has been made in the realm of angiogenic growth factors. These advancements can be achieved through either the administration of recombinant proteins or the utilization of gene therapy techniques. These methods have been proven to effectively stimulate neovascularization in various animal models.[39] Clinical trials have made use of various factors, including VEGF isoforms, fibroblast growth factor-1 (FGF-1), HGF, hypoxic inducible factor-1 (HIF-1), and SDF-1α. A thorough examination of 17 studies involving a total of 1988 patients, the majority of whom had CLTI, was carried out by Forster *et al.* The patients were treated with various gene therapies, primarily nonviral plasmids, such as VEGF, HGF, and FGF. However, the authors did not observe any significant advantages in terms of amputation-free survival, amputation rates, or all-cause mortality rates. The review found that while certain outcomes, such as major amputation and mortality, were adequately reported in the studies, others, such as amputation-free survival and quality of life, had limited data available. Meta-analyses conducted in the review showed mixed results for amputation-free survival, with concerns raised about heterogeneity and potential biases affecting the quality of evidence for specific outcomes.[40] Khachigian *et al.* focused their review on the use of adenovirus, and adeno-associated virus (AAV). The potential of AAV vectors in AAV-based therapies for PAD lies in their ability to enhance limb perfusion, vessel density, and overall function in patients with PAD. These innovative approaches show great promise for advancing the treatment of PAD and improving patient outcomes.[41, 42]

The effectiveness of gene therapy in PAD still requires validation through larger, well-designed randomized control trials. The development of more efficient gene transfer systems and methods to maintain the health of transplanted cells may enhance the efficacy of these therapies in the future.

Biomaterials

Biomaterials represent an emerging and potentially transformative approach to the treatment of PAD, offering a means to enhance cell-based therapies and improve clinical outcomes.

Bioengineering approaches are essential for enhancing the survival and function of transplanted cells in treating peripheral artery disease (PAD). These approaches seek to create a supportive microenvironment that mimics physiological tissue conditions and overcomes the challenges associated with cell therapies. By doing so, they play a crucial role in improving the efficacy of cell-based treatments for PAD.[43]

The encapsulation of cells within hydrogels offers a protective environment for the cells, which enhances their retention at the site of injury and promotes cell viability in an ischemic setting. Hydrogels serve as polymer scaffolds with high water content, facilitating cell survival and function.[44]

Foster and colleagues designed shear-thinning injectable hydrogels named SHIELD.

The primary objective was to enhance the efficacy of encapsulated induced pluripotent stem cell-derived endothelial cells (iPSC-ECs) within living organisms. In a mouse model of leg ischemia, it was demonstrated that iPSC-ECs homed to the affected area and promoted improved vascularization.[45]

Microporous biodegradable films have been engineered to promote therapeutic angiogenesis, which involves increasing blood vessel density and restoring blood

flow to ischemic tissue. These biodegradable films are composed of poly(lactic-co-glycolic acid) (PLGA), a biocompatible polymer that is frequently utilized in medical applications.

The porous structure of the films serves as a localized biophysical stimulus that activates the expression of pro-angiogenic genes in vivo, resulting in increased blood vessel density and the restoration of blood flow in ischemic tissues.[46]

The same researchers have exhibited enhanced in vitro angiogenesis through the combination of platelet-rich plasma with highly porous biodegradable microspheres fabricated from 75:25 poly(DL-lactide-co-glycolide) (PLGA) prepared via thermally induced phase separation.[47]

Peripheral artery disease (PAD) is significantly influenced by exosomes due to their capacity to facilitate cell-to-cell communication, promote tissue repair, and stimulate angiogenesis. Exosomes derived from diverse cell types, including endothelial cells and mesenchymal stem cells, contain pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which can trigger angiogenesis and lead to the formation of new blood vessels in ischemic tissues impacted by PAD.

Biomaterials possess the capability to direct the arrangement and behavior of grafted cells.

Maiullari *et al.* adopted a bioprinting method in conjunction with the formulation of a bioink composed of bioactive EVs. This research explores a new strategy for regenerative medicine by employing 3D bioprinting technology to support the application of angiogenic cargo from human endothelial cell-derived extracellular vesicles (EVs). The study utilized EVs derived from human endothelial cells and subjected to various stress conditions, which were collected and used as bio-additives for the formulation of advanced bioinks. The 3D structures bioprinted with these bioinks and loaded with EVs were found to support the formation of functional vasculature in vivo upon sub-cutaneous implantation. The researchers demonstrated that the bioprinted structures recapitulated blood-perfused micro vessels that followed the printed pattern. This approach enabled precise control over the spatial localization of EVs within a three-dimensional matrix, thereby overcoming the limitations of random biodistribution in vivo and maximizing the expression of their inherent angiogenic potential.[48, 49]

LABORATORY MEDICINE AND VASCULAR REGENERATIVE MEDICINE: SYNERGIES AND NEW OPPORTUNITIES

Laboratory Medicine is the scientific area, which is devoted to obtaining, explore and employ knowledge about using various techniques for the analysis of body fluids composition and properties of cells and tissues, and interpretation of the results in relation to health and disease. Laboratory Medicine could be considered both the clinical discipline and the separate medical science. Laboratory Medicine includes within itself, Molecular Genetics, Cytogenetics, Pathological Anatomy, Microbiology and Clinical Pathology; the latter is composed of Clinical Chemistry, Immunochemistry, Hematology and Separative techniques (gas chromatography, liquid chromatography, mass spectrometry, etc.).

It is estimated that laboratory results can be the basis of 60% -70% of medical decisions.[50] In addition to routine diagnostics in symptomatic patients, laboratory tests are used for screening, treatment monitoring and medical jurisprudence.

Laboratory medicine is indispensable in the planning and development of stem cell therapies for vascular regeneration. It provides the necessary tools for stem cell characterization, understanding differentiation processes, and evaluating therapeutic potential. However, laboratory findings also highlight the need for rigorous clinical validation to ensure the safety and efficacy of these therapies in human patients.

In the realm of vascular regenerative medicine, the clinical laboratory has emerged as a critical component.

Laboratory Medicine supports Regenerative Medicine through various activities:

1. provides the quantitative measurement of analytes and biomarkers involved in the regeneration processes inherent in human biology.
2. Allows to adequately identify, separate, and preserve cell derivatives or cell lines useful for regenerative therapy.
3. Allows to identify and monitor specific biomarkers, capable of predicting the risk of developing a disease in a specific individual, also using Artificial Intelligence applications able to develop personalized risk indices, based on clinical history, even at family level.

Flow cytometry

Flow cytometry is a technology that provides rapid multi-parametric analysis of single cells in solution. Flow cytometers utilize lasers as light sources to produce both scattered and fluorescent light signals that are read by detectors.

Cell populations can be analyzed and/or purified based on their fluorescent or light scattering characteristics. A variety of fluorescent reagents are utilized in flow cytometry. These include fluorescently conjugated antibodies, nucleic acid binding dyes, viability dyes, ion indicator dyes, and fluorescent expression proteins. Flow cytometry is a powerful tool that has applications in immunology, molecular biology, bacteriology, virology, cancer biology, and infectious disease monitoring. It has seen dramatic advances over the last 30 years, allowing unprecedented detail in studies of the immune system and other areas of cell biology.

In the area of our interest, flow cytometry allows the identification, count and separation in suspension of viable cell lines useful for the preparation of Cell-Based Therapies as described in the previous related paragraph of this chapter.

SUMMARY

Vascular Surgery since his birth as an autonomous discipline, both in Italy and Europe, has never appeared as a static entity, but has made dynamism and resilience its existential "creed". In the last decade of the last century, Endovascular Surgery made its appearance in the therapeutic armamentarium followed by hybrid surgery and enhanced recovery after surgery.

Surgery, even when accompanied by correct pharmacotherapy, is not always able to resolve the complex issues of patients suffering from a pathology, especially affecting the lower limbs, complicated by critical comorbidities. Unfortunately, many patients are not good candidates for revascularization. The help provided by regenerative medicine is linked to neovascularization, with involvement of some or all the process of angiogenesis, arteriogenesis and vasculogenesis. The process of angiogenesis is regulated by a complex interaction of pro and antiangiogenic growth factors, local tissue environment and genetic factors.

The field of cell-based therapies has emerged as a promising way for treating a lot of vascular diseases, offering innovative approach to promote angiogenesis, vascular repair and tissue regeneration. Numerous preclinical studies have been conducted to evaluate the safety and efficacy of stem-cell therapies for vascular diseases. Animal models of ischemic cardiovascular diseases, PAD, CLTI, and other vascular conditions have been utilized to investigate the potential of stem cells in promoting angiogenesis, reducing inflammation and improving tissue perfusion. Gene therapy for PAD/CLTI primarily targets therapeutic angiogenesis.

Biomaterials represent an emerging and potentially transformative approach to the treatment of PAD offering a means to enhance cell-based therapies and improve clinical outcomes. Bioengineering approaches are essential for enhancing the survival and function of transplanted cells in treating PAD.

Vascular Surgery is a Discipline in continuous, constant evolution and can seize all the opportunities offered by modern biomedical technology in order to fight in the most appropriate and absolutely innovative way that pathology which, given the increase in the average lifespan of the population, afflicts the vast majority of the elderly patients. However, even young patients, both due to the presence of a lot of comorbidities and the need for a correct reintegration into a socio-economic context, can and will be able to benefit, in an increasingly consistent and targeted way, from the modern supports offered by regenerative medicine.

REFERENCES

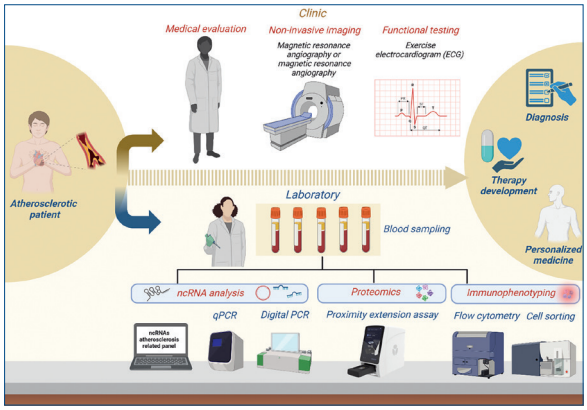
1. Semenza GL. Vasculogenesis, angiogenesis, and arteriogenesis: mechanisms of blood vessel formation and remodeling. J Cell Biochem 2007;102:840–7.
2. Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. Nat Rev Mol Cell Biol 2007;8:464–78.
3. Odent Grigorescu G, Rosca AM, Preda MB, *et al.* Synergic effects of VEGF-A and SDF-1 on the angiogenic properties of endothelial progenitor cells. J Tissue Eng Regen Med 2017;11:3241–52.
4. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669–76.
5. Stellos K, Langer H, Daub K, *et al.* Platelet-derived stromal cell-derived factor-1 regulates adhesion and promotes differentiation of human CD34+ cells to endothelial progenitor cells. Circulation 2008;117:206–15.
6. Cai WJ, Koltai S, Kocsis E, *et al.* Remodeling of the adventitia during coronary arteriogenesis. Am J Physiol Heart Circ Physiol 2003;284:H31–40.
7. Ghosh D, Mehta N, Patil A, *et al.* Ethical issues in biomedical use of human embryonic stem cells (hESCs). J Reprod Health Med 2016;2:S37–47.
8. Asahara T, Masuda H, Takahashi T, *et al.* Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res 1999;85:221–8.
9. Asahara T, Kawamoto A. Endothelial progenitor cells for postnatal vasculogenesis. Am J Physiol Cell Physiol 2004;287:C572–9.
10. Cooke JP, Losordo DW. Modulating the vascular response to limb ischemia: angiogenic and cell therapies. Circ Res 2015;116:1561–78.
11. Lu J, Pompili VJ, Das H. Neovascularization and hematopoietic stem cells. Cell Biochem Biophys 2013;67:235–45.
12. Nielsen JS, McNagny KM. Novel functions of the CD34 family. J Cell Sci 2008;121:3683–92.
13. Mackie AR, Losordo DW. CD34-positive stem cells: in the treatment of heart and vascular disease in human beings. Tex Heart Inst J 2011;38:474–85.
14. Mohler ER. Annex B. Regenerative Medicine for Peripheral Artery Disease. Amsterdam: Elsevier; 2016. p.71-90.
15. Velagapudi P, Turagam M, Kolte D, *et al.* Intramyocardial autologous CD34+ cell therapy for refractory angina: A meta-analysis of randomized controlled trials. Cardiovasc Revasc Med 2019;20:215–9.
16. Mizrak D, Brittan M, Alison M. CD133: molecule of the moment. J Pathol 2008;214:3–9.
17. Bao L, Meng Q, Li Y, *et al.* C-Kit Positive Cardiac Stem Cells and Bone Marrow-Derived Mesenchymal Stem Cells Synergistically Enhance Angiogenesis and Improve Cardiac Function After Myocardial Infarction in a Paracrine Manner. J Card Fail 2017;23:403–15.
18. Guerin CL, Rossi E, Saubamea B, *et al.* Human very Small Embryonic-like Cells Support Vascular Maturation and Therapeutic Revascularization Induced by Endothelial Progenitor Cells. Stem Cell Rev Rep 2017;13:552–60.
19. Feng W, Madajka M, Kerr BA, *et al.* A novel role for platelet secretion in angiogenesis: mediating bone marrow-derived cell mobilization and homing. Blood 2011;117:3893–902.
20. Zhang Q, Cannavicci A, Kutryk MJ. Exploring Endothelial Colony-Forming Cells to Better Understand the Pathophysiology of Disease: An Updated Review. Stem Cells Int 2022;2022:4460041.
21. Suszynska M, Zuba-Surma EK, Maj M, *et al.* The proper criteria for identification and sorting of very small embryonic-like stem cells, and some nomenclature issues. Stem Cells Dev 2014;23:702–13.
22. Suszynska M, Ratajczak MZ, Ratajczak J. Very Small Embryonic Like Stem Cells (VSELs) and Their Hematopoietic Specification. In: Working with Stem Cells. Cham: Springer; 2016. p.97–110.
23. Grunewald M, Avraham I, Dor I, *et al.* VEGF-induced adult neovascularization: recruitment, retention and role of accessory cells. Cells 2006;124:175–89.
24. Tammela T, Enholm B, Alitalo K, *et al.* The biology of vascular endothelial growth factors. Cardiovasc Res 2005;65:550–63.
25. Gnecchi M, Zhang Z, Ni A, *et al.* Paracrine mechanisms in

adult stem cell signaling and therapy. Circ Res 2008;103:1204–19.
26. Ryu JC, Davidson BP, Xie A, *et al.* Molecular imaging of the paracrine proangiogenic effects of progenitor cell therapy in limb ischemia. Circulation 2013;127:710–9.
27. Palviainen M, Puutio J, Østergaard RH, *et al.* Beyond Basic Characterization and Omics: Immunomodulatory Roles of Platelet-Derived Extracellular Vesicles Unveiled by Functional Testing. bioRxiv 2024. [Epub ahead of print].
28. Brown PA, Brown PD. Extracellular vesicles and atherosclerotic peripheral arterial disease. Cardiovasc Pathol 2023;63:107510.
29. Todorova D, Simoncini S, Lacroix R, *et al.* Extracellular Vesicles in Angiogenesis. Circ Res 2017;120:1658–73.
30. Smiler DG, Soltan M, Soltan C, *et al.* Growth factors and gene expression of stem cells: bone marrow compared with peripheral blood. Implant Dent 2010;19:229–40.
31. van Weel V, Seghers L, de Vries MR, *et al.* Expression of vascular endothelial growth factor, stromal cell-derived factor-1, and CXCR4 in human limb muscle with acute and chronic ischemia. Arterioscler Thromb Vasc Biol 2007;27:1426–32.
32. Boonkaew B, Suwanpitak S, Pattanapanyasat K, *et al.* Efficient generation of endothelial cells from induced pluripotent stem cells derived from a patient with peripheral arterial disease. Cell Tissue Res 2022;388:89–104.
33. Jiang B, Wang X, Rivera-Bolanos N, *et al.* Generation of Autologous Vascular Endothelial Cells for Patients with Peripheral Artery Disease. J Cardiovasc Transl Res 2024;17:558–69.
34. Arango-Rodríguez ML, Mateus LC, Sossa CL, *et al.* A novel therapeutic management for diabetes patients with chronic limb-threatening ischemia: comparison of autologous bone marrow mononuclear cells versus allogenic Wharton jelly-derived mesenchymal stem cells. Stem Cell Res Ther 2023;14:221.
35. Fadini GP, Agostini C, Avogaro A. Autologous stem cell therapy for peripheral arterial disease meta-analysis and systematic review of the literature. Atherosclerosis 2010;209:10–7.
36. Gao W, Chen D, Liu G, *et al.* Autologous stem cell therapy for peripheral arterial disease: a systematic review and meta-analysis of randomized controlled trials. Stem Cell Res Ther 2019;10:140.
37. Pu H, Huang Q, Zhang X, *et al.* A meta-analysis of randomized controlled trials on therapeutic efficacy and safety of autologous cell therapy for atherosclerosis obliterans. J Vasc Surg 2022;75:1440–1449.e5.
38. Isner JM, Pieczek A, Schainfeld R, *et al.* Clinical evidence of angiogenesis after arterial gene transfer of phVEGF165 in patient with ischaemic limb. Lancet 1996;348:370–4.
39. Bobek V, Taltynov O, Pinterova D, *et al.* Gene therapy of the ischemic lower limb—therapeutic angiogenesis. Vascul Pharmacol 2006;44:395–405.
40. Forster R, Liew A, Bhattacharya V, *et al.* Gene therapy for peripheral arterial disease. Cochrane Database Syst Rev 2018;10:CD012058.
41. Khachigian LM, Varcoe RL, Suoranta T, *et al.* Gene Therapeutic Strategies for Peripheral Artery Disease and New Opportunities Provided by Adeno-Associated Virus Vectors. Arterioscler Thromb Vasc Biol 2023;43:836–51.
42. Ribieras AJ, Ortiz YY, Li Y, *et al.* E-Selectin/AAV Gene Therapy Promotes Myogenesis and Skeletal Muscle Recovery in a Mouse Hindlimb Ischemia Model. Cardiovasc Ther 2023;2023:6679390.
43. Huang NF, Stern B, Oropeza BP, *et al.* Bioengineering Cell Therapy for Treatment of Peripheral Artery Disease. Arterioscler Thromb Vasc Biol 2024;44:e66–81.
44. Crosby CO, Valliappan D, Shu D, *et al.* Quantifying the Vasculogenic Potential of Induced Pluripotent Stem Cell-Derived Endothelial Progenitors in Collagen Hydrogels. Tissue Eng Part A 2019;25:746–58.
45. Foster AA, Dewi RE, Cai L, *et al.* Protein-engineered hydrogels enhance the survival of induced pluripotent stem cell-derived endothelial cells for treatment of peripheral arterial disease. Biomater Sci 2018;6:614–22.
46. Hendow EK, Moazen M, Iacoviello F, *et al.* Microporous Biodegradable Films Promote Therapeutic Angiogenesis. Adv Healthc Mater 2020;9:e2000806.
47. Hendow EK, Day RM. A facile approach to therapeutic angiogenesis using a platelet concentrate and microsphere composite. Nano Select 2022;3:1042–7.
48. Maiullari F, Chirivì M, Costantini M, *et al. In-vivo* organized neovascularization induced by 3D bioprinted endothelial-derived extracellular vesicles. Biofabrication 2021;13.
49. Maiullari F, Costantini M, Milan M, *et al.* A multi-cellular 3D bioprinting approach for vascularized heart tissue engineering based on HUVECs and iPSC-derived cardiomyocytes. Sci Rep 2018;8:13532.
50. Forsman RW. Why is the laboratory an afterthought for managed care organizations? Clin Chem 1996;42:813–6.

5.4 COUPLING TRANSCRIPTOMICS, PROTEOMICS, AND IMMUNE CELL LANDSCAPE TO DEVELOP NEW BIOMARKERS FOR THE DIAGNOSIS AND MONITORING OF ATHEROSCLEROSIS

Martina Mutoli, Andrea Rampin, Alberto M. Settembrini, Giovanni Nano, Massimiliano Martelli, Antonino Bruno, Gaia Spinetti

GRAPHICAL ABSTRACT



INTRODUCTION TO THE CLINICAL AND SCIENTIFIC PROBLEM

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, and their impact is predicted to grow in the next few years, as they have been estimated to cause 23.4 million deaths in 2030.[1] They are caused the most by atherosclerosis, which is a complex disease involving various vascular segments such as the aorta, carotid, coronary, and peripheral arteries. Atherosclerotic plaque is the hallmark of atherosclerosis, and it stands as a sentinel of vascular health yet harbors the potential for catastrophic consequences. The term atherosclerosis comes from the ancient Greek words ἀθήρα (athḗra) 'gruel', and σκλήρωσις (sclerosis) 'hardening', which well describe the atherosclerotic plaque, characterized by the accumulation of cells and lipids within the core, covered by a fibrous cap. The atherosclerotic lesions can develop as early as in the second decade of life and progress into clinical disease. Plaques can be asymptomatic for many years, the cardiovascular outcome of the lesion being the result of thrombus formation secondary to plaque rupture. This pathology has multiple risk factors, classified as modifiable and non-modifiable: age, gender, and genetic predisposition to hypercholesterolemia, hypertension, diabetes, and systemic inflammation are non-modifiable; meanwhile, cigarette-smoking, a diet rich in saturated fats, and a sedentary lifestyle are modifiable risk factors. An atherosclerotic plaque is a formidable clinical and scientific problem, casting a long shadow over cardiovascular health and challenging clinicians and researchers. Despite advancements in diagnostic modalities and therapeutic interventions, the management of atherosclerotic plaque remains a clinical conundrum, necessitating a multidisciplinary approach and individualized treatment strategies tailored to patient-specific factors.[2, 3]

Carotid and peripheral districts are the arterial conduits most affected by atherosclerotic processes.[4] Extracranial cerebrovascular disease, predominately manifesting as carotid bifurcation atherosclerosis, accounts for up to one-third of all strokes many of which occur without warning.[5] Peripheral arterial disease (PAD) is a medical condition that occurs when there is a narrowing or blockage of the arteries that supply blood to the extremities due to lipidic deposits or calcified plaques. It manifests as intermittent claudication, rest pain, and critical limb ischemia, heralding the threat of limb loss and functional impairment. Arterial calcifications are usually the pathologic core in patients with PAD, especially in older patients with diabetes mellitus and chronic kidney disease,[6] causing in patients affected by critical limb-threatening ischemia (CLTI) an increase in mortality by 50% and the rate of significant amputation by 500%.[7]

ATHEROSCLEROSIS'S TRANSCRIPTOME ALTERATION: ALTERED ncRNA EXPRESSION CAN REVEAL/INDICATE THE STAGE OF THE ILLNESS

While imaging is still the major method for early diagnosis of atherosclerosis, recent advancements in medical technology have shown promise in improving screening through the use of molecular biomarkers like non-coding RNAs (ncRNAs).[8]

ncRNAs are crucial biological regulators consisting of fragments of RNA not translated into proteins but that can regulate gene expression with different mechanisms and they are a major area of interest in epigenetic research. ncRNAs have received particular attention since they constitute the vast majority of the human transcriptome. The most prevalent types of ncRNAs are tRNAs, ribosomal RNAs, circular RNAs (circRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs).[9, 10]

Research suggests that ncRNAs play a crucial role in vascular biology and numerous illnesses including atherosclerosis can be linked to abnormal ncRNA expression, supporting their potential as biomarkers.[9, 11]

ncRNAs influence cell phenotypes and biological processes including programmed cell death and migratory ability. As such, they may also be used as therapeutic targets for a variety of disorders including atherosclerosis.[9, 11]

Several studies indicate that many ncRNAs are significantly altered and play regulatory roles during the development of atherosclerosis and its progression including plaque instability, plaque formation, and endothelial

damage.[11]. Notably, ncRNAs act as regulatory molecules of the immune system, which is central to atherosclerosis. Diverse studies have demonstrated that ncRNAs are responsible for immune cell development, differentiation, and activation.[12, 13] Some lncRNAs can control the expression of genes involved in the immune response mechanism either in cis or in trans. Also, immune-related ncRNAs are direct or indirect targets of specific transcription factors responsible for inflammatory mediator production.[13, 14] ncRNAs participate in the activation of inflammatory and immunological pathways, such as Nuclear Factor kappa B (NF-kB), arachidonic acid, mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling.[15]

Therefore, ncRNAs could serve as biomarkers of atherosclerosis evolution. Some examples are listed in Table 5.4.I.

TRADITIONAL METHODOLOGICAL APPROACHES IN TRANSCRIPTOMIC RESEARCH THAT ARE USEFUL FOR QUANTIFYING ncRNAs

It is of considerable translational value that ncRNAs are released into the bloodstream, where they are sufficiently stable to be easily detected using standard laboratory procedures such as reverse transcription-real time quantitative polymerase chain reaction (RT-qPCR) and digital PCR. Therefore, measuring ncRNAs in patient blood behind imaging assessment may be helpful to enhance atherosclerosis screening. To assess potential detrimental effects in atherosclerotic patients, it could be helpful, for instance, to choose a particular panel of ncRNAs linked to plaque instability.

The first step for technical analysis is RNA purification from blood samples by conventional phenol-based techniques or silica column isolation kits; however, contaminating substances like heparin need to be taken into account since they can affect the measurement.[22] Before applying downstream analysis techniques, RNA must be quantified and quality-checked using spectrophotometry, electrophoresis, and RNA integrity number (RIN) values.[23]

In research, relative quantification of ncRNAs using RT-qPCR is used to distinguish between individuals with and without illness but it is also possible to achieve an absolute quantification of ncRNAs by creating a standard curve. However, an innovative method for ncRNA quantification, more sensitive than RT-qPCR is digital PCR which does not require the creation of a standard curve.[24, 25]

Next-generation sequencing (NGS), in particular RNA-sequencing (RNA-Seq) is the only method available for identifying novel ncRNAs with potential as therapeutic targets. Of note, NGS also allows researchers to get ncRNA expression profiles of a biological sample to identify molecular alterations contributing to atherosclerosis.[25]

THE JOINT REGULATION OF PROTEINS AND ncRNAs IN ATHEROSCLEROSIS

ncRNAs can regulate translation not only by binding target mRNAs but also by modulating key protein activity, localization, and structure.

Table 5.4.I ● ncRNAs that could serve as atherosclerosis biomarkers.

ncRNA	Origin	Expression level in atherosclerosis	Group of patients	References
miR-21	PBMNCs	Up	Vulnerable vs. stable patients	(16)
miR-146a	PBMNCs	Up	Vulnerable vs. stable patients	
miR-155	PBMNCs	Down	Vulnerable vvs.s. stable patients	
miR-124	Serum	Up	Symptomatic vs. asymptomatic with ICAS	(17)
miR-134	Serum	Up	Symptomatic vs. asymptomatic with ICAS	
miR-133a	Serum	Down	Symptomatic vs. asymptomatic with ICAS	
let-7c	Plasma	Down	Stable CAD vs. healthy	(18)
miR-145	Plasma	Down	Stable CAD vs. healthy	
miR-155	Plasma	Down	Stable CAD vs. healthy	
CircZNF609	PBMNCs	Down	CAD vs. healthy	(19)
APO1-AS1	PBMNCs	Up	CAD vs. healthy	(20)
HIF1A-AS2	PBMNCs	Up	CAD vs. healthy	
KCNQ1OT1	PBMNCs	Up	CAD vs. healthy	
MIAT	Serum	Up	CAD vs. healthy	(21)

PBMNCs: peripheral blood mononuclear cells; ICAS: internal carotid artery stenosis; CAD: coronary artery disease; CircZNF609: Circular RNA ZNF609; APOA1-AS: Apolipoprotein A-1 antisense RNA; HIF1A-AS2: HIF1A Antisense RNA 2; KCNQ1OT1: KCNQ1 Opposite Strand/Antisense Transcript 1; MIAT: Myocardial Infarction Associated Transcript.

The lncRNA Lipid Associated Single nucleotide polymorphism gEne region (LASER), binds to lysine-specific demethylase 1 (LSD1) causing decreased methylation of histone H3 lysine 4 (H3K4me) at the Hepatic Nuclear Factor 1 Alpha (*HNF-1α*) gene's promoter region, therefore increasing protein convertase subtilisin/kexin type 9 (*PCSK9*) expression in hepatocytes.[26] PCSK9 is known to drive its target low-density lipoprotein receptor (LDLR) to degradation, hence increasing circulating low-density lipoprotein (LDL). Consistently, *LASER* expression in cultured human hepatocytes is positively linked with intracellular cholesterol levels, while in peripheral blood mononuclear cells (PB-MNCs) from 175 subjects who were not taking statins, it correlated with circulating total cholesterol, LDL, and apolipoprotein B-100 (apo B-100) plasma levels. Treatment with statin boosts *LASER* expression and decreases the amount of atherogenic lipids in circulation by preventing the liver from producing cholesterol. As a result, its expression is controlled by a feedback loop mediated by cholesterol and may be targeted to enhance the benefits of statin therapy. Moreover, Liver-expressed liver X receptor-induced sequence (LeXis), is a lncRNA that binds the ribonucleoprotein RALY in hepatocytes and prevents it from binding to the promoters of genes involved in cholesterol biosynthesis, including sterol regulatory element binding protein 2 (*SREBP2*).[27] Reduction in atherosclerosis and hepatic and circulatory lipid levels were linked to the use of a liver-specific adeno-associated virus 8 (AAV8)-based genetic method to boost *LeXis* expression in *Ldlr*$^{-/-}$ mice fed a western diet.[28, 29] This suggests that LXR and SREBP transcription factors may interact through LeXis and that this interaction could be therapeutically used to help cardiovascular-risk patients maintain cholesterol homeostasis.

A panel of biomarkers composed of ncRNAs and proteins may strengthen prevention. By analyzing the transcriptome and proteome profiles of plaques and plasma from patients with carotid stenosis after surgery, Matic *et al.* designed an integrative approach to find biomarkers for carotid atherosclerosis. The study validated the proposed model across plaques with different characteristics, while demonstrating the role of the serum response factor-based regulatory network in intimal intraplaque hemorrhage. Moreover, it was shown that patients with carotid atherosclerosis had higher levels of biliverdin reductase B (BLVRB) in both their plaques and plasma, which was especially connected to intraplaque hemorrhage. These findings present BLVRB as a viable biomarker for detecting end-stage vulnerable plaques in patients at higher risk of stroke.[25, 30]

PROXIMITY EXTENSION ASSAY PROTEOMICS AND GENOMICS INTEGRATION FOR PRECISION MEDICINE

Integrating human genomics and proteomics can help elucidate pathological mechanisms, identify novel biomarkers, and uncover therapeutic targets.[31] Genomic-wide association studies during the last decade have demonstrated how genetic mutations affecting not only protein-coding DNA sequences but also ncRNA expression and functionality are associated with the onset and development of atherosclerosis.[32, 33] Phenome-wide association studies (PheWAS) can now analyze many phenotypes compared to a single genetic variant (or other attributes). However, until recently, little was known about the mechanisms linking such genetic variants to the final pathological phenotype. With the recent technological advancement of proteomics techniques, it is now possible to characterize human plasma protein profiles in faster, relatively cheaper, and substantially more reproducible ways. Hence, the growing availability of larger clinical datasets and cryopreserved biological samples has allowed the implementation of the rising field of proteogenomics to bridge the gap between genomics and pathological phenotypes. One such technological breakthrough is represented by the proximity extension assay (PEA) that enables operators to inquire about the proteomic content of a biological sample, such as human plasma with previously unmatched specificity and sensitivity, thanks to double antibody-based epitope recognition and the PCR amplification step, respectively. The study of proteogenomics provides a continuously updated characterization of the genetic architecture of the plasma proteome, leveraging population-scale proteomics to provide novel, extensive insights into the complex effects of genetic mutations, whether they are located in coding or non-coding genomic regions, across multiple biological domains.[34]

ncRNA CELL-SPECIFIC EFFECT ON IMMUNE CELLS INVOLVED IN THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

In this section, we provide some examples of ncRNAs involved in the cross-talk between selected immune cells, endothelial cells (ECs), and stromal cells present in atherosclerotic plaques that could represent disease biomarkers or innovative targets for therapy. Preclinical data obtained *in vitro* and *in vivo* using animal models of atherosclerosis are reported to provide evidence of molecular pathways and cellular function associated with the mentioned ncRNA.

1. Monocytes/macrophages

Macrophages represent the most abundant innate immunity subsets in the atherosclerotic plaques and actively participate in plaque development. Once activated, plaque infiltrating macrophages release diverse pro-inflammatory and cytotoxic molecules.[35] Following monocyte recruitment and phagocytosis of oxidized-LDL (oxLDL), a peculiar plaque-infiltrating macrophage subtype, namely foam cells, is generated in the plaque lesion. Eventually, dying macrophages build up the necrotic core in developing plaques, fueling the pro-inflammatory environment.[36]

Several miRNAs control macrophage activities within the plaque in a complicated network of interactions. Here below we list some of the more studied.

miR-33 controls macrophage intracellular lipid accumulation.[37-43] Moreover, by targeting the energy sensor AMP-activated protein kinase (AMPK) miR-33 induces pro-inflammatory M1-like polarization-associated genes. miR-33 antagonism results in atheroprotective features inducing M2-like macrophages and Tregs.[44] Preclinical data *in vivo* confirmed that miR-33 controls macrophage activity in atherosclerosis.[45]

miR-155 plays a major role in macrophage pro-inflammatory activation. Mild-oxLDL, interferon gamma (IFNγ), or activation of TLR signaling induce miR-155. In turn, miR-155 represses the suppressor of cytokine signaling 1 (SOCS-1) and B-cell lymphoma 6 (BCL6), while promoting diverse pro-inflammatory cytokines, such as C-C Motif Chemokine Ligand 2 (CCL2), interleukin-5 (IL-5), nitric oxide synthase 2 (NOS2) and TNFα to support macrophage-mediated inflammation.[46-50] However, anti-atherogenic activity has also been reported for miR-155 (51). In *Ldlr*$^{-/-}$ mice, hematopoietic miR-155 deficiency is associated with an increase in CD11b^{+}Ly6C^{hi} monocyte inflammatory subset and decreased plaque stability.[52] A possible explanation for these contrasting activities of miR-155 could rely on the stage of atherosclerotic development studied.[53] Of note, miR-342 increases the pro-inflammatory activity of plaque resident macrophages by suppressing the Akt-1-mediated repression of miR-155.[54]

miR-146a plays a protective role in macrophages by repressing M1 polarization and the NF-kB signaling cascade, and by limiting cell migration thus inducing macrophage entrapment in the atherosclerotic vessel wall.[55-58]

miR-223 regulates myeloid cell plaque infiltration and has been demonstrated to support the generation of M2-like macrophages.[59]

miR-21 negatively regulates pro-inflammatory responses in atherosclerosis. Thus, in its absence, atherosclerosis is accelerated and macrophages exhibit a pro-inflammatory phenotype, impaired phagocytic activity, and increased apoptosis.[60]

ncRNAs can exert a paracrine regulatory function by being transferred from vascular cells to monocytes/macrophages and vice versa at least in part encapsulated in extracellular vesicles (EVs). As a matter of fact, following injury, ECs release EVs, which ncRNA content represses monocyte activation and vascular inflammation. EV-encapsulated miR-10a, released by ECs, can be transferred to monocytes, thereby blocking their pro-inflammatory activation.[61] Following treatment with interleukin-6 (IL-6): ECs-derived EV miRNA-126content decreases, resulting in increased monocyte adhesion; on the contrary, elevated levels of miRNA-126 exhibit opposite effects.[62] EC-EVs delivering miRNA-126 and miRNA-210 limit macrophage accumulation and ameliorate atherosclerotic lesions.[63] On the other hand, macrophages can deliver EV-encapsulated miRs, such as miR-150, increasing EC migration.[63, 64] In addition, EVs from pro-inflammatory M1 macrophages exert an anti-angiogenic effect on ECs via miR-155 transfer.[65]

Moreover, *in vitro* exposure of VSMCs to EVs derived from nicotine-treated-, oxLDL activated-, or M1-macrophages resulted in their increased proliferation and migration, leading to atherosclerotic development, through the delivery of miRNA-21, miR-106a and miR-222 respectively.[66-68]

Less evidence is available on the role of lncRNAs immune-vascular cell interactions in plaque.

Among these, TNFα and hnRNPL-related immunoregulatory LincRNA (THRIL) is highly expressed in oxLDL and Pam3CysSerLys4 (Pam3CSK4)-treated macrophages, increasing the expression of TNFα and foam cell formation.[69, 70] Increased expression of lncRNA RP5–833A20.1 was detected in human foam cells, in association with reduced expression of nuclear factor IA (*NFIA*) by inducing miR-382expression.[71] LncRNA-E330013P06 is highly induced in macrophages of diabetic mice and implicated in the induction of foam cells.[72]

Loss of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in monocyte-derived macrophages amplifies the inflammatory responses, which can then exacerbate atherosclerosis development.[73]

Macrophage-Associated atherosclerosis lncRNA Sequence (MAARS) plays a pro-atherosclerotic role in regulating macrophage apoptosis, efferocytosis, and plaque necrosis in *Ldlr*$^{-/-}$ mice atherosclerosis.[74]

The ability of macrophages to efficiently recognize, engulf, and metabolize apoptotic cell debris in the atherosclerotic plaque is exerted by efferocytosis. Defective efferocytosis contributes to necrotic core formation and plaque destabilization.[75] In this regard, the lncRNA Myocardial Infarction Associated Transcript (MIAT) blocks macrophage efferocytosis favoring the formation of the necrotic core.[76] MIAT knockdown reduced atherosclerotic lesion area, augmented fibrous cap thickness, diminished the presence of apoptotic cells, and decreased plaque instability.

LincRNA-Cox2 controls the inflammatory response, regulating C-C Motif Chemokine Ligand 5 (CCL5) IL-6 expression, and NF-kB pathways, finally increasing the inflammatory response in atherosclerosis.[77]

The lncRNA taurine upregulated gene 1 (TUG1) is associated with atherosclerosis progression through macrophage apoptosis modulation by sponging miR-133a.[78]

Finally, the knockdown of lncRNA NEAT1 (nuclear paraspeckle assembly transcript 1) in macrophages reduces apoptosis and inflammation following oxLDL treatment by sponging miR-342.[79]

2. Neutrophils

Neutrophils play a role in plaque development,[80, 81] erosion,[82] and rupture.[83, 84] Neutrophil-derived microvesicles (NMVs) are enriched in diverse miRNAs regulating inflammation, such as miR-9, miR-150, miR-155, miR-186, and miR-223. NMVs were found to deliver

miR-155 into ECs, in association with reduced *BCL6* expression. Moreover, mice fed with a high-fat diet for 1 week augmented the ability of NMVs to increase miR-155 expression levels in primary human coronary artery EC (HCAEC). Also, NMVs increased *miR-155* and reduced *Bcl6* expression in atheroprone regions in Apolipoprotein E (*ApoE*)$^{-/-}$ mice. Finally, NMVs enhanced plaque formation in a miR-155-dependent manner, by activating the NF-kB pathway.[85]

3. T and B cells

The presence of activated T lymphocytes, mainly CD4^{+}, at all stages of atherosclerosis, suggests that they are involved in this vascular disease process, though their specific role remains unclear. Foxp3-dependent *miR-155* expression in mice regulatory T cells (Tregs) was shown to induce T-regs development and homeostasis, at least in part by targeting the Suppressor Of Cytokine Signaling 1 (SOCS-1),[86, 87] indicating potential atheroprotective properties. The miR-17–92 cluster is a crucial effector for T and B cell development,[88, 89] and by repressing thrombospondin-1 in T cells,[90] it might be involved in supporting uncontrolled T cell activation, thus exacerbating atherosclerotic vascular alterations. T cell-mediated autoimmune, Th-1 sustained and IFNγ-mediated immune responses are considered detrimental processes in atherosclerosis.[91-93] In this portrait, miR-29 and a repression of the miR-17–92 cluster, in T cells, could result in atheroprotective features.

B cells regulate atherosclerotic plaque formation through the production of antibodies and cytokines. Two major specific B cell subsets have been characterized in atherosclerosis, referred to as B1 and B2 cells. B1 cells exhibit atheroprotective functions, both in humans and mice, by spontaneous immunoglobulin M (IgM) antibody production (94). On the contrary B2 cells have pro-atherogenic activities, by sustaining the pro-inflammatory environment in the atheroma and producing large amounts of immunoglobulin G (IgG).[94] Deficiency in miR-155 or miR-185 during antibody generation impaired germinal B cell generation and class-switch recombination of the immunoglobulin locus,[95, 96] possibly priming auto-antibody generation thus supporting atherosclerosis progression.

IMMUNOPHENOTYPING

Immune cell alterations, together with those occurring in endothelial and stromal cells, strongly impact all stages of atherosclerosis and govern atherosclerotic plaque fate. Indeed, the possibility to trace immune cells during atherosclerosis by immunophenotyping, the detailed characterization of the types and states of immune cells, offers a powerful tool to trace the dynamics and possible outcomes of the pathology.[97-99] Since immunophenotyping could be used in detecting alterations of the tissue/local, but also of the circulating immune environment, it is a relevant liquid-biopsy-based approach to studying atherosclerosis.

Two methodological approaches can be applied:

1. *Multicolor flow cytometry (FC):* a major technology used by immunologists,[100] allows to monitoring of up to 30 parameters, simultaneously, in immune cells derived from peripheral blood and/or atherosclerotic plaques. By FC not only surface antigens but also intracellular and nuclear factors, can be measured in the bulk immune cell populations analyzed. When coupled with cell sorting, FC also allows to physically isolate the immune cell subset of interest, for downstream molecular and biochemical analysis.
2. *Mass cytometer* (MC): this application is the simultaneous measurement of multiple markers at a single-cell level using metal-conjugated antibodies. MC combines flow cytometry and mass spectrometry to provide a high-dimensional view of immune cell phenotypes.[101]

Moreover, *single cell RNA-Sequencing* is an innovative phenotyping approach allowing to profile of gene expression at a single-cell resolution, revealing the phenotype and functional states of individual cells in the analyzed samples.[98, 101]

PERSONALIZED THERAPY FOR ATHEROSCLEROTIC PATIENTS: TREATMENT APPROACHES USING NCRNAS AS TARGETS

Precision and customized medicine techniques are rising to prominence in clinical care as a result of advancements in medical technology.[102] ncRNAs may be useful as therapeutics in the treatment of atherosclerosis.[11] Low cytotoxicity, non-immunogenicity, and simplicity of mass production are desirable traits for ncRNA carriers in precision and personalized medicine.[11] To transport ncRNAs for atherosclerosis therapy, vesicles of the classes of exosomes, liposomes, and micelles have all been evaluated as potential carriers.[103-105]

Exosomes are EVs generated from endosomes that are usually 50-200 nm in size and can carry RNA, proteins, and lipids.[106] The contents of exosomes released by various cells differ in composition. Exosomes can have therapeutic effects on atherosclerosis. In addition to the previously mentioned examples of immune cells EV-carried ncRNAs, also mesenchymal stem cell exosomes produced from adipose tissue can repress the expression of miR-342, potentially minimizing endothelial cell damage in atherosclerosis.[68] Furthermore, exosomes can be enriched by electroporation with short interfering RNAs (siRNAs), synthetic ncRNAs that interfere with the expression of specific RNAs, to boost their therapeutic effect.[107, 108] With the advancement of molecular engineering technologies, ligands can be added to exosomes to create more capable targets for the focused treatment of atherosclerosis.[109] To better transport the contents for the treatment of atherosclerosis, a recent study assessed modified M2 macrophage-derived exosomes with increased inflammatory tropism and anti-inflammatory properties.[110]

Lipid bilayer particles, or liposomes, are biocompa-

tible and bioavailable particles that can be subjected to surface modifications to improve stability and targeting in plasma.[111, 112] In a recent study, miR-146a encapsulation into liposomes resulted in enhanced stability that could be retained for over two months, reducing inflammation and decreasing the generation of foam cells.[113] Liposomes are now commonly employed to deliver ncRNA medicines.

The acidic environment of the atherosclerotic lipid core led to the recent proposal of pH low-insertion peptide (pHLIP), a new water-soluble membrane molecule as a carrier for atherosclerosis-targeted therapy. Without harming the overall level of miR-33, pHLIP was used to deliver antisense oligonucleotides targeting miR-33 to macrophages in the atherosclerotic plaque. This work effectively decreased lipid formation in macrophages by suppressing miR-33 expression, encouraging atherosclerotic regression, and boosting atherosclerotic plaque stability. It is also shown that pHLIP might be a great vector for miRNA-target therapy *in vivo*.[114]

Therefore, targeting ncRNAs to reverse their aberrant expression may have therapeutic benefits for atherosclerosis.

ncRNAs AND DNA SHORT ANTISENSE OLIGONUCLEOTIDES AS PHARMACEUTICALS

Pharmaceutical approaches include the use of siRNAs or miRNAs, as well as DNA short antisense oligonucleotides (ASOs) or miRNA sponges.[115]

siRNAs are usually designed to target a single specific mRNA, therefore they differ from miRNAs, which can target several genes with finely tuned efficiency, as they do not require complete complementarity.

Although lipid metabolism in the liver is the primary focus of the developing field of RNA therapies (Table 5.4.II), there is considerable interest in the development of new treatment approaches that will primarily target the plaque itself.

Olpasiran is a siRNA-based medication being developed by Amgen, currently in a phase III clinical trial for the treatment of atherosclerosis. It has demonstrated potential for lowering lipoprotein (a) levels by blocking apolipoprotein (a) translation.[116] Furthermore, Olpasiran has been shown to lower LDL cholesterol and apolipoprotein B.[117]

Inclisiran is another siRNA-based medication, approved for use in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia by the European Medicines Agency (EMA) in 2020 and by the Food and Drug Administration (FDA) in 2021.[118] Inclisiran works by suppressing PCSK9 mRNA in the liver, lowering LDL levels in the blood. Because PCSK9 promotes LDL receptor degradation, lowering PCSK9 levels increases hepatocyte absorption of LDL and thereby lowers blood LDL levels.[119, 120] Moreover, ORION-10 and ORION-11 clinical trials have shown that Inclisiran also lowers lipoprotein (a) (Lp(a)) levels.[121] ORION-4 (NCT03705234) and VICTORION-2P (NCT05030428) clinical outcomes trials are currently investigating the efficacy of Inclisiran in the treatment of atherosclerosis-based cardiovascular disease and are scheduled to end in 2026 and 2027, respectively.[122-124]

Potential innovative treatment approaches for stabilizing plaques and averting acute atherosclerosis problems could involve modifying the activity of particular ncRNAs linked to endothelial function and plaque stability.

Table 5.4.II ● List of RNA/DNA-based drugs for atherosclerosis.

Drugs	Type of RNA-based therapeutic	Target disease	Activity	Status	Reference (s)
Olpasiran	siRNA	Atherosclerosis	Lowering of Lp(a) levels by blocking apolipoprotein (a) translationLowering LDL cholesterol and apolipoprotein B levels.	Phase III clinical trial	(116, 117)
Inclisiran	siRNA	Adults with primary hypercholesterolemia or mixed dyslipidemia	PCSK9 mRNA suppression in the liver lowers LDL levels in the blood	Approved by EMA in 2020 and by FDA in 2021	(118)
		Atherosclerosis	PCSK9 mRNA suppression	Phase III clinical trial	(122)
Pelacarsen	ASO	CVDs	Lowering of Lp(a), apo B-100, LDL, the percentage of oxidized apo(a) and apolipoprotein B	Phase III clinical trial	(129, 130)

siRNA: short interfering RNA; Lp(a): lipoprotein (a); LDL: low-density lipoproteins; PCSK9: protein convertase subtilisin/kexin type 9; EMA: European Medicines Agency; FDA: Food and Drug Administration; ASO: short antisense oligonucleotide; CVD: cardiovascular diseases; apo B-100: apolipoprotein B-100.

ASOs are complementary oligonucleotides that bind to certain RNAs, including both miRNAs and mRNAs. ASOs, also known as antisense oligodeoxynucleotides, were originally designed as single-stranded DNA molecules.[125, 126] DNA nucleotides and chemically modified nucleotide sections are the most common components of modern ASOs. These oligonucleotides are chemically modified to increase their potency and shield them from cellular nucleases. ASOs work in multiple ways, one of which is by inducing Ribonuclease H (RNase H) to cleave DNA/RNA hybrids.[127]

Pelacarsen is an ASO targeting Lp(a) mRNA currently being investigated for its impact on major adverse cardiovascular events (MACEs) by the Lp(a) HORIZON phase III clinical trial (NCT04023552).[128] In previous phase II clinical trials, Pelacarsen was demonstrated to efficiently lower not only Lp(a) but also apo B-100, LDL, and the percentage of oxidized apo(a) and apolipoprotein B.[129, 130]

CONCLUSIONS AND FUTURE PERSPECTIVES

The last ten years have seen a major increase in interest in the study of ncRNAs for diagnostic and therapeutic purposes. Numerous ncRNAs are essential in controlling the function of immune and vascular cells contributing to atherosclerosis onset and progression. Thus, since the aberrant production in tissue and the peripheral blood of some ncRNAs is associated with the diseases, ncRNA could serve as biomarkers. ncRNA measurement requires a minimally invasive procedure and realizing a panel with ncRNAs and proteins related to atherosclerosis represents a huge resource for disease management. The addition of immunophenotyping analysis completes the picture considering that inflammation in atherosclerosis is regulated by ncRNAs. Moreover, targeting ncRNAs or delivering RNA-targeting drugs in a variety of ways has shown therapeutic promise in several preclinical and clinical studies. A large number of RNA therapies are either in development or have been shelved. The ability of drugs based on siRNAs and ASOs to efficiently target particular genes has led to their successful application opening the door to precision medicine and personalized approaches to lower the burden of atherosclerosis.

ACKNOWLEDGMENTS

M.M. is a Ph.D. student on the Ph.D. program in "Life Science and Biotechnology" at Università degli Studi dell'Insubria. Graphical abstract was created with BioRender.com, Agreement number: ES26WLV6TA.

REFERENCES

1. Mathers C, Fat DM, Boerma JT. The global burden of disease: 2004 update. Geneva, Switzerland: World Health Organization; 2008.
2. Mazzone A, De Servi S, Ricevuti G, *et al.* Increased expression of neutrophil and monocyte adhesion molecules in unstable coronary artery disease. Circulation 1993;88:358-63.
3. de Weerd M, Greving JP, de Jong AW, *et al.* Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke 2009;40:1105-13.
4. Yamaguchi T, Morino K. Perivascular mechanical environment: A narrative review of the role of externally applied mechanical force in the pathogenesis of atherosclerosis. Front Cardiovasc Med 2022;9:944356.
5. Inzitari D, Eliasziw M, Gates P, *et al.* The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000;342:1693-700.
6. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv 2014;83:E212-20.
7. Huang CL, Wu IH, Wu YW, *et al.* Association of lower extremity arterial calcification with amputation and mortality in patients with symptomatic peripheral artery disease. PLoS One 2014;9:e90201.
8. Meng H, Ruan J, Yan Z, *et al.* New Progress in Early Diagnosis of Atherosclerosis. Int J Mol Sci 2022;23(16).
9. Spinetti G, Mutoli M, Greco S, *et al.* Cardiovascular complications of diabetes: role of non-coding RNAs in the crosstalk between immune and cardiovascular systems. Cardiovasc Diabetol 2023;22:122.
10. Hombach S, Kretz M. Non-coding RNAs: Classification, Biology and Functioning. Adv Exp Med Biol 2016;937:3-17.
11. Yu Z, Yin J, Tang Z, *et al.* Non-coding RNAs are key players and promising therapeutic targets in atherosclerosis. Front Cell Dev Biol 2023;11:1237941.
12. Mumtaz PT, Bhat SA, Ahmad SM, *et al.* LncRNAs and immunity: watchdogs for host pathogen interactions. Biol Proced Online 2017;19:3.
13. Carpenter S, Fitzgerald KA. Transcription of inflammatory genes: long noncoding RNA and beyond. J Interferon Cytokine Res 2015;35:79-88.
14. Chen L, Deng H, Cui H, *et al.* Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2018;9:7204-18.
15. Mathy NW, Chen XM. Long non-coding RNAs (lncRNAs) and their transcriptional control of inflammatory responses. J Biol Chem 2017;292:12375-82.
16. Zhu GF, Chu T, Ruan Z, *et al.* Inflammation-Related MicroRNAs Are Associated with Plaque Stability Calculated by IVUS in Coronary Heart Disease Patients. J Interv Cardiol 2019;2019:9723129.
17. Badacz R, Przewlocki T, Gacon J, *et al.* Circulating miRNA levels differ with respect to carotid plaque characteristics and symptom occurrence in patients with carotid artery stenosis and provide information on future cardiovascular events. Postepy Kardiol Interwencyjnej 2018;14:75-84.
18. Faccini J, Ruidavets JB, Cordelier P, *et al.* Circulating miR-155, miR-145 and let-7c as diagnostic biomarkers of the coronary artery disease. Sci Rep 2017;7:42916.
19. Liang B, Li M, Deng Q, *et al.* CircRNA ZNF609 in peripheral blood leukocytes acts as a protective factor and a potential biomarker for coronary artery disease. Ann Transl Med 2020;8:741.
20. Zhang Y, Zhang L, Wang Y, *et al.* KCNQ1OT1, HIF1A-AS2 and APOA1-AS are promising novel biomarkers for diagnosis of coronary artery disease. Clin Exp Pharmacol Physiol 2019;46:635-42.
21. Tan J, Liu S, Jiang Q, *et al.* LncRNA-MIAT Increased in Patients with Coronary Atherosclerotic Heart Disease. Cardiol Res Pract 2019;2019:6280194.
22. Boeckel JN, Thome CE, Leistner D, *et al.* Heparin selectively affects the quantification of microRNAs in human blood samples. Clin Chem 2013;59:1125-7.
23. de Gonzalo-Calvo D, Marchese M, Hellemans J, *et al.* Consensus guidelines for the validation of qRT-PCR assays in

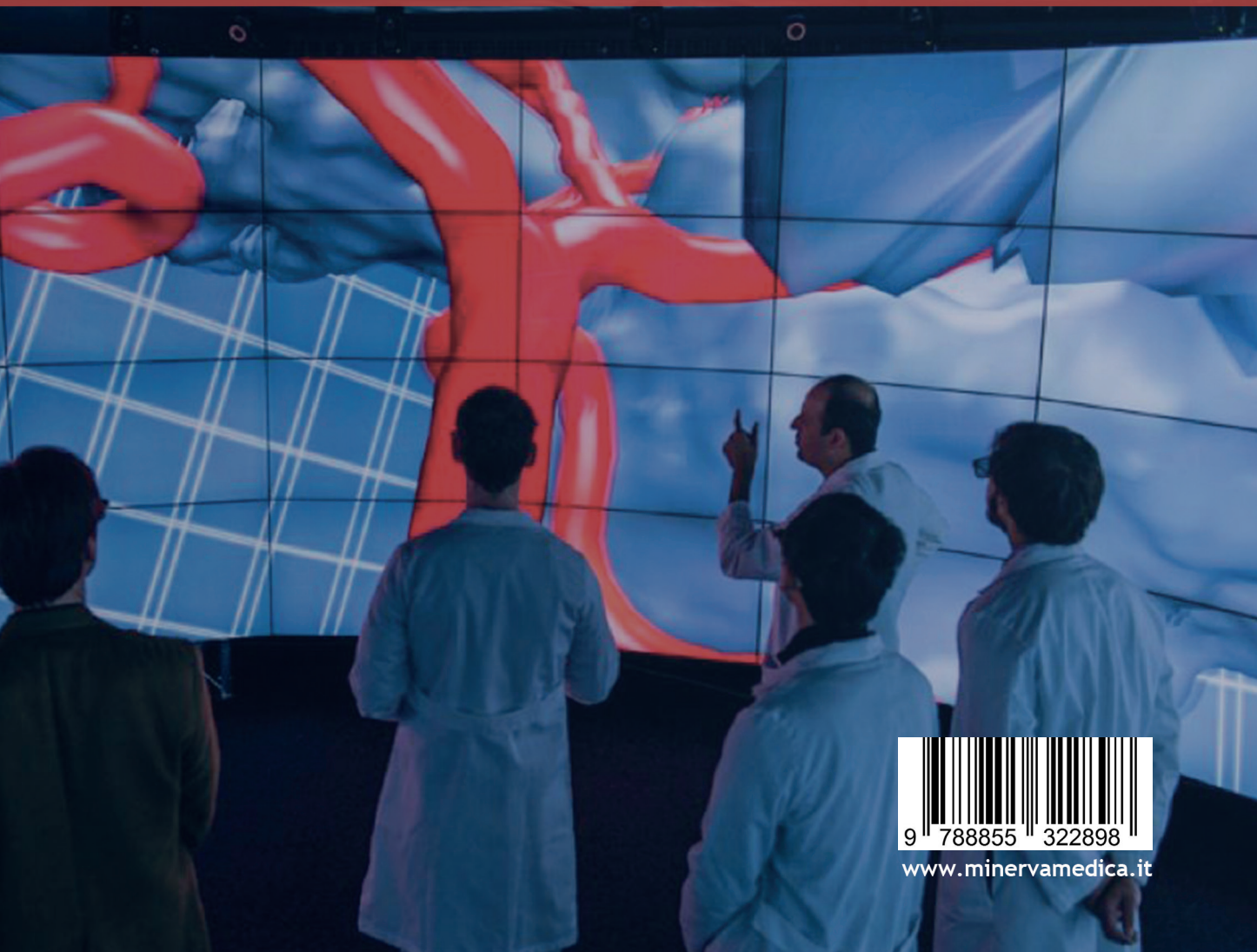
clinical research by the CardioRNA consortium. Mol Ther Methods Clin Dev 2022;24:171-80.
24. Dodd DW, Gagnon KT, Corey DR. Digital quantitation of potential therapeutic target RNAs. Nucleic Acid Ther 2013;23:188-94.
25. Sopić M, Karaduzovic-Hadziabdic K, Kardassis D, *et al.* Transcriptomic research in atherosclerosis: Unravelling plaque phenotype and overcoming methodological challenges. Journal of Molecular and Cellular Cardiology Plus 2023;6:100048.
26. Li C, Hu Z, Zhang W, *et al.* Regulation of Cholesterol Homeostasis by a Novel Long Non-coding RNA LASER. Scientific Reports 2019;9:7693.
27. Sallam T, Jones MC, Gilliland T, *et al.* Feedback modulation of cholesterol metabolism by the lipid-responsive non-coding RNA LeXis. Nature 2016;534:124-8.
28. Tontonoz P, Wu X, Jones M, *et al.* Long Noncoding RNA Facilitated Gene Therapy Reduces Atherosclerosis in a Murine Model of Familial Hypercholesterolemia. Circulation 2017;136:776-8.
29. Josefs T, Boon RA. The Long Non-coding Road to Atherosclerosis. Curr Atheroscler Rep 2020;22:55.
30. Jin H, Goossens P, Juhasz P, *et al.* Integrative multiomics analysis of human atherosclerosis reveals a serum response factor-driven network associated with intraplaque hemorrhage. Clin Transl Med 2021;11:e458.
31. Dhindsa RS, Burren OS, Sun BB, *et al.* Rare variant associations with plasma protein levels in the UK Biobank. Nature 2023;622:339-47.
32. Goedeke L, Rotllan N, Canfran-Duque A, *et al.* MicroRNA-148a regulates LDL receptor and ABCA1 expression to control circulating lipoprotein levels. Nat Med 2015;21:1280-9.
33. Wagschal A, Najafi-Shoushtari SH, Wang L, *et al.* Genome-wide identification of microRNAs regulating cholesterol and triglyceride homeostasis. Nat Med 2015;21:1290-7.
34. Sun BB, Chiou J, Traylor M, *et al.* Genetic regulation of the human plasma proteome in 54,306 UK Biobank participants. bioRxiv 2022:2022.06.17.496443.
35. Xiao Q, Hou R, Xie L, *et al.* Macrophage metabolic reprogramming and atherosclerotic plaque microenvironment: Fostering each other? Clin Transl Med 2023;13:e1257.
36. Seimon T, Tabas I. Mechanisms and consequences of macrophage apoptosis in atherosclerosis. J Lipid Res 2009;50 Suppl(Suppl):S382-7.
37. Herrera-Merchan A, Cerrato C, Luengo G, *et al.* miR-33-mediated downregulation of p53 controls hematopoietic stem cell self-renewal. Cell Cycle 2010;9:3277-85.
38. Rotllan N, Ramirez CM, Aryal B, *et al.* Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in Ldlr-/- mice--brief report. Arterioscler Thromb Vasc Biol 2013;33:1973-7.
39. Rayner KJ, Suarez Y, Davalos A, *et al.* MiR-33 contributes to the regulation of cholesterol homeostasis. Science 2010;328:1570-3.
40. Goedeke L, Vales-Lara FM, Fenstermaker M, *et al.* A regulatory role for microRNA 33* in controlling lipid metabolism gene expression. Mol Cell Biol 2013;33:2339-52.
41. Goedeke L, Salerno A, Ramirez CM, *et al.* Long-term therapeutic silencing of miR-33 increases circulating triglyceride levels and hepatic lipid accumulation in mice. EMBO Mol Med 2014;6:1133-41.
42. Davalos A, Goedeke L, Smibert P, *et al.* miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A 2011;108:9232-7.
43. Cirera-Salinas D, Pauta M, Allen RM, *et al.* Mir-33 regulates cell proliferation and cell cycle progression. Cell Cycle 2012;11:922-33.
44. Ouimet M, Ediriweera HN, Gundra UM, *et al.* MicroRNA-33-dependent regulation of macrophage metabolism directs immune cell polarization in atherosclerosis. J Clin Invest 2015;125:4334-48.
45. Price NL, Rotllan N, Canfran-Duque A, *et al.* Genetic Dissection of the Impact of miR-33a and miR-33b during the Progression of Atherosclerosis. Cell Rep 2017;21:1317-30.
46. Li C, He H, Liu A, *et al.* Natural Functional SNPs in miR-155 Alter Its Expression Level, Blood Cell Counts, and Immune Responses. Front Immunol. 2016;7:295.
47. Nazari-Jahantigh M, Wei Y, Noels H, *et al.* MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. J Clin Invest 2012;122:4190-202.
48. Du F, Yu F, Wang Y, *et al.* MicroRNA-155 deficiency results in decreased macrophage inflammation and attenuated atherogenesis in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2014;34:759-67.
49. Tian FJ, An LN, Wang GK, *et al.* Elevated microRNA-155 promotes foam cell formation by targeting HBP1 in atherogenesis. Cardiovasc Res 2014;103:100-10.
50. Jablonski KA, Gaudet AD, Amici SA, *et al.* Control of the Inflammatory Macrophage Transcriptional Signature by miR-155. PLoS One 2016;11:e0159724.
51. Li X, Kong D, Chen H, *et al.* miR-155 acts as an anti-inflammatory factor in atherosclerosis-associated foam cell formation by repressing calcium-regulated heat stable protein 1. Sci Rep 2016;6:21789.
52. Donners MM, Wolfs IM, Stoger LJ, *et al.* Hematopoietic miR155 deficiency enhances atherosclerosis and decreases plaque stability in hyperlipidemic mice. PLoS One 2012;7:e35877.
53. Wei Y, Zhu M, Corbalan-Campos J, *et al.* Regulation of Csf1r and Bcl6 in macrophages mediates the stage-specific effects of microRNA-155 on atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35:796-803.
54. Wei Y, Nazari-Jahantigh M, Chan L, *et al.* The microRNA-342-5p fosters inflammatory macrophage activation through an Akt1- and microRNA-155-dependent pathway during atherosclerosis. Circulation 2013;127:1609-19.
55. Hou J, Wang P, Lin L, *et al.* MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. J Immunol 2009;183:2150-8.
56. He X, Tang R, Sun Y, *et al.* MicroR-146 blocks the activation of M1 macrophage by targeting signal transducer and activator of transcription 1 in hepatic schistosomiasis. EBioMedicine 2016;13:339-47.
57. Peng L, Zhang H, Hao Y, *et al.* Reprogramming macrophage orientation by microRNA 146b targeting transcription factor IRF5. EBioMedicine 2016;14:83-96.
58. Li K, Ching D, Luk FS, *et al.* Apolipoprotein E enhances microRNA-146a in monocytes and macrophages to suppress nuclear factor-kappaB-driven inflammation and atherosclerosis. Circ Res 2015;117:e1-e11.
59. Zhuang G, Meng C, Guo X, *et al.* A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation. Circulation 2012;125:2892-903.
60. Canfran-Duque A, Rotllan N, Zhang X, *et al.* Macrophage deficiency of miR-21 promotes apoptosis, plaque necrosis, and vascular inflammation during atherogenesis. EMBO Mol Med 2017;9:1244-62.
61. Njock MS, Cheng HS, Dang LT, *et al.* Endothelial cells suppress monocyte activation through secretion of extracellular vesicles containing antiinflammatory microRNAs. Blood 2015;125:3202-12.
62. Ohta M, Kihara T, Toriuchi K, *et al.* IL-6 promotes cell adhesion in human endothelial cells via microRNA-126-3p suppression. Exp Cell Res 2020;393:112094.
63. Ong SG, Lee WH, Huang M, *et al.* Cross talk of combined gene and cell therapy in ischemic heart disease: role of exosomal microRNA transfer. Circulation 2014;130(11 Suppl 1):S60-9.

64. Zhang Y, Liu D, Chen X, *et al.* Secreted monocytic miR-150 enhances targeted endothelial cell migration. Mol Cell 2010;39:133-44.
65. Liu S, Chen J, Shi J, Zhou W, *et al.* M1-like macrophage-derived exosomes suppress angiogenesis and exacerbate cardiac dysfunction in a myocardial infarction microenvironment. Basic Res Cardiol 2020;115:22.
66. Liu Y, Zhang WL, Gu JJ, *et al.* Exosome-mediated miR-106a-3p derived from ox-LDL exposed macrophages accelerated cell proliferation and repressed cell apoptosis of human vascular smooth muscle cells. Eur Rev Med Pharmacol Sci 2020;24:7039-50.
67. Wang Z, Zhu H, Shi H, *et al.* Exosomes derived from M1 macrophages aggravate neointimal hyperplasia following carotid artery injuries in mice through miR-222/CDKN1B/CDKN1C pathway. Cell Death Dis 2019;10:422.
68. Zhu J, Liu B, Wang Z, *et al.* Exosomes from nicotine-stimulated macrophages accelerate atherosclerosis through miR-21-3p/PTEN-mediated VSMC migration and proliferation. Theranostics 2019;9:6901-19.
69. Li Z, Chao TC, Chang KY, *et al.* The long noncoding RNA THRIL regulates TNFalpha expression through its interaction with hnRNPL. Proc Natl Acad Sci U S A 2014;111:1002-7.
70. Song X, Gao F, Li H, *et al.* Long noncoding RNA THRIL promotes foam cell formation and inflammation in macrophages. Cell Biol Int 2023;47:156-66.
71. Hu YW, Zhao JY, Li SF, *et al.* RP5-833A20.1/miR-382-5p/NFIA-dependent signal transduction pathway contributes to the regulation of cholesterol homeostasis and inflammatory reaction. Arterioscler Thromb Vasc Biol 2015;35:87-101.
72. Reddy MA, Chen Z, Park JT, *et al.* Regulation of inflammatory phenotype in macrophages by a diabetes-induced long noncoding RNA. Diabetes 2014;63:4249-61.
73. Gast M, Rauch BH, Nakagawa S, *et al.* Immune system-mediated atherosclerosis caused by deficiency of long non-coding RNA MALAT1 in ApoE-/-mice. Cardiovasc Res 2019;115:302-14.
74. Simion V, Zhou H, Haemmig S, *et al.* A macrophage-specific lncRNA regulates apoptosis and atherosclerosis by tethering HuR in the nucleus. Nat Commun 2020;11:6135.
75. Yurdagul A, Jr., Doran AC, Cai B, *et al.* Mechanisms and Consequences of Defective Efferocytosis in Atherosclerosis. Front Cardiovasc Med 2017;4:86.
76. Ye ZM, Yang S, Xia YP, *et al.* LncRNA MIAT sponges miR-149-5p to inhibit efferocytosis in advanced atherosclerosis through CD47 upregulation. Cell Death Dis 2019;10:138.
77. Carpenter S, Aiello D, Atianand MK, *et al.* A long noncoding RNA mediates both activation and repression of immune response genes. Science 2013;341:789-92.
78. Zhang L, Cheng H, Yue Y, *et al.* TUG1 knockdown ameliorates atherosclerosis via up-regulating the expression of miR-133a target gene FGF1. Cardiovasc Pathol 2018;33:6-15.
79. Wang L, Xia JW, Ke ZP, *et al.* Blockade of NEAT1 represses inflammation response and lipid uptake via modulating miR-342-3p in human macrophages THP-1 cells. J Cell Physiol 2019;234:5319-26.
80. de Jager SC, Bot I, Kraaijeveld AO, *et al.* Leukocyte-specific CCL3 deficiency inhibits atherosclerotic lesion development by affecting neutrophil accumulation. Arterioscler Thromb Vasc Biol 2013;33:e75-83.
81. Zernecke A, Bot I, Djalali-Talab Y, *et al.* Protective role of CXC receptor 4/CXC ligand 12 unveils the importance of neutrophils in atherosclerosis. Circ Res 2008;102:209-17.
82. Quillard T, Araujo HA, Franck G, *et al.* TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. Eur Heart J 2015;36:1394-404.
83. Naruko T, Ueda M, Haze K, *et al.* Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation 2002;106:2894-900.
84. Ionita MG, van den Borne P, Catanzariti LM, *et al.* High neutrophil numbers in human carotid atherosclerotic plaques are associated with characteristics of rupture-prone lesions. Arterioscler Thromb Vasc Biol 2010;30:1842-8.
85. Gomez I, Ward B, Souilhol C, *et al.* Neutrophil microvesicles drive atherosclerosis by delivering miR-155 to atheroprone endothelium. Nat Commun 2020;11:214.
86. Kohlhaas S, Garden OA, Scudamore C, *et al.* Cutting edge: the Foxp3 target miR-155 contributes to the development of regulatory T cells. J Immunol 2009;182:2578-82.
87. Lu LF, Thai TH, Calado DP, *et al.* Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity 2009;30:80-91.
88. Ventura A, Young AG, Winslow MM, *et al.* Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. Cell 2008;132:875-86.
89. Xiao C, Srinivasan L, Calado DP, *et al.* Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. Nat Immunol 2008;9:405-14.
90. Li SS, Ivanoff A, Bergstrom SE, *et al.* T lymphocyte expression of thrombospondin-1 and adhesion to extracellular matrix components. Eur J Immunol 2002;32:1069-79.
91. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol 2011;12:204-12.
92. Buono C, Binder CJ, Stavrakis G, *et al.* T-bet deficiency reduces atherosclerosis and alters plaque antigen-specific immune responses. Proc Natl Acad Sci U S A 2005;102:1596-601.
93. Kleemann R, Zadelaar S, Kooistra T. Cytokines and atherosclerosis: a comprehensive review of studies in mice. Cardiovasc Res 2008;79:360-76.
94. Pattarabanjird T, Li C, McNamara C. B Cells in Atherosclerosis: Mechanisms and Potential Clinical Applications. JACC Basic Transl Sci 2021;6:546-63.
95. Calame K. MicroRNA-155 function in B Cells. Immunity 2007;27:825-7.
96. Teng G, Hakimpour P, Landgraf P, *et al.* MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. Immunity. 2008;28(5):621-9.
97. Roy PA-OX, Orecchioni MA-O, Ley KA-O. How the immune system shapes atherosclerosis: roles of innate and adaptive immunity. (1474-1741 (Electronic)).
98. Kott KA, Vernon ST, Hansen T, *et al.* Single-Cell Immune Profiling in Coronary Artery Disease: The Role of State-of-the-Art Immunophenotyping With Mass Cytometry in the Diagnosis of Atherosclerosis. (2047-9980 (Electronic)).
99. Bruno A, Teresa Palano M, Cucchiara M, *et al.* Immunoprofiling and immunoscoring in cor onary artery disease: From vascular research to the bedside? (2352-9067 (Print)).
100. Holmberg-Thyden S, Grønbæk K, Gang AO, *et al.* A user's guide to multicolor flow cytometry panels for comprehensive immune profiling. (1096-0309 (Electronic)).
101. Fernandez DM, Giannarelli C. Immune cell profiling in atherosclerosis: role in research and precision medicine. (1759-5010 (Electronic)).
102. Wang XS, Ding XZ, Li XC, *et al.* A highly integrated precision nanomedicine strategy to target esophageal squamous cell cancer molecularly and physically. Nanomedicine 2018;14:2103-14.
103. Terashima T, Ogawa N, Nakae Y, *et al.* Gene Therapy for Neuropathic Pain through siRNA-IRF5 Gene Delivery with Homing Peptides to Microglia. Mol Ther Nucleic Acids 2018;11:203-15.
104. Aoki M, Matsumoto NM, Dohi T, *et al.* Direct Delivery of Apatite Nanoparticle-Encapsulated siRNA Targeting TIMP-1 for Intractable Abnormal Scars. Mol Ther Nucleic Acids 2020;22:50-61.
105. Scholz J, Weil PP, Pembaur D, *et al.* An Adenoviral Vector as a Versatile Tool for Delivery and Expression of miRNAs. Viruses 2022;14(9).

106. Shao H, Im H, Castro CM, *et al.* New Technologies for Analysis of Extracellular Vesicles. Chem Rev 2018;118:1917-50.
107. Familtseva A, Jeremic N, Tyagi SC. Exosomes: cell-created drug delivery systems. Mol Cell Biochem 2019;459:1-6.
108. Alvarez-Erviti L, Seow Y, Yin H, *et al.* Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol 2011;29:341-5.
109. Liang Y, Duan L, Lu J, *et al.* Engineering exosomes for targeted drug delivery. Theranostics 2021;11:3183-95.
110. Wu G, Zhang J, Zhao Q, *et al.* Molecularly Engineered Macrophage-Derived Exosomes with Inflammation Tropism and Intrinsic Heme Biosynthesis for Atherosclerosis Treatment. Angew Chem Int Ed Engl 2020;59:4068-74.
111. Yan Y, Li XQ, Duan JL, *et al.* Nanosized functional miRNA liposomes and application in the treatment of TNBC by silencing Slug gene. Int J Nanomedicine 2019;14:3645-67.
112. Scheideler M, Vidakovic I, Prassl R. Lipid nanocarriers for microRNA delivery. Chem Phys Lipids 2020;226:104837.
113. Ho D, Lynd TO, Jun C, *et al.* MiR-146a encapsulated liposomes reduce vascular inflammatory responses through decrease of ICAM-1 expression, macrophage activation, and foam cell formation. Nanoscale 2023;15:3461-74.
114. Zhang X, Rotllan N, Canfran-Duque A, *et al.* Targeted Suppression of miRNA-33 Using pHLIP Improves Atherosclerosis Regression. Circ Res 2022;131:77-90.
115. Lam JK, Chow MY, Zhang Y, *et al.* siRNA Versus miRNA as Therapeutics for Gene Silencing. Mol Ther Nucleic Acids 2015;4:e252.
116. Koren MJ, Moriarty PM, Baum SJ, *et al.* Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med 2022;28:96-103.
117. O'Donoghue ML, Rosenson RS, Gencer B, *et al.* Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. N Engl J Med 2022;387:1855-64.
118. Mercep I, Friscic N, Strikic D, *et al.* Advantages and Disadvantages of Inclisiran: A Small Interfering Ribonucleic Acid Molecule Targeting PCSK9-A Narrative Review. Cardiovasc Ther 2022;2022:8129513.
119. Fitzgerald K, White S, Borodovsky A, *et al.* A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. N Engl J Med 2017;376:41-51.
120. Leiter LA, Teoh H, Kallend D, *et al.* Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial. Diabetes Care 2019;42:173-6.
121. Ray KK, Wright RS, Kallend D, *et al.* Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med 2020;382:1507-19.
122. Alhomoud IS, Talasaz A, Mehta A, *et al.* Role of lipoprotein(a) in atherosclerotic cardiovascular disease: A review of current and emerging therapies. Pharmacotherapy 2023;43:1051-63.
123. Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). ClinicalTrianls.gov Identifier: NCT05030428. Accessed June 05, 2024. https://clinicaltrials.gov/ct2/show/NCT05030428.
124. A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4). ClinicalTrianls.gov Identifier: NCT03705234. Accessed June 05, 2024. http://clinicaltrials.gov/ct2/show/NCT03705234.
125. Bijsterbosch MK, Manoharan M, Rump ET, *et al.* In vivo fate of phosphorothioate antisense oligodeoxynucleotides: predominant uptake by scavenger receptors on endothelial liver cells. Nucleic Acids Res 1997;25:3290-6.
126. Brown DA, Kang SH, Gryaznov SM, *et al.* Effect of phosphorothioate modification of oligodeoxynucleotides on specific protein binding. J Biol Chem. 1994;269(43):26801-5.
127. Dhuri K, Bechtold C, Quijano E, *et al.* Antisense Oligonucleotides: An Emerging Area in Drug Discovery and Development. J Clin Med 2020;9(6).
128. Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD (Lp(a)HORIZON). ClinicalTrianls.gov Identifier: NCT04023552. Accessed June 05, 2024. https://clinicaltrials.gov/ct2/show/NCT04023552.
129. Tsimikas S, Viney NJ, Hughes SG, *et al.* Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. Lancet 2015;386:1472-83.
130. Malick WA, Goonewardena SN, Koenig W, *et al.* Clinical Trial Design for Lipoprotein(a)-Lowering Therapies: JACC Focus Seminar 2/3. J Am Coll Cardiol 2023;81:1633-45.

TECHNOLOGICAL LEAPS IN VASCULAR SURGERY

As Thomas Kuhn had already understood in 1962, the scientific progress tends to occur by alternating two distinct phases: periods of normality, during which the scientific activity usually respects established paradigms, are typically followed by periods of profound crisis, during which a bloom of new theories, innovative ideas, and related technologies eventually emerges. These sparks of scientific revolution challenge the previous paradigms, but only a few of them, the best, will really lead to the birth of new and updated paradigms. Since the turn of the last millennium, we have been experiencing the digital revolution, the advanced development of robotics, the rise of genetic engineering and nanotechnology, the imposition of the "Internet of Things". Last but not least, we are well aware that we are entering the new era of Artificial Intelligence. These and other *technological leaps* have contributed to a profound transformation in the way we approach healthcare. And Vascular Surgery, of course, is not exempt. This book collects a selected series of recent innovations in the field of Vascular and Endovascular Surgery, exhaustively described by renowned international experts engaged in their development and application. It is aimed at trainees and specialists interested in understanding and improving the most complex aspects of surgical therapy for vascular diseases. With this volume, SICVE makes a bet on the future, trying to indentify which *cutting-edge* technologies will represent the "game-changers" in our wonderful surgical discipline.



9 788855 322898
www.minervamedica.it