Moving Computational Tools for Aortic Disease from the Bench to the Bedside

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the Computational Mechanics and Advanced Materials Group Department of Civil Engineering and Architecture

February 12, 2018
“Az me schmirt, furt men”

Yiddish proverb
Abstract

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by Rodrigo Maximiliano ROMAROWSKI

Computational Fluid Dynamics (CFD) have been in the focus of the biomedical community for many years. In particular, blood flow simulations in the aorta are now well established among researchers. Despite these developments, numerical tools do not constitute every day tools in the bedside. The aim of this thesis is to fill the methodological and conceptual gaps between CFD and medical needs in the field of thoracic aortic disease.

In Chapter 2, pathologies of the aorta will be described in deep to understand which are the current medical needs. Subsequently, CFD in the aorta will be explained with all the ingredients needed to make robust and simple simulations.

Chapter 3 focuses on tuning boundary conditions, a topic where much work has been done in the research community but there is no actual consensus. We propose a novel and simple, yet cheap and reliable, methodology for calibrating the so-called 3 Element Windkessel model.

Three applications of CFD in the aorta will be shown in Chapter 4 as a proof-of-concept on moving from a single case to bigger cohorts. These are the iCardioCloud project, a database of CFD on patients with thoracic aortic disease; the impact of the ageing aorta on hemodynamics and the predictive value of computational simulations for embodeviation in TAVI.

More advanced applications of computational simulations suited for TEVAR will be approached in Chapter 5. First, CFD will be applied in healthy aortas in order to evaluate the impact aortic arch angulation on blood flow for a better TEVAR planning. Then, a framework for merging virtual stent-graft deployment together with pre-operative imaging will be proposed so as to reliably predict hemodynamics after TEVAR. Finally, virtual endografting of the ascending aorta will be analysed as an alternative to open repair.

We conclude that the developed methods and tools satisfactorily fill the different gaps needed for simulating big cohorts of patients and extract both single-patient and population-based results.
Acknowledgements

The last three years in Pavia gave me the opportunity of carrying out several research activities and also build many unforgettable friendships. Changing hemisphere and crossing the Atlantic ocean was a successful choice in my professional an personal life.

Thanks have to open with my gratefulness to Alessandro Veneziani who kindly invited me to his lab at Emory University back in 2014 when I was nothing but an inexperienced biomedical engineer. There he installed inside me the passion and love for research and the continuous perseverance for finding the scientific truth. During the first semester of 2017, I had once again the pleasure to visit him in Atlanta in order to improve and continue my work with excellent results.

Also, a special thanks to our group head Ferdinando Auricchio, who trusted in me from the beginning and supported me in every single idea that came up never having a "no" as an answer. Along these journey I much appreciated his way to approach and solve the problems and enthusiasm for research.

My highest gratitudes go to my supervisor Simone Morganti and Michele Conti, who supported me and pushed me everyday to the limit in order to get the best out of myself. Their advices on both research as well as on the human side have been priceless and incented me to reach my goals. Furthermore, Adrien Lefieux and Elena Faggiano were among those that dedicated part of their precious time to make me understand things that my brain could not easily absorb.

I am also really thankful to Santi Trimarchi and Massimiliano Marroco Trischitta from the Policlinico San Donato, who gave me the possibility to ride the train of their projects in the amazing world of vascular surgery. Many thanks to the dutch crew with whom we got to build extremely fruitful discussions and friendships.

Thanks to all my colleagues in the CompmMech group (an amazing total of 31 people) who made my daily work a fun experience and always kindly tasted my new cooking recipes. Specially to Marco and Vale, my fellow chefs and office mates.

None of this would have been possible without the support and deep love of my family. My eternal thanks to my parents Julia and Daniel who made me the person I am nowadays and my brother Gonzalo who unconditionally stands next to me since the day I was born.

Finally, I would like to thank the love of my life Margherita. Your constant smile, love and support make every day the most special one.
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<td>2 element Windkessel</td>
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<tr>
<td>3WK</td>
<td>3 element Windkessel</td>
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<tr>
<td>AA</td>
<td>Ascending Aorta</td>
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<td>BAV</td>
<td>Bicuspid Aortic Valve</td>
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<td>Boundary Conditions</td>
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<td>Penetrating Aortic Ulcer</td>
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<td>Phase Contrast - Magnetic Resonance Imaging</td>
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<td>PLZ</td>
<td>Proximal Landing Zone</td>
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<td>Patient Specific</td>
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<td>TL</td>
<td>True Lumen</td>
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<td>ToA</td>
<td>Type of Arch</td>
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<td>TAVI</td>
<td>Transcatheter Aortic Valve Implantation</td>
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<td>TAWSS</td>
<td>Time Averaged Wall Shear Stress</td>
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<td>University of Nebraska - Medical Center</td>
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<tr>
<td>WSS</td>
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A mi bobe Berta.
Chapter 1

Introduction

The human being is a complex and optimized machine. Physical, chemical and metabolic systems work synchronously to keep the state of homoeostasis, which guarantees an equilibrium in our body. However, evolution has not caught up with one crucial change in our life which is ageing. In the 1960’s, world’s average life expectancy at birth was roughly 52.5 years. For those born in the 1990, like me, by the time we were born, we were expected to live 65.4 years. Interestingly, last numbers say that for babies born in 2015, life expectancy at birth climbed up to 71.7 years. It is not hard to conclude that we are getting older (source World Bank).

Ageing has obvious negative consequences, which can be compared to a fatigue phenomena that a machine undergoes. By the age of 70 our heart will have pumped enough blood to fill 74 olympic-sized swimming pools, our bladder get filled and emptied 179 thousand times and we will have walked 4.5 times the circumference of the earth. We can not disregard that impact that this long-term use of our organs will have in our body.

The circulatory system, as a complex maze of arteries and veins that visit every single corner of our body, is not exempt of the effects of ageing. Curiously, the incidence of cardiovascular disease remains constant in young individuals and trouble starts by the age of 50 (Lloyd-Jones et al., 2006). Arteries and valves get stiffer, coronaries get occluded and, as a consequence, the heart increases its size. The major artery in our body, the aorta, connects the central pump with the main organs and limbs. Though it might seem just a tube, changes in its morphology and physiology have significant impact in the function of peripheral organs and the brain.

Description of aortic complications and techniques for major surgery have been in the focus of medical research from the late 50’s (Parmley et al., 1958; Bentall and De Bono, 1968). However, since the 90’s another community that was far from being interested in the so-called aortic hemodynamics had developed tools that would change the approach to cardiovascular research (Makhijani et al., 1997; Krafczyk et al., 1998). Computational scientists,
mathematicians and physicists were using a set of tools based on complex mathematical models in order to simulate the behaviour of a fluid in a certain geometry.

If aortic disease is related to a change in the normal hemodynamics inside the vessel, why not simulating a set of virtual scenarios that would give a better understanding of the complications? With the improvement of computational power and the increase in the quality of medical imaging, in almost 30 years many steps have been given towards answering this question. Nevertheless, we do not see physicians run computational analyses while we have our visit, meaning that the gap between theory and practise has not yet been fulfilled.

With all this considerations in mind, the aim of this thesis is to give a step towards adding the necessary components for introducing computational tools in the medical practise. One of the key pillars will be showing that not always the most precise and complex models are the most useful, but rather a balance has to be achieved among time, complexity, understanding and cost.

The main work consists on aortic CFD and has been conducted within the iCardioCloud project in very close collaboration with physicians of IRCCS Policlinico San Donato. A framework for running blood flow simulations in aneurysmatic patients was developed with a strong focus on the choice of boundary conditions. Then, this framework has been applied as a diagnostic tool in the so-called arch project to give a new insight on TEVAR classification. Besides providing improved understanding of probable complications and disease evolution, the predictive capabilities of computational tools can be also used to provide support to vascular surgeons during the decision-making process. In this context, as moving from diagnosis to treatment, the last part of the work consisted in virtually reproducing TEVAR surgery to predict hemodynamics after intervention.

More precisely, this thesis is structured as follows:

• Chapter 2 builds the bases for knowing the aorta, its most common diseases related with ageing which are Thoracic Aortic Aneurysm and Thoracic Aortic Dissection and enumerates their complications. Current surgical options are analysed in deep. Then, an overview for understanding the bases of CFD with all its ingredients will be explained. A special focus on the concept of patient-specific approach will be made.

• Chapter 3 will try to give a comprehensive analysis of boundary conditions and the proposal of a calibration technique of the 3 element Windkessel model. The focus will be realistic and application-oriented, taking into account the limitations of the medical environment.

• Chapter 4 will illustrate three concrete applications of the use of CFD in the thoracic aorta for medical purposes. The first one, namely iCardioCloud project, is a cloud-based platform to share images and CFD simulations in patients with thoracic aortic
disease. The second one, analyses 9 cohorts of healthy individuals from 5 to 100 year old in order to assess hemodynamic changes in the aorta with ageing. The last one, reproduces computationally a set of in-vitro experiments aiming at analysing the concept of embodeviation to avoid stroke caused by emboli during TAVI.

- Chapter 5 will focus on the TEVAR procedure. We will describe in detail three applications in which computational tools such as FEA and CFD may have a concrete impact on TEVAR planning. The first one, is the re-assessment of Proximal Landing Zones during operative planning by combining arch angulation and the concept of Displacement Force. The goal is to create an updated arch-map with both morphological and hemodynamic features. The second one, represents a framework for predicting hemodynamics after TEVAR by virtually deploying a stent-graft. The main novelty is the merging of the deployed stent with the surrounding aorta so as to have a realistic 3D reconstruction that does not loose details on angulation and bird beak. Finally, a case report on a single patient with an ascending aortic pseudoaneurysm will expose the current limitations of TEVAR in the ascending aorta and will propose a simulation strategy that combines patient-specific device modelling and deployment.

- Chapter 6 will finally draw the conclusions of this work focusing on our successful experience in translating knowledge to the bedside. Unsolved limitations that computational techniques should overcome in the near future to pursue the aim of getting deeper in the clinical practise will also be addressed.
Chapter 2

Thoracic Aortic Disease and CFD

2.1 Aneurysm and dissection: origin, complications and treatment

2.1.1 The normal aorta

The aorta is the ultimate conduit, carrying, in an average lifetime, almost 200 million litres of blood to the body. As depicted in Figure 2.1, it is divided by the diaphragm into the thoracic (ascending, arch and descending) and abdominal aorta.

The aortic wall is composed histologically of three layers: a thin inner tunica intima lined by the endothelium; a thick tunica media characterized by concentric sheets of elastic and collagen fibres with the border zone of the lamina elastica interna and -externa, as well as smooth muscle cells; and the outer tunica adventitia containing mainly collagen, vasa vasorum and lymphatic vessels. These layers are shown in a transversal cut in Figure 2.2.

In addition to the conduit function, the aorta plays an important role in the control of systemic vascular resistance and heart rate, via pressure-responsive receptors located in the ascending aorta and aortic arch. An increase in aortic pressure results in a decrease in heart rate and systemic vascular resistance, whereas a decrease in aortic pressure results in an increase in heart rate and systemic vascular resistance. Through its elasticity, the aorta has the role of a ‘second pump’ (Windkessel function) during diastole, which is of utmost importance—not only for coronary perfusion.

In healthy adults, aortic diameters do not usually exceed 40 mm and taper gradually downstream. They are variably influenced by several factors including age, gender, body size and blood pressure (Lam et al., 2010). In this regard, the rate of radial expansion is about 0.9 mm in men and 0.7 mm in women for each decade of life (Vriz et al., 2013). This slow but progressive aortic dilation over mid-to-late adulthood is thought to be a consequence of
ageing, related to a higher collagen-to-elastin ratio, along with increased stiffness and pulse pressure (Braverman, Thompson, and Sanchez, 2012; Kälsch et al., 2013).

2.1.2 Origin, prognosis and complications of TAA and TAD

Also with ageing, the aortic wall might become pathologically remodelled, so in this work we focus extensively in the two most common aortic syndromes which particularly affect hemodynamics: Thoracic Aortic Aneurysm (TAA) and Thoracic Aortic Dissection (TAD).

Thoracic Aortic Aneurysm

By definition, an aneurysm is an enlargement of more than 50% of the normal diameter of the aortic lumen (Johnston et al., 1991). It constitutes the second most frequent disease of the aorta after atherosclerosis and, depending on its location, is divided into TAA (in
2.1. Aneurysm and dissection: origin, complications and treatment

Figure 2.2: Axial section of the aorta showing its layers: intima, media and adventitia. Reproduced from www.deltagen.com.

the thoracic aorta) or AAA (in the abdominal aorta). Causes and origin of TAA are not completely clear besides congenital pathologies such as Marfan syndrome and bicuspid aortic valve (BAV).

Patients with TAA are most often asymptomatic and the diagnosis is made following imaging, performed either for other investigative reasons or for screening purposes. TAA is less frequently revealed by clinical signs of compression, chest pain, aortic valve murmur, or during a complication. In general, patients undergo contrast enhanced CT scans which can visualize thorax vasculature. If an enlargement is seen, the whole aorta tends to be reconstructed and measured in order to isolate the extent of the disease. Figure 2.3 shows a CT slice of a normal aorta and of an aneurysmatic case, together with their 3D reconstruction.

Initial diameter and female sex constitute the primary independent risk factors associated with TAA catastrophic rupture (Brown, Powell, et al., 1999). However, decision to treat TAA is based on many variables such as familial history, rate of growth, location within the arch and, naturally, the general condition of the patient. The principal risk derived from an aneurysm is its rupture with a consequent internal bleeding. Depending on the location of the TAA (ascending aorta, arch or descending aorta), prognosis is known to be different since they are associated with diverse growth rates (Erbel et al., 2014).

In a first stage, medical therapy constitutes an appropriate step to reduce shear stress
on the diseased segment of the aorta by reducing blood pressure and cardiac contractility. A large number of patients with aortic diseases have comorbidities such as coronary artery disease, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, etc. Therefore treatment and prevention strategies must be similar to those indicated for these diseases. In chronic conditions, blood pressure should be controlled below 140/90 mmHg, with lifestyle changes and use of antihypertensive drugs, if necessary. An ideal treatment would be the one that reverses the formation of an aneurysm, even though this is still an open issue.

**Thoracic Aortic Dissection**

Thoracic Aortic Dissection is a member of the so-called *acute aortic syndromes*. It is defined as the disruption of the medial layer provoked by intramural bleeding, resulting in separation of the aortic wall layers and subsequent formation of a True Lumen (TL) and a False Lumen (FL) with or without communication. In most cases, an intimal tear is the initiating condition, resulting in tracking of the blood in a dissection plane within the media. This process is followed either by an aortic rupture in the case of adventitial disruption or by a re-entering into the aortic lumen through a second intimal tear. The dissection can be either antegrade or retrograde.

The Stanford classification, as shown in Figure 2.4, takes into account the extent of dissection, rather than the location of the entry tear. The propagation can also affect side branches. Complications include tamponade, aortic valve regurgitation, and proximal or
2.1. Aneurysm and dissection: origin, complications and treatment

distal malperfusion syndromes. The inflammatory response to thrombus in the media is likely to initiate further necrosis and apoptosis of smooth muscle cells and degeneration of elastic tissue, which potentiates the risk of medial rupture.

Figure 2.4: Stanford classification of TAD. If the ascending aorta is involved, dissection is defined as Type A. Otherwise, is defined as Type B.

Opposedly to TAA, abrupt onset of severe chest and/or back pain is the most typical feature of TAD. The pain may be sharp, ripping, tearing, knife-like, and typically different from other causes of chest pain; the abruptness of its onset is the most specific characteristic. Anterior chest pain is more commonly associated with Type A TAD, whereas patients with Type B dissection present more frequently with pain in the back or abdomen. The pain may migrate from its point of origin to other sites, following the dissection path as it extends through the aorta.

Following CT scan to confirm diagnosis, the main determinant whether to conduct surgery is the extent of the disease and organ ischaemia. Type A dissection usually involves disruption of the wall in the aortic branches of the arch which feed the brain. In this case, surgery is conducted immediately. Patients with acute Type A dissection suffer double the mortality of individuals presenting with Type B dissection: 25% and 12%, respectively (Moro et al., 1999).

In the case of type B dissection, the contrast enhanced scan shows whether the arteries supplying blood to the kidneys, liver and intestine initiate at the TL or the FL. In the first case, the patient is recommended medical therapy as described earlier for TAA. In the later, surgery is planned in order to reestablish blood flow to peripheral organs.
Besides end-organ ischaemia, complications associated with TAD are aortic valve regurgitation with the subsequent development of congestive heart failure, myocardial ischaemia or infarction and the development of a post-dissecting aneurysm. When a patient presents no further risk, medical therapy is conducted and follow-up scans are scheduled yearly.

It may also be the case in which TAD has no symptoms for years and it is first diagnosed in its chronic phase. Chronicity of aortic dissection is suggested by CT imaging characteristics: thickened, immobile intimal flap, presence of thrombus in the FL, or aneurysms of the thoracic aorta, mostly developed in the distal aortic arch. In symptomatic patients, signs of (contained) rupture such as mediastinal haematoma or pleural effusion may be present. Figure 2.5 shows a typical diagnosis CT for TAD. Notably, in the acute case both the TL and FL are permeable to the contrast medium whereas the chronic case has a fully clotted FL.

**Figure 2.5:** Axial CT slices of acute (A) and chronic (B) TAD in the descending aorta.

### 2.1.3 Current treatment options: open surgery and TEVAR

Currently, there are different treatment options based on the location of the disease.

**Open aortic repair**

If the aneurysm is located in the ascending aorta, the main principle of surgery is that of preventing the risk of dissection or rupture by restoring the normal dimension of the portion. A tubular graft is placed under a short period of aortic clamping, with the distal anastomosis just below the aortic arch. Surgical mortality for isolated elective replacement of the ascending aorta (including the aortic root) ranges from 1.6 –4.8% and is dependent largely on age and other well-known cardiovascular risk factors at the time of operation (Kallenbach et al., 2013). Even though mortality rates for elective ascending/arch repair remain low (Perreas
et al., 2012; Achneck et al., 2007), potential use of TEVAR in the ascending aorta will be discussed deeper in Chapter 5.

In the case of the arch reconstruction, risk of surgery has been also significantly reduced. Innovative arch prostheses, including branching for supra-aortic vessel reconnection, have made the timing of arch reconstruction more predictable. This is the case for the majority of reconstructions, including acute and chronic dissection, requiring total arch replacement and arrest times from 40 to 60 minutes. Various extents and variants of aortic rerouting (left subclavian, left common carotid and finally brachiocephalic trunk, autologous vs. alloplastic) might also be used. Nowadays, many arch replacements are re-operations for dilated aneurysms after Type A dissection following limited ascending aorta replacement or proximal arch repair performed in emergency.

The surgical approach to the descending aorta is a left thoracotomy between the fourth and seventh intercostal spaces, depending on the extension of the aortic pathology. Usually the section to be operated is by-passed and a centrifugal pump is used. Since there are no important vessels emerging from this portion, the procedure is much safer. Again, the diseased part is replaced with an arterial graft.

**TEVAR**

Thoracic Endovascular Aortic Repair aims at excluding an aortic lesion (i.e. aneurysm or FL after dissection) from the circulation by the implantation of a membrane-covered stent-graft across the lesion, in order to prevent further enlargement and ultimate aortic rupture.

Careful planning is of utmost importance for a successful TEVAR procedure. Contrast-enhanced CT represents the imaging modality of choice for planning TEVAR, taking slices from the proximal supra-aortic branches down to the femoral arteries. The diameter and length of the healthy proximal and distal landing zone (LZ) are evaluated to assess the feasibility of TEVAR, along with assessment of the length of the lesion and its relationship to side branches and the iliofemoral access route. Device producers’ criteria vary for the LZ characteristics but in average the healthy neck should be of at least 2cm.

In TAA, the stent-graft diameter should exceed the reference aortic diameter at the landing zones by at least 10 to 15%. This concept is named oversizing and aims at increasing device mechanical stability. In patients with Type B dissection, the stent-graft is implanted across the proximal entry tear to obstruct blood flow into the FL, depressurize the FL, and induce a process of aortic remodelling with shrinkage of the FL and enlargement of the TL. In contrast to TAA, almost no oversizing of the stent-graft is applied.

In situations involving important aortic side branches (mostly when the lesion is in the arch), TEVAR is often preceded by limited surgical revascularization of these branches. Another option is a surgical de-branching or the use of fenestrated and branched endografts
or the ‘chimney technique’. An alternative may be a single, branched stent-graft. Figure 2.6 shows a fenestrated and a branched stent-graft together with a scheme of the chimney technique.

**Figure 2.6**: Top: fenestrated and a branched devices for arch endovascular replacement. Bottom: the chimney procedure, all the supraortic vessels are rerouted from the proximal ascending aorta. Reproduced from Kuratani, (2014).
2.1. Aneurysm and dissection: origin, complications and treatment

TEVAR is performed by retrograde transarterial advancement of a delivery device carrying the collapsed self-expandable stent-graft as shown in Figure 2.7. Arterial access is obtained either surgically or by the percutaneous approach, using suture-mediated access site closure. From the contralateral femoral side or from a brachial/radial access, a pigtail catheter is advanced for angiography. The stent-graft is delivered over a stiff guide wire. In dissections, it may be challenging to navigate the guide wire into a narrow TL, which is essential for stent-graft placement. When the target position is reached, the blood pressure is reduced either pharmacologically or using rapid right ventricular pacing to avoid downstream displacement, and the stent-graft is then deployed. Completion angiography is performed to detect any proximal Type I endoleak (an insufficient proximal seal), which usually mandates immediate treatment.

![Figure 2.7: Deployment of a stent-graft for TEVAR. A catheter-guided wire reaches the aneurysmatic section and the the stent-graft is deployed. Reproduced from http://www.aorta.ca/treatment/tevar/.

TEVAR complications

Surgery complications In TEVAR, vascular complications at the puncture site, as well as aortic and neurological complications, and/or endoleaks have been reported. Ideally, access site complications may be avoided by careful pre-procedural planning. Paraparesis/paraplegia and stroke rates range between 0.8 –1.9% and 2.1 –3.5%, respectively, and appear lower than those for open surgery (Ben-Shlomo et al., 2014). Mostly along the descending aorta, small vessels name *vertebral arteries* supplying blood to the spinal cord might be covered with the endoprosthesis fabric, causing stroke. Retrograde dissection of the ascending aorta after TEVAR is reported in 1.3% of patients (Eggebrecht et al., 2009).
Long term complications  Endoleak describes perfusion of the excluded aortic pathology and occurs both in thoracic and abdominal (T)EVAR. Different types of endoleaks are illustrated in Figure 2.8. Type I and Type III are regarded as treatment failures and warrant further treatment to prevent the continuing risk of rupture, while Type II endoleaks are normally managed conservatively by a ‘wait-and-watch’ strategy to detect aneurysmal expansion, except for supra-aortic arteries.

Endoleaks Types IV and V are indirect and have a benign course. Treatment is required in cases of aneurysm expansion. It is important to note that plain chest radiography can be useful as an adjunct to detect material fatigue of the stent-graft and to follow ‘stent-graft’ and ‘no stent-graft’-induced changes in width, length and angulation of the thoracic aorta.

Stent-graft migration is another complication related to the wrong apposition of the device to the arterial wall, which can happen during surgery and in a long-term basis. Usually, prostheses migrate proximally to the heart opposedly to the direction of blood flow. Device migration can cause type I endoleak, damage the arterial wall or obstruct peripheral vessels. Figure 2.9 shows a post-TEVAR patient with a successful surgery that presented proximal migration after 14 months of surgery.

Complete details on TEVAR planning, complications and clinical outcomes can be found in Grabenwöger et al., (2012) and Fillinger et al., (2010)

2.2 Computational Fluid Dynamics on cardiovascular diseases

Having described the physiopathology and anatomopathology of TAA and TAD, we will now focus on the components of blood flow computational analysis.

2.2.1 Basics of CFD

Equations and modelling assumptions

As a first premise, we will herein describe blood flow inside the aorta with a rigid wall model. On the one side, this choice is based on a strong simplifying assumption (i.e., neglecting aortic compliance and deformability); however, on the other side, it is recognized that it may represent a valid computational tool for clinical purposes (Brown et al., 2012; Jin, Oshinski, and Giddens, 2003). Moreover, in dealing with fluid-structure interaction models, it is well known that accuracy relies on a good estimate of the structural constitutive parameters (e.g., vessel wall stiffness), which, varying patient by patient, are quite hard to achieve.
2.2. Computational Fluid Dynamics on cardiovascular diseases

Following standard assumptions, we model aortic hemodynamics with the unsteady incompressible Navier-Stokes Equations (NSE) for a Newtonian fluid (a valid assumption in big vessels). The fluid is then described by the velocity \( u(x, t) \) and the pressure fields \( p(x, t) \), where \( t > 0, \ x \in \Omega \) and \( \Omega \) denotes the aortic domain of interest.

The NSE read:

\[
\begin{align*}
\frac{\partial u}{\partial t} + \rho (u \cdot \nabla) u - \mu \nabla \cdot (\nabla u + \nabla u^T) + \nabla p &= 0 \\
\nabla \cdot u &= 0.
\end{align*}
\]

\[ \text{in } (\Omega, t > 0) \quad (2.1) \]
Here $\mu$ is the constant viscosity set to $3.5cP$ and $\rho$ the blood density set to $1.06g/cm^3$. The equations must be equipped with both boundary conditions and velocity initial conditions. The initial conditions are set to 0 and in our numerical analysis, six heart beats will always be simulated to reach a reasonable periodic state.

**Domain of interest**

Aortic geometry - the major factor governing aortic hemodynamics - has been extensively investigated (Chandran, 1993) and its 3D subject-specific reconstruction is currently a standard procedure as will be explained in the following section. For what attains the boundary conditions, as shown in Figure 2.10, the boundary of the domain of interest is split into (i) the aortic wall, i.e., the physical boundary of the aorta; (ii) the inlet boundary corresponding to the Ascending Aorta (AA); (iii) the outlet boundaries corresponding to the major branching (supraortic) vessels, Brachiocephalic Trunk (BCT), Left Common Carotid Artery (LCCA), Left Subclavian Artery (LSA) and, finally, the main outlet represented by the Descending Aorta (DA). Collateral vessels of the descending thoracic tract are often dropped (i.e., vertebral arteries) as their reconstruction from images is generally quite troublesome.

On the aortic wall, boundary conditions stem from the selected physical model. In Fluid Structure Interaction (FSI) models, the arterial wall displacement is part of the problem and these conditions depend on the structural model and the inclusion of external surrounding
2.2. Computational Fluid Dynamics on cardiovascular diseases

Figure 2.10: Sketch of the CFD computational domain: inlet and outlet boundaries are highlighted.

In the case of rigid vessels, these conditions simply resort to enforcing null velocity. For the sake of notation, we split the boundary of $\Omega$ in three subregions (see also sketch in Figure 2.10).

1. **Wall** $\Gamma_w$: representing the physical wall of the artery.

2. **Inlet** $\Gamma_{\text{in}}$: representing the main inflow section of the domain, i.e., the ascending aorta entrance, approximately in correspondence of the sinotubular junction, as reconstructed in the geometrical model.

3. **Outlet** $\Gamma_{\text{out}}$: representing the set of (not connected) outlet sections consisting of the BCT, the LCCA, the LSA and the DA. The supraaortic vessels BCT, LCCA and LSA will be treated at the same way, so for easiness of notation they will be collectively denoted by $\Gamma_{\text{sup}}$, and we indicate DA outlet with $\Gamma_{DA}$, so that $\Gamma_{\text{out}} = \Gamma_{BCT} \cup \Gamma_{LCCA} \cup \Gamma_{LSA} \cup \Gamma_{DA} = \Gamma_{\text{sup}} \cup \Gamma_{DA}$.

On $\Gamma_w$ we prescribe the no slip conditions

$$u(\Gamma_w, t) \equiv 0. \quad (2.2)$$
Meshing

Meshing is one of the key steps of performing a successful simulation and a correct trade-off between many aspects is necessary. First, naturally, the computational domain should resemble the original geometry from the body. This is the first step we will describe, which is called *image segmentation*. Then, the discretization should be fine enough to capture local flow phenomena with a decent resolution without exaggerating since we will pay with computational time. Since each node of the mesh, namely degree of freedom, represents an unknown to be found by the finite element method, finer meshes will need more computational time for calculation.

Creation of a mesh starts with the *image segmentation*. This step aims at isolating the region of a CT limited by the aortic wall in order to identify its inner volume. We use the Levelset Segmentation algorithm from the Vascular Modeling Toolkit library (VMTK, http://www.vmtk.org/, Antiga et al., 2008). In short, the level set method can be thought as a mathematical function that deforms a 2D circle based on "forces" that push every point on the circumference inwards or outwards. These forces are driven by local parameters of the region of interest such as the curvature of the grayscale gradient. Hence, an initial 3D region serves as initialization for the levelset and is then iteratively expanded or collapsed until finding the edges of the aorta. The initialization pattern for an aorta is shown in Figure 2.11.

VMTK allows several initialization methods, one of them being *colliding fronts*. As its name indicates, two seeds are placed at the boundaries of the region and both a lower and upper intensity threshold are selected. While running, the volume matching the intensity criteria between the seeds is included. Initialization is performed by parts of the aorta which are then merged. The output of the levelset procedure is a 3D image resembling the initial CT scan, with values between -X and X based on the distance to the target surface, which has the value 0. Figure 2.12 shows an axial slice of a levelset image of an aorta. In our cases, the following parameters are used for the levelset: 100 iterations, propagation scaling = 0.3, curvature scaling = 1.0, and advection scaling = 1.0.

Once the segmentation is obtained, it is converted into a 3D surface with the marching cubes algorithm (Lorensen and Cline, 1987). As an output, we have a triangulated surface representation of the vessel. Frequently, a Taubin surface smoothing (Taubin, 1995) with 20 iterations and passband = 0.01 is applied to improve the quality of the reconstruction.

It is important to know that surface meshes created with VMTK are not always conforming. A conforming surface mesh is that in which the sides of each triangle are coincident only with the sides of the surrounding triangles and never with either a vertex or the middle surface of an element. Furthermore, a mesh cannot have holes unless they will later constitute a certain inflow/outflow boundary of the simulation. As an example, Figure 2.13
shows a zone in the reconstruction of a vessel where holes and nonconformities are present. In case the mesh has to be manually corrected, the nonconforming portion of the surface is removed and refilled with the software MeshLab (Cignoni et al., 2008).

With the 3D surface representation ready, the next step consists on clipping the vessel where the computational boundaries will be present. Caps are interactively removed and flow extensions are plugged at the input/output vessels. The role of flow extensions is different in the inflow boundaries than in the outflow boundaries and has been extensively discussed in literature (Gallo et al., 2012; Ralovich et al., 2012). In the first case, the role is to let the flow develop before entering the region of interest and avoid that the choice of the input profile affects the velocity field proximally. More advanced boundary conditions including pointwise 3D velocity vectors ensure a realistic choice of inflow pattern, even tough they are subjected to other complications. In the second case, many authors choose not to extend the boundaries, however they help managing backflow stabilizations (Bertoglio et al., 2017).

The following step consists on the real volume meshing of the domain based on TetGen.
by VMTK (Si, 2015). The software creates tetrahedra in the volume confined by the surface taking as a refinement reference the side length of the surface triangles in a process called Delaunay tetrahedralization. It is of utmost importance to choose the correct element size which can differ in various parts of the mesh. The mesh should be fine enough to resolve the spatial distribution of the Navier-Stokes velocity field. Higher velocities would then need finer meshes since flow is less organized and velocity field has a higher local variability. In the ascending aorta, Reynolds number can climb up to 6000 and very fine meshes have to be produced.

However, finer meshes represent a higher computational cost. In order to avoid an excessive refinement and have stable simulations, different strategies are used to "laminarize" the flow within the domain. One of them is the inclusion of streamline diffusion which consists on adding artificial viscosity and thus lowering the Reynolds number. Another way
2.2. Computational Fluid Dynamics on cardiovascular diseases

Figure 2.13: Non-conforming surface mesh. Yellow arrow indicates non-conforming triangles. Orange arrow shows a hole in the mesh.

to tackle the problem is to use a local refinement. When performing the Delaunay triangulation of the surfaces, regions with higher Reynolds number are given a smaller triangle size. The criteria is based both in the local velocity field and the hydraulic radius of the section, the two major component of Reynolds number. Figure 2.14 shows a typical case of refinement in a peripheral branch, where the vessel tapers significantly.

Boundary conditions

Opposedly to intuition, boundary conditions are as important for the set-up of the simulations as the geometry itself. In this section we will only identify the corresponding sections, describe the mathematical background and discuss the requirements in a patient-specific environment. Details on the selection and tuning are exposed in the next chapter.

Inflow conditions  In the inflow boundary, in our case the AA, either velocity or pressure has to be imposed in each node. A patient-specific approach requires that, whatever the choice is, the corresponding wave has to be retrieved from a dedicated measurement. Studies are available for both quantities, however pressure measurements are only made invasively whereas velocity (or flow) in a certain section of the aorta can be extracted by imaging techniques. For example, PC-MRI produces as output the flow rate and velocity along the cardiac cycle in the sections of interest (more details of the acquisition will be discussed in Chapter 4). In Figure 2.15 an example of PC-MRI is shown. For these peculiar MRI sequences, the grey-scale of the picture is used to extract blood velocities pixelwise. In particular, each pixel records a specific (upward or downward) velocity. An in-house code
has been written to extract the aortic cross-section from PC-MRI images, store pixel velocities and compute the averaged one (in space) to obtain the profile depicted also in Figure 2.15.

The flow is imposed at the inlet with the flat profile assumption instead of using the complete velocity data measured in each pixel, available from PC-MRI, for different reasons. Noisy PC-MRI data need to be interpolated both spatially and temporally in order to retrieve the corresponding velocity vector at each node of the mesh. This is not always a straightforward step, which may introduce fluctuations based on the model used for the interpolation. Moreover, a mapping procedure would be necessary to adapt the PC-MRI velocity data, recorded at a compliant aortic cross-section, to a rigid, non-deforming one; which represents an additional source of approximation.

From the mathematical point of view, the prescription of an arbitrary velocity profile - that may affect significantly the results in the neighbourhood of the boundary - can be avoided by also other approaches. In particular, in Formaggia et al., (2002), the flow rate
conditions are regarded as a constraint for the solution to be enforced by a Lagrange multiplier approach. The arbitrariness of the assumption necessary to fill the gap between the available data and the required mathematical conditions turns out to be on the profile of the normal stress at the boundary, that is supposed to have less impact on the final results as confirmed by numerical evidence. In Formaggia, Veneziani, and Vergara, (2008) and Formaggia, Veneziani, and Vergara, (2010), the difference between data and the computed flow rate is minimized in a variational constrained minimization approach, by acting on appropriate control variables. The choice of those variables drives the way the gap between data and conditions is filled. Even though these techniques are more accurate and in principle do not need the aforementioned flow extensions, they suffer from some numerical drawback, mostly the additional computational costs intrinsic to the nature of the two methods. For this reason these techniques are not routinely used in computational hemodynamics for patient-specific simulations.

**Outflow conditions** Flow rates and velocities as extracted from PC-MRI are actually available over \( \Gamma_{out} \) too. In principle, we could prescribe them as we do for the inflow. However, this is prevented by a significant inconsistency between the data and the assumption of rigid walls. In fact, since the aorta is not actually rigid, the instantaneous balance of the measured flow rates does not sum up to 0, as required by the fluid incompressibility constraint and the rigid-wall assumption.

The rationale of the approach that will be described in the next chapter is that the impact of arbitrary modelling assumption at the boundary, in presence of defective conditions on the velocity, is mitigated if these assumptions refer to the pressure rather than to the velocity field. In our data set, we can collect flow rate data and we do not have pressure measures...
within our domain of interest. To overcome this problem, we "convert" available data on
the flow rate to pressure condition through the well known concept of impedance. As a
matter of fact, impedance is the transfer function of flow into pressure in the Fourier domain
or frequencies. The arbitrary yet reliable assumption for ultimately filling the gap with
pressure conditions is that pressure is constant along each surface of $\Gamma_{out}$ and related to
flow rate through a 3-Element Windkessel impedance.

2.2.2 Quantities of interest

Velocity and pressure

The immediate output of any CFD solver after each time iteration consists on the unknowns
of the NSE which are the velocity and pressure values in each node of the mesh. This
information is stored in text files which can be in Ensit or VTK format, for which Paraview
(Ahrens, Geveci, and Law, 2005) is used as visualizer.

Based on the characteristic of flow that wants to be highlighted, we can produce:

- Slices of the pressure or velocity field
- Volume render of the velocity magnitude
- Streamlines: curves tangent to the velocity vector of flow
- Glyphs: 3D vectorial representation of the pointwise velocity

Figure 2.16 summarizes all these possibilities.

Wall Shear Stress and Oscillatory Shear Index

The shear induced by blood in the wall of the vessel is known to be responsible for the
initiation of atherosclerosis (Ku et al., 1985). Both its magnitude and its oscillatory nature
account for endothelial damage. We then calculate the WSS as:

$$\tau = \sigma \cdot n - (n \cdot \sigma \cdot n) \cdot n, \quad \sigma \equiv \mu \left(\nabla u + \nabla u^T\right)$$

(2.3)

where $\sigma$ is the stress tensor, $u$ is the velocity field and $n$ the normal to the surface el-
ement. Naturally, WSS varies along the cardiac cycle and we then define its time average
as:

$$TAWSS = \frac{1}{T} \int_0^T |\tau| dt$$

(2.4)
where $T$ is the duration of the cardiac cycle. In general, values below 0.4Pa are atherogenic whereas TAWSS above 1.5Pa are atheroprotective as will be discussed in the next chapter (Malek, Alper, and Izumo, 1999).

Another associated indicator is OSI, which quantifies the oscillatory nature of the flow along the cycle:

$$OSI = 0.5 \left[ 1 - \left( \frac{\int_0^T \tau dt}{\int_0^T |\tau| dt} \right) \right]$$

### 2.2.3 LifeV library and parallelization

The NSE as presented earlier are solved by the LifeV finite element library (www.lifev.org). LifeV is an open source library of algorithms and data structures for the numerical solution of partial differential equations with high performance computing (HPC) technologies. High performance computing is supported by LifeV through the interplay with third-party software, in particular the linear algebra package Trilinos (Heroux et al., 2005). LifeV is maintained and developed by an international network of universities and research centres across Europe and the US, whose core members are the Politecnico di Milano (Italy),
the École Polytechnique Fédérale de Lausanne (Switzerland) and Emory University (USA). Other institutions contribute to the project, including INRIA (France), Florida State University (USA), Georgia Institute of Technology (USA) and the University of Houston (USA).

Numerically, NSE are discretized in time using a second-order Backward Differentiation Formula (BDF2) (Quarteroni, Sacco, and Saleri, 2010) and in space using inf-sup stable elements such as P1Bubble-P1 or P2-P1 for the velocity and pressure fields, respectively. For each of the terms of the discrete equation, there is an associated matrix which finally yields a system of the form (all details are specified in Passerini et al., 2013):

\[ A x^{n+1} = b^{n+1} \]  

(2.6)

where \( A \) is a matrix assembled with the different NSE terms, \( x^{n+1} \) is a column vector composed by \( u(x, n+1) \) and \( p(x, n+1) \) at the following iteration and \( b^{n+1} \) is an array accounting for the initial and boundary conditions. The system is first left-preconditioned and then solved with the GMRES iterative method (Saad and Schultz, 1986).

Therefore, there are three main steps to tackle with the software at each temporal iteration: the assembly of the matrix \( A \), its preconditioning and the linear solver. Mesh is first partitioned among the cores of the computer with ParMETIS (Karypis and Kumar, 1998), which is an open source library for domain decomposition. The mesh, or more precisely the finite element domain, is partitioned into \( N \) sub-domains corresponding to the available processors. For the parallelization, all the libraries rely on Message Passing Interface (MPI) so any implementation of it can be chosen based on user’s choice and type of network.

To compile the NS application used for blood flow, the following libraries are required:

- C++ Compiler such as GCC, Intel, etc
- MPI implementation such as OpenMPI, MVAPICH2, IntelMPI, MPICH, etc
- Boost
- METIS and ParMETIS
- SuiteSparse
- ANN (only for Emory branch)
- Trilinos
- LifeV core library
- Application Blood Flow
We have tested lifeV in our local cluster with 4 nodes of 64 cores each and in three different supercomputing architectures such as Comet\(^1\), Stampede\(^2\) and Marconi\(^3\) running in up to 2304 cores. As an example, Figure 2.17 shows the output time log of the first 10 iterations of an analysis on a 10 million node mesh distributed in 1152 processors.

![Figure 2.17: Duration of each timestep in a 1152 core simulation in Marconi HPC system.](image)

From the execution point of view we need:

- ApplicationBloodFlow.exe which is the linked executable file containing the lifeV together with the NS implementation.
- Mesh file
- data file containing the path to the mesh file, time and space discretization parameters and the choice of boundary conditions
- flow or pressure files describing inflow/outflow waves if needed as boundary conditions
- solvers options file with the tuning of Trilinos routines

Finally, the application will produce as an output two files containing the velocity and pressure fields at each timestep. WSS, TAWSS and OSI are calculated a posteriori with an ad-hoc application based on LifeV.

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\(^1\)https://portal.xsede.org/sdsc-comet/
\(^2\)https://portal.xsede.org/tacc-stampede/
\(^3\)https://www.cineca.it/it/content/marconi/
Chapter 3

Boundary conditions for reliable simulations of aortic blood flow

This chapter proposes a technique to tune the 3-element Windkessel parameters to carry out a sufficiently accurate patient-specific simulation with a reasonable computational cost and without requiring extra medical effort for data collection. First, literature on boundary conditions will be reviewed and then our approach will be exposed followed by three concrete examples in patients from our database.

3.1 Literature review

On the artificial (i.e., non-physical) inlet and outlets detailed in section 2.2.1, modelling assumptions are required, possibly based on patient-specific data where authors describe different choices.

The do-nothing approach

The early contribution of Wood et al., (2001) and more recent studies such as Shang et al., (2015) used either literature or patient-specific MRI velocity data at the inflow applied to the boundary by piecewise linear interpolation and constant pressure at the outflows. This choice was based mostly in the lack of information about the outflow velocities and distal vasculature. The main drawback of this approach is that the assumption of constant pressure in the outlets is not fully justified by evidence. It has a major impact on the flow distribution and turned out to be quite unreliable, mostly due to the sensitivity of the method to changes in the geometry (Rannacher, 1996).
Enforcing more Dirichlet boundaries

Other authors choose enforcing velocity (or flow as a velocity profile) boundary conditions in more vessels than only the inlet.

One case is the approach by Tse et al., (2011) who obtain non-patient specific flow and pressure waveforms from the literature and impose them in the inflow. In the case of the outflow boundaries, they specify a fixed flow split. This choice of BC is realistic but not patient-specific. In diseased patients, flow split can considerably be affected compared to healthy subjects. Backflows or reflections inside the domain are also mitigated by the fact that instant outflow velocities are only a scaled version of the ascending aortic flow.

Another strategy, implemented by Gallo et al., (2012), is to directly impose the velocity profiles derived from accurate PC-MRI at the inflow and in all the outflows but one, where a stress-free condition is specified. This approach is strictly sticking to the patient-specific data, yielding excellent results. However, no filtering of the noise is enforced and care must be taken for the possible inconsistencies between the measured data and the rigidity assumption of the mathematical model. Further weaknesses of this strategy have been described by Brown et al., (2012) where the alignment of the waveforms in a rigid wall model constitutes the main flaw. Other drawbacks are the overall computational cost of the data extraction and elaboration which may be not worth, depending on the final scope of the numerical simulation.

Multiscale modelling: 3D-0D coupling

At a conceptual level, other than using Dirichlet boundaries, an alternative is to resort to pressure boundary conditions, or more precisely to traction/Neumann conditions. The numerical advantage is that the solution (in particular for the velocity field) is less sensitive to these natural (or Neumann) conditions, so results are more robust with respect to the errors in the data prescribed and the associated arbitrary modelling assumptions. However, from the numerical standpoints, these conditions lead to less stable problems to solve suffering from the so called backflow instabilities (Moghadam et al., 2011). Even more importantly, in the aorta, acquisition of the pressure wave is only performed invasively.

A classical way for imposing this kind of BC is the geometrical multiscale approach (see Peiró and Veneziani, (2009), Formaggia, Quarteroni, and Veneziani, (2009), and Quarteroni, Veneziani, and Vergara, (2016)). This is the set of methodologies designed for incorporating in a 3D simulation the local impact of the vascular network connected to a district of interest. In particular, the definition of a relation between the pressure to prescribe and the available flow data can rely on the introduction of a lumped parameter model (or 0D model) describing peripheral districts.
3.2 Lumped parameter models

3.2.1 Two element Windkessel model

Frank, (1899) presented a model consisting on two parameters which constituted an electrical analogue to the systemic circulation. These two elements were the total peripheral resistance, $R_2$, and the total arterial compliance, $C$ (see Figure 3.1). His initial goal was to find the cardiac output. Following Poiseuille’s law, $R_2$ was calculated as the mean pressure over mean flow and $C$ was retrieved from the characteristic decay time of the pressure wave. During the following years, authors proposed different methods for calculating $C$ with various pros and cons (Westerhof, Lankhaar, and Westerhof, 2009). One of the simplest yet most reliable approaches was the pulse pressure method defined by Stergiopulos, Meister, and Westerhof, (1994) and Stergiopulos, Segers, and Westerhof, (1999). In short, $R_2$ is calculated as the ratio between mean pressure and mean flow in a given vessel and $C$ is found iteratively by comparing a target pulse pressure with an estimated pulse pressure retrieved by feeding the flow wave in a 2WK circuit.

![Figure 3.1: 2-Element Windkessel circuit. P: peripheral pressure, Q: peripheral flow.](image)

3.2.2 Three element Windkessel model

As more reliable flow and pressure measurements became available, the research community noticed that the shape of the pulse wave was poorly predicted by the 2WK, mostly due to the filtering of high order modes. A frequency analysis of aortic input impedance (Westerhof, Stergiopulos, and Noble, 2010) showed that its modulus was different from zero and
its phase different from $-\frac{\pi}{2}$ at high frequencies. Thus a characteristic impedance or proximal resistance, $R_1$, was added in series to the initial two components. Even though this new component is associated with the oscillatory phenomena of wave propagation, it has the same units as a resistance and, in the circuit, it is considered as a resistor. Now, in low frequency, the ratio of mean pressure to mean flow would no longer be equal to $R_2$ but to $R_1 + R_2$. Figure 3.2 shows the 3-element Windkessel model (3WK) with the components of the circuit.

![3-Element Windkessel circuit](image)

**Figure 3.2:** 3-Element Windkessel circuit. Pressure $P$ can be seen as the fluid analogue of the voltage whereas $Q$ as the analogue to the electrical current.

**Frequency analysis**

The impedance of the lumped parameter model reads as follows, where $\omega$ is the frequency of the Fourier domain and $j = \sqrt{-1}$,

$$Z(\omega) = \frac{R_1 + R_2 + \omega^2 C^2 R_2^2 R_1}{1 + \omega^2 C^2 R_2^2} - j \frac{\omega CR_2^2}{1 + \omega^2 C^2 R_2^2}$$

(3.1)

As an example, Figure 3.3 reports the absolute value and the phase of $Z(\omega)$ in a human artery.

**Implementation as pressure boundary condition**

In mathematical terms, this model reads as follows. Let $Q(t)$ be the available flow rate in any of the sections of $\Gamma_{out}$ and $P(t)$ the pressure, which is supposed to be space independent
Figure 3.3: Impedance of the 3-Element Windkessel Model in the Fourier domain for a supraortic vessel. Top: modulus; bottom: phase.
over the same section. The 3WK prescribes the differential-algebraic system

\[ P(t) = R_1 Q(t) + P_p(t) \]
\[ C \frac{dP_p}{dt} + \frac{P_p(t)}{R_2} = Q(t) \]

where \( R_1, R_2 \) and \( C \) are the lumped parameters of the model and \( P_p(t) \) represents the peripheral pressure. We apply the method of integrating factors to the second equation, to obtain

\[ P_p(t) = P_p(0) e^{-t/(CR_2)} + \frac{e^{-t/(CR_2)}}{C} \int_0^t Q(\tau) e^{\tau/(CR_2)} d\tau \]

Finally we have the relation converting flow rates into pressure,

\[ P(t) = R_1 Q(t) + P_p(0) e^{-t/(CR_2)} + \frac{e^{-t/(CR_2)}}{C} \int_0^t Q(\tau) e^{\tau/(CR_2)} d\tau \]

In practice, numerical approximation is used in a time advancing setting. For instance, solving the integral by the trapezoidal rule on the instants \( t^n \) and \( t^{n+1} \) (with \( \Delta t = t^{n+1} - t^n \)) for \( n \) integer generic index, we have

\[ p(t^{n+1}) = R_1 Q(t^{n+1}) + P_p(t^n) e^{-\Delta t/(CR_2)} + \frac{e^{-\Delta t/(CR_2)}}{C} \frac{\Delta t}{2} \left( Q(t^{n+1}) e^{\Delta t/(CR_2)} + Q(t^n) e^{-\Delta t/(CR_2)} \right) \]

Eventually, the 3WK conditions are prescribed as traction or normal stress conditions and read

\[ p \mathbf{n} - \mu \nabla \cdot (\nabla \mathbf{u} + \nabla \mathbf{u}^T) = P(t) \mathbf{n} = \left( R_1 Q(t) + P_p(0) e^{-t/(CR_2)} + \frac{e^{-t/(CR_2)}}{C} \int_0^t Q(\tau) e^{\tau/(CR_2)} d\tau \right) \mathbf{n}. \]

Notice that the initial peripheral pressure can be set arbitrarily (as for the other initial conditions) as it is eventually adjusted periodically by the solver over the heart beats.

In aortic districts, the coupling of 3D with 0D models (Windkessel in particular) has been used in several papers. A critical step in this approach is the parameter tuning and it is not straightforward to find a clear procedure for parameter estimates. Strictly speaking, this step attains to the general field of data assimilation (Bertagna et al., 2014; Bertoglio, Moireau, and Gerbeau, 2012; Schiavazzi and Marsden, 2015). Parameters are obtained as the result of the minimization of a mismatch between the computed solution and measures. The minimization is generally obtained as an iterative process. This step may be computationally
demanding and surrogate models are somehow critical to customize the estimates for the patient with an acceptable computational cost.

Some examples are Kim et al., (2009) and Brown et al., (2012) who use 3WK in the outlet vessels but lack extensive details on how the parameters were calibrated. Les et al., (2010) proposed an approach for parameter tuning which makes an assumption on the proximal resistance $R_1$ that does not hold true in a general cohort of patients. Itu et al., (2015) also proposes a minimization approach, but the mathematical implementation is not trivial. Alimohammadi et al., (2014a) uses another minimization approach based on matching the maximum and minimum pressure from a CFD simulation in each vessel with an invasive pressure acquisition. Even though their results are meant to be the most accurate, the parameter update takes place at each CFD iteration thus making the computational cost prohibitive in some cases. Furthermore, calibration is performed using a pressure wave measured invasively, which is not in every case available.

A simple and patient specific yet accurate and robust methodology of parameter tuning in which incomplete patient data can be used is up to now missing.

Important considerations

There are two main drawbacks of incorporating a third component: firstly, its addition overestimates the circuit impedance in low frequencies and, secondly, there is a new parameter to estimate. To solve the first complication, a fourth inductive element was proposed to be added in series with $R_1$ in order to mitigate its influence in low frequencies. We will not discuss the so-called four element Windkessel in this article. Regarding the estimation of $R_1$, Westerhof, Lankhaar, and Westerhof, (2009) proposed using the vessel pulse wave velocity, $PWV$, yielding

$$R_1 = \frac{PWV \rho}{A}.$$  

(3.8)

where $A$ is the vessel cross-sectional area. Other studies such as Les et al., 2010; Westerhof and Elzinga, 1991 suggest that $R_1$ can be calculated as a fixed fraction of $R_2$.

Calculation of $C$ also changes from the 2WK to the 3WK and many of the methods are revisited in Westerhof, Lankhaar, and Westerhof, 2009; Stergiopulos, Meister, and Westerhof, 1995. Interestingly, Stergiopulos, Westerhof, and Westerhof, (1999) explain that, regardless of the calculation method, values of $R_1$, $R_2$ and $C$ are different between 2WK and 3WK. This was justified earlier in Stergiopulos, Meister, and Westerhof, 1995 where the right set of parameters, being those with a physiological meaning, are not accurate to represent the peripheral vasculature. Another set of numerically accurate parameters do better represent
the arterial tree even though they do not have a physiological significance. As an example, \( C \) calculated with the pulse pressure method was validated towards \( \Delta V/\Delta P \) while \( C \) calculated with the 3WK has a much higher value. To our understanding, some of this concerns were overlooked by the engineering community when 3WK were used, for example, as boundary conditions in CFD. Methods for 2WK were often mixed with methods for 3WK (see i.e. Les et al., (2010)).

Which is then the way of tuning \( R_1, R_2 \) and \( C \) which accurately describes the relationship between flow and pressure? How can it be applied to a patient-specific environment where often data is not available? A measured flow fed into a 3WK with the numerically correct parameters should retrieve a pressure wave as similar as possible to the measured one. Therefore, calibration is based on minimizing the error between a target pressure wave, \( P_t \), and an estimated pressure wave, \( P_e \). The idea was first presented by Toorop, Westerhof, and Elzinga, 1987 where the three circuit parameters are tuned until the error between \( P_t \) and \( P_e \) is minimized in a least-square sense. Back then, computational tools were not available and even though this method has been further revisited, it has not been extensively explained to the best of our knowledge. Again, other authors (Stergiopulos, Meister, and Westerhof, 1995) find \( C \) by mixing this minimization procedure with a priori assumptions on \( R_1 \) and \( R_2 \).

### 3.3 Proposed tuning using non-invasive measurements

#### 3.3.1 The minimization approach

**Discrete domain frequency equations**

We can redefine the transfer function of the 3WK circuit from equation 3.1 in the Laplace domain as

\[
H(s) = \frac{R_1 + R_2 + sR_1R_2C}{1 + sR_2C}
\]  

(3.9)

which is the impedance of the circuit

\[
Z(s) = H(s) = \frac{P(s)}{Q(s)}
\]  

(3.10)

where \( P(s) \) and \( Q(s) \) are the Laplace transform of pressure \( P(t) \) and flow \( Q(t) \) waves respectively.

For each signal, we define the sampling frequency \( f_s \) and sampling time \( T_s \) as

\[
f_s = 1/T_s = N/t_b
\]  

(3.11)
where $N$ is the number of samples in the discretization of the data and $t_b$ is the duration of the beat. In order to proceed in a discrete environment, we will use the bilinear transform replacing

$$s = \frac{2}{T_s} \frac{z - 1}{z + 1}$$

into Equation 3.9 giving as a result an equivalent transfer function of the discrete filter in the $z$-transform domain:

$$H(z) = \frac{(R_1 + R_2 + \frac{2}{T_s} R_1 R_2 C) + (R_1 + R_2 - \frac{2}{T_s} R_1 R_2 C) z^{-1}}{(1 + \frac{2}{T_s} R_2 C) + (1 - \frac{2}{T_s} R_2 C) z^{-1}}$$  

Using Python we retrieve the discrete filter coefficient by computing the bilinear transform, which uses as input values the coefficients of the numerator and denominator of Equation 3.9. Then the filter finds $P$ based on these coefficients and $Q(t)$.

We can then consider the filter as a black box with input parameters $Q(t), R_1, R_2, C$ and $t_b$ giving back $P_e(t)$. To facilitate reading from this point, we define a function that will be called $WK3$ describing this filter

$$P_e(t) = WK3(R_1, R_2, C, Q(t), t_b)$$  

Non-linear least squares

The selected method based on Toorop, Westerhof, and Elzinga, (1987) aims at finding the value of $n$ parameters belonging to a non-linear model that would fit a set of $m$ observations with $m > n$. In our particular case, the $n$ parameters are $R_1, R_2$ and $C$, the non-linear model is Equation 3.14 and $m$ are number of values of our target pressure wave $P_t(t)$ along the cardiac cycle.

The model will minimize the sum of squares

$$S = \sum_{i=1}^{m} r_i^2$$  

where

$$r_i = P_t^i - WK3^i(R_1, R_2, C)$$

The function $S$ has a minimum where its gradient is zero. Therefore we need to solve the global minimization problem by using the Trust Region Reflective algorithm (Branch, Coleman, and Li, 1999). Although this method requires an initial seed for each estimated
parameter, we tested different values which demonstrated not to be sensitive to the initial guess.

### 3.3.2 Validation

It is important to know which is the best estimation this method can give in the case both \( Q(t) \) and \( P(t) \) are accurately known in a certain vessel. Therefore, we validated our method against invasively measured flow and pressure waveforms from Stergiopulos, Westerhof, and Westerhof, (1999) and calculated the L2-norm error for pressure estimation as

\[
\| e \|_{L^2} = \sqrt{\frac{\sum_i \| P_i^e - P_i^t \|^2}{\sum_i \| P_i^t \|^2}}
\]

where \( i \) stands for the discrete index of each sample in the signal, which yielded errors of 3.1% and 2.4% for the type A (adult or aged pressure waveform) and type C (child or young pressure waveform) respectively. Figure 3.4 illustrates the measured as approximated pressures with our computational implementation.

### 3.3.3 Using defective data

In our clinical case, \( Q(t) \) is extracted from PC-MRI but there is no information about the pressure other than the cuff measurement provided by the physician. Based on the requirements of the model, we will use a generic aortic pressure waveform \( P_t(t) \) from Stergiopulos, Westerhof, and Westerhof, (1999).

Brachial mean pressure and pulse pressure are calculated from cuff systolic \( P_s \) and diastolic \( P_d \) measurements as:

\[
P_{\text{mean}} = \frac{1}{3} P_s + \frac{2}{3} P_d,
\]

(3.18)

and

\[
PP_b = P_s - P_d,
\]

(3.19)

respectively.

Even though mean pressure remains equal along the arterial tree, pulse pressure suffers amplification from the heart to the arms. Nichols, O’Rourke, and Vlachopoulos, 2011 defined the augmentation index and in order to calculate the central pulse pressure, we define:

\[
PP_c = PP_b / (−0.012a + 1.97)
\]

(3.20)
3.3. Proposed tuning using non-invasive measurements

where \( a \) is the patient’s age.

In order to have a more patient-specific representation of the pressure wave, we scale

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3_4}
\caption{Predictions with a 3WK in a type A (top) and type C (bottom) invasively measured aortic pressure waves from Stergiopulos, Westerhof, and Westerhof, (1999).}
\end{figure}
\( P_t(t) \) to match both \( P_{\text{mean}} \) and \( PP_c \). A rescaling of the pressure wave in one of our patients is shown in Figure 3.5.

![Figure 3.5: Original (blue) and scaled (green) pressure wave as adapted for one of the individuals in our study.](image)

### 3.3.4 Impact of assumptions in the minimization

We will test the following assumptions as have been used previously in literature for CFD in three patients from our database:

- **As 1**: \( R_1 \) is calculated from Equation 3.8 and \( R_2 = \frac{P_{\text{mean}}}{Q_{\text{mean}}} - R_1 \) (Westerhof, Lankhaar, and Westerhof, 2009). Only \( C \) is found by minimization.

- **As 2**: \( R_1 \) is empirically calculated as the average of the 3rd to 10th harmonics of \( H(s) \) and \( R_2 = \frac{P_{\text{mean}}}{Q_{\text{mean}}} - R_1 \) (Stergiopulos, Westerhof, and Westerhof, 1999). Only \( C \) is found by minimization.

- **As 3**: All \( R_1, R_2 \) and \( C \) are calculated by minimization.

Table 3.1 shows the parameter models calculated in each of the output vessels in our three patients where assumptions proposed earlier in literature have been made for finding \( R_1 \) and \( R_2 \). Relative error from \( P_e \) to \( P_t \) are calculated with Equation 3.17.
### 3.4 Boundary condition strategies impact on CFD computations within a cohort of patients

Three patients from our iCardioCloud database (see Chapter 4) with thoracic aortic aneurysms have been chosen to test the various parameter tuning approaches.

For the BC, we move from the poorest case of having only the patient-specific vessel geometry available (i.e., CT scan data) to the richest case of having both CT and PC-MRI images at different aortic cross-sections available. In the first case, the simplest modelling choice is to take inflow/outflow parameters from the literature; in the second case, to impose the measured inlet and properly calibrate 3WK elements at all the outlets as mentioned in the previous section.

To summarize, we consider and compare different combinations of boundary conditions as follows:

- **BC1**: literature inflow profile taken from Morbiducci et al., (2009) and literature outflow 3WK BC taken from Kim et al., (2009);
- **BC2**: patient specific inflow extracted from patient’s PC-MRI and literature outflow 3WK BC taken again from Kim et al., (2009);
- **BC3**: patient specific flow as extracted from PC-MRI directly imposed in the AA and 3WK calibrated with our strategy in the output vessels. In the DA, parameters were tuned enforcing mass conservation through subtraction of the supraortic flow to the AA flow;

<table>
<thead>
<tr>
<th>Table 3.1: 2WK and 3WK parameter values calculated under different assumptions usually found in literature. DA (S): flow wave for calibration corresponded to subtraction. DA (P): flow wave for calibration corresponded to PC-MRI slice.</th>
<th>2WK</th>
<th>3WK</th>
<th>4WK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td><strong>Patient 2</strong></td>
<td><strong>Patient 3</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BCT</strong></td>
<td>As 1</td>
<td>As 2</td>
<td>As 3</td>
</tr>
<tr>
<td>R1</td>
<td>0</td>
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<td>399</td>
</tr>
<tr>
<td>R2</td>
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<td>12753</td>
<td>13025</td>
</tr>
<tr>
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<td>1,36E-04</td>
<td>1,30E-04</td>
</tr>
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<td>E%</td>
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<td>6,65%</td>
<td>5,07%</td>
</tr>
<tr>
<td><strong>LCCA</strong></td>
<td>As 1</td>
<td>As 2</td>
<td>As 3</td>
</tr>
<tr>
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<td>2257</td>
</tr>
<tr>
<td>R2</td>
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<td>12753</td>
<td>13025</td>
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<td>5,54%</td>
</tr>
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<td>As 2</td>
<td>As 3</td>
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<td>8,30E-05</td>
</tr>
<tr>
<td>E%</td>
<td>8,60E-05</td>
<td>1,14E-04</td>
<td>1,21E-04</td>
</tr>
<tr>
<td><strong>DA (S)</strong></td>
<td>As 1</td>
<td>As 2</td>
<td>As 3</td>
</tr>
<tr>
<td>R1</td>
<td>0</td>
<td>752</td>
<td>664</td>
</tr>
<tr>
<td>R2</td>
<td>21948</td>
<td>21197</td>
<td>21284</td>
</tr>
<tr>
<td>C</td>
<td>6,72E-05</td>
<td>8,36E-05</td>
<td>8,30E-05</td>
</tr>
<tr>
<td>E%</td>
<td>8,60E-05</td>
<td>1,14E-04</td>
<td>1,21E-04</td>
</tr>
<tr>
<td><strong>DA (P)</strong></td>
<td>As 1</td>
<td>As 2</td>
<td>As 3</td>
</tr>
<tr>
<td>R1</td>
<td>0</td>
<td>752</td>
<td>664</td>
</tr>
<tr>
<td>R2</td>
<td>21948</td>
<td>21197</td>
<td>21284</td>
</tr>
<tr>
<td>C</td>
<td>6,72E-05</td>
<td>8,36E-05</td>
<td>8,30E-05</td>
</tr>
<tr>
<td>E%</td>
<td>8,60E-05</td>
<td>1,14E-04</td>
<td>1,21E-04</td>
</tr>
</tbody>
</table>
• **BC4**: patient specific flow as extracted from PC-MRI directly imposed in the AA and 3WK calibrated with our strategy in the output vessels. In the DA, parameters were tuned using flow directly from PC-MRI at its slice.

### 3.5 Results

#### 3.5.1 Flow and pressure profiles at the outlets

Figures 3.6, 3.7 and 3.8 show the flow and pressure waves calculated from the different types of BC in each vessel. PC-MRI data and the adjusted pressure wave used for calibration were included as reference.

![Graphs showing flow and pressure profiles](image)

**Figure 3.6**: Comparison of the flows and pressures among four different models of boundary conditions for each input and output vessel in Patient 1.

The relative error of the volume of blood through each vessel along one single cycle was calculated as:

\[
\Delta Q\% = \frac{\int_0^T Q(t)_{SIM} - \int_0^T Q(t)_{MRI}}{\int_0^T Q(t)_{MRI}}
\]

where \(Q(t)_{SIM}\) is the flow wave resulting from each simulation and \(Q(t)_{MRI}\) is the flow extracted from the MRI. These errors together with are reported in Figure 3.9.
3.5. Results

3.5.2 Velocity

Velocity contours are shown in Figure 3.10 at the systolic peak (17% of the cycle) and in Figure 3.11 at the early diastole (44% of the cycle) in all the four schemes for Patient 1. It is important to note that in BC1 and BC2 an acceleration is seen in the LCCA compared with BC3 and BC4. In BC1, the accelerations along the descending portion are not evident since a lower ascending flowrate is proposed as obtained from the literature.

3.5.3 WSS

Figures 3.12 depicts the averaged values of wall shear stress along a cardiac cycle calculated with all the BC schemes. The lower TAWSS values are found in the bottom part of the aneurysm sac in correspondence of lower speed due to recirculation, a fact that becomes more evident on BC0 and BC1 due to the adopted colorscale. The highest values are found on the constrictions and the places where the anatomic shape does not align with the direction of the flow. It is important to notice that significant numerical differences are seen at these critical points among the schemes such as the sac and the proximal and distal narrowings.
Chapter 3. Boundary conditions for reliable simulations of aortic blood flow

3.6 Discussion

In the last decades, CFD has been spreading in the medical research community, thanks to both hardware and software advances of computational technologies. Due to the ability of simulating blood flow, in fact, CFD is recognized as a potentially very powerful tool, even though the prediction of pathology evolution, as well as the exploration of possible future scenarios is still under investigation. Besides the geometrical description of the vessel of interest, it is well known that also boundary conditions strongly impact on the obtained solution. Accordingly we focus on the use of boundary conditions by proposing a simple procedure for tuning outflow parameters with non-invasive measurements and comparing the obtained results with different options found in the literature.

Many set-ups for boundary conditions can be found in literature with an underestimated impact on the simulation results. All of them are adapted to the author’s availability of data and numerical tools. Different limitations were found in all these scenarios. For example, imposing only the flow in the AA and a stress-free BC in the outflow vessels, the so-called do-nothing approach, has demonstrated high sensitivity to the geometry reconstruction and
Then, the most intuitive patient-specific approach represented by the direct prescription of flow data as Dirichlet boundary conditions in as many as possible inflow and outflow sections, also presented significant drawbacks. In particular, it is not correct to impose at the inlet and outlets the flow measured with ECG-gated PC-MRI without considering a temporal mismatch due to flow propagation from the inlet to the outlets. Moreover, supraortic vessels have a small radius compared to the voxel size of the PC-MRI scan and less reliable flow information is extracted from the scanner. It is though risky to impose as a Dirichlet BC data which are known to be noisy, especially in vessels characterized by reduced dimensions. Another issue of this method is that pressure can only be extracted as a relative value from the zero pressure boundary and needs thus to be rescaled to match the real patient’s values. This rescaling might be arbitrary. We can then confirm that particular attention
Chapter 3. Boundary conditions for reliable simulations of aortic blood flow

Figure 3.10: Volume rendering of the velocity in the systolic peak in the four BC schemes.

Figure 3.11: Volume rendering of the velocity in the early diastole in the four BC schemes.

should be paid when prescribing this type of BC assuming rigid walls.

Later in our analysis, we showed how a multiscale approach has also been used with accurate results by many authors. Using a 3WK in the outflow boundaries has demonstrated to reliably imitate downstream vasculature, therefore improving results within the 3D domain. Unfortunately, some of these methods rely either on invasive data, on strong (though not always proved) modelling assumptions and/or very complex adaptive numerical methods which increase notoriously the computational cost.
3.6. Discussion

Figure 3.12: TAWSS in the four tested BC schemes. Significant differences can be seen in the region of the aneurysm sac as well as in the DA.

Considering the wide variety of choices for parameter tuning, we came back to analyse the numerical meaning of these quantities and thus compared different approaches for estimating the 3WK elements based on their interpretation in literature. The debate between physiologically correct and numerically correct has been raised by calculating either $C$ or all $R_1$, $R_2$ and $C$ under different assumptions with the so-called minimization method which was originally proposed by Toorop, Westerhof, and Elzinga, (1987). We gave a deeper understanding of its origin and evolution than those found in literature and showed that in a cohort of three patients, when less constraints bound the parameters, which is the case of As 3, a better agreement is achieved between the estimated pressure wave and the target pressure wave. This demonstrates that the best parameter fit is achieved without taking into account the clinical meaning of each parameter, which was Frank’s initial goal when he proposed the Windkessel. Naturally, this result can be improved with better flow information, which in small vessels is not always reliable, or even with better pressure information. It is exactly due to this lack of “correct” data that we designed our strategy to weakly impose the BC in a Neumann scheme (in contrast with a Dirichlet scheme such as (Gallo et al., 2012).

In order to use the all parameter estimation approach, complete pressure data might be missing and thus we resorted to a pressure wave from literature that was later modified in a patient-specific fashion (see Figure 3.5). Here raises one of the core advantages of this parameter estimation method: assumptions can be made in whichever information is missing, such as the pressure wave, the flow wave or even the number of components in the
circuit. Results show that, as predicted by Stergiopulos, Westerhof, and Westerhof, (1999), $R_1$ is sistematically lower in As 2 compared to As 3. Also, $C$ is systematically higher in As 3 than in the estimation with 2WK (see Table 3.1).

With the parameter tuning strategy validated with invasive data from two patients, we moved to the actual application of the framework which are the CFD simulations. While calculations in the supraortic vessels were univocal, the descending aorta showed consistent mass loss in the MRI flow. In other words, stroke volume as calculated from the PC-MRI in the DA slice was significantly different than the subtraction yield by the AA and the three supraortic vessels. This mass loss effect can be caused by intercostal vessels that drain blood from the DA which are not captured by the CT. In order to account, and quantify, the impact of this phenomenon, the 3WK parameters in the descending aorta were calibrated both enforcing mass conservation (BC3) and by using data as extracted from MRI (BC4).

The following step was to compare the impact of different choices of 3WK in a CFD cohort of three patients with thoracic aortic disease. The first tested option, which we call BC1, reproduces a scenario in which only the geometry has been retrieved from patient specific imaging. Since there is no information on the flow, both the inflow waveform and the outflow 3WK values were taken from literature. As posted in the results section (and as conceivably expected) all the flow waves differ significantly when compared to patient’s PC-MRI. The pressure values, even though they are in a range which can be pathological, are too high. Flow splits in most of the vessels also underlay significant differences with PC-MRI. We can then say that, as expected, non patient-specific flow gives much less accurate results, and very careful conclusions should be drawn from the obtained results. It is important to note that this is the case that researchers face, for example, when they have to make CFD with retrospective data from patients who only have contrast enhanced CT.

We then considered the case of patient-specific flow in the ascending aorta while keeping the same literature boundary conditions as BC1 in the outflows. This option, named BC2, improved significantly pressure profiles along the aorta but still held high differences when comparing the flows with PC-MRI. In some vessels, the volume of blood in a whole cardiac cycle doubled. Regarding this scheme, we would like to point out the importance of the tuning of outflow boundary conditions. Many authors, as cited in the introduction, do not take this aspect into account when doing a patient-specific analysis, even though a correct inflow wave is used.

As seen in the results section, the choice of BC3 following our method yields the lowest difference in volume when comparing it with the PC-MRI flows. A more precise flow split can give us the hint that all the hemodynamic scenario is more accurate along the aorta. Error in the flow split is in some vessels below 1%. Furthermore, both mean and pulse pressure are respected from the calibration. Interestingly when not enforcing mass conservation for parameter estimation (BC4) comparable L2 errors in flow were found to
3.6. Discussion

BC3. Flow split differed significantly, mostly because of the impact of supraortic vessels in the average. Regarding the pressure, mixed results were found. In Patients 1 and 2, pressure wave difference between BC3 and BC4 was only a constant (different mean pressure) whereas its shape and pulse pressure remained equal. In Patient 3, not only did the mean pressure differed, but the wave was different. We suspect that these difference is due to the variety of mass loss percentage in our patients.

When analysing the velocity and TAWSS results of these patients, the various choices of BC showed significantly different haemodynamic patterns in the aneurysmatic sac, the previous and later narrowings (which are our zones of interest) and the descending aorta. An accurate choice of BC is therefore crucial to have meaningful results in these zones, as well as in the supraortic vessels. Though not shown, this trend has been confirmed when applying the proposed procedure also to the other two patients.

In our opinion, one of the most valuable aspects of the proposed framework is the trade-off between various aspects of computational simulations in a biomedical environment. First, all the input data used to calculate the lumped parameter model values are routine studies for diagnosing aortic disease. There is no need to add further examinations, such as invasive pressure measurements. Secondly, the computational cost of the 3WK parameter calculations is negligible compared to the time the CFD simulation takes as opposed to other techniques (Les et al., 2010). Other methods which are undoubtedly more precise (e.g., considering to apply Kalmann filters to estimate parameters from the measurements/observations such as Pant et al., (2014)) usually require online updates of the parameter values in order to make the solution converge making this simulation practically unsuitable for the daily clinical practise.
Chapter 4

Application to real cases

In this chapter we will discuss three projects developed during the PhD program in which CFD was used in a medical environment with different goals. The first one is iCardioCloud, which aims at prospectively collecting CT images and PC-MRI flow information of the thoracic aorta in order to create a database of CFD simulations. The second one is an analysis of the evolution of WSS in the entire aorta with ageing. The last one, consists in a set-up of a simulation framework both in vitro and in silico for quantifying embodeviation during aortic valve replacement in order to avoid stroke.

4.1 The iCardioCloud experience

4.1.1 Moving from proof-of-concept to clinical practise

The project iCardioCloud started from the following three main arguments:

- Cardiovascular disease (CVD) is a social and an economical emergency. Each year, CVD causes 3.9 million deaths in Europe costs 210 billion euro (Wilkins et al., 2017).

- An important contribution to the development of novel diagnostic/therapeutic tools and options is represented by in silico analysis, relying on computer-based simulations.

- Unfortunately, the implementation of in silico analysis into the clinical practice requires a significant integration of knowledge and an elevated high-tech know-how, which is already available in the Lombardy region but not yet fully addressed.

As illustrated by Figure 4.1, iCardioCloud project aims at creating a cloud platform in which doctors can interact with engineers in order to develop new tools for improving endovascular surgery. To achieve this, biomedical technologies associated with imaging and numerical simulations, have to be placed inside the medical decision process. Up to date,
studies in the field of computational hemodynamics (including all the methodologies addressed in the previous chapters) have been limited to only small cohorts or single centre studies. Therefore, by prospectively enrolling a high number of patients in multi centre studies, new treatment guidelines could be created by learning from data.

**Figure 4.1:** iCardioCloud philosophy. Interaction between doctors and engineers is based in a shared cloud technology for exchanging data.

The final goal is to build a CFD database of simulations in patients with thoracic aortic disease. The project moves from a strong collaboration between the University of Pavia and the medical research hospital IRCCS Policlinico San Donato of Milan with the participation of the Department of Mathematics and Computer Science of Emory University, USA.

### 4.1.2 The iCardioCloud Data Set

We focus on two main pathologies, TAA and TAD as explained in Chapter 2. When a patient is diagnosed with thoracic aortic disease, informed consent is first asked for enrolment in the study. Then, the following studies are performed:
• **Contrast Enhanced CT of the thorax:** this constitutes the most important imaging technique for diagnosis and is performed in a regular bases for patients with suspected aortic disease. At the IRCCS Policlinico San Donato, images are acquired with a Siemens SOMATOM Definition AS (Siemens Medical Solutions, Erlangen, Germany) scanner. The standard scans have the following characteristics: slice thickness = 1mm, pixel size = 0.8mm x 0.8mm, 160-650mA, 120kV. It is of utmost importance for our study to have a device with a high spatial resolution since it constitutes the foundations for a good 3D reconstruction of the vessel. In case patients undergo any kind of endovascular treatment, post-operative CT images are also acquired and uploaded to the platform. For those that are not operated, all the follow-up images are also stored.

• **Phase Contrast - Magnetic Resonance Imaging:** this study consists of a particular sequence available in the MRI scanner which retrieves the flow pattern and velocity within a user-defined slice crossing the domain. First, an initial scan is made in the thorax and then the operator selects the slices (i.e., cross-sections of the vessel) in which information about flow are to be extracted. In our case, these slices are the AA right after the annulus, the supraaortic branches and the DA at the height of the diaphragm. In particular, we use a Siemens MAGNETOM Aera (Siemens Medical Solutions, Erlangen, Germany) scanner. TR/TE:37.1/2.5ms, 30 samples/beat, pixel size 2.08mm x 2.08mm. Then, as synchronized with the ECG-monitor, a given number of images are recorded along many cardiac cycles and averaged to create a single 2D image consisting on the velocity field at each slice (see as reference Figure 2.15). This is done by integrating the grayscale image. Usually PC-MRI scans, due to their low spatial resolution, are not performed to every patient in which an aortic pathology is suspected, so this constitutes an extra study from the normal clinical protocol.

• **Clinical history:** on top of the sequence of images acquired and the associated diagnoses, it is important to keep record of the surgical procedures relevant to the cardiovascular health of the patient. Therefore, clinical history is also shared with the bioengineering unit. Another crucial data is patient’s cuff pressure, which is used to calibrate the boundary conditions as required in Chapter 3.

Then, image reconstruction, CFD analyses and post-processing is performed according to section 2.2.

### 4.1.3 The cloud approach for sharing information

One of the pillars of the iCardioCloud philosophy is to facilitate the exchange of medical data. In general, technical details are difficult to understand for physicians and so protocols
should be as simple as possible. Therefore, we rely on a cloud-based repository in which only significant and straightforward information is available.

Radiologists involved in the project currently have a friendly interface to upload DICOM images to the server so that they become immediately available for pre-processing by the researchers. In the other "direction", once results of CFD have been post-processed, parameters such as velocity, pressure, TAWSS and OSI are plotted and videos are made to see their evolution along a cardiac cycle. By uploading to our server only images and videos, physicians are not required to interact with, often complicated, numerical data that bioengineers deal with. All this information also becomes immediately available so as to take diagnostic and operative decisions based on medical analysis and our results.

CFD analyses may thus be performed with different aims: (i) to realistically reproduce preoperative patient’s hemodynamics in order to offer to the surgeon a richer set of information, which may help in the decision-making process; (ii) if the surgeon decides not to operate, CFD analysis results can be explored as predictive tools of pathology evolution and progress; (iii) several idealized postoperative configurations may be analysed to investigate possible scenarios and find optimal therapeutic solutions.

Up to now, being a single-centre study, our in-house computational facilities are sufficient to lodge raw and processed information about the enrolled patients. However, thanks to the modularity of the different components of the framework, data can be stored in one facility, whereas numerical analysis can be run in another computer and finally results post-processed even in a different operative unit.

### 4.1.4 The current database

Up to now, 21 patients have been enrolled in the project. Table 4.1 shows the enrolled patients, their disease characteristics and the chronology of imaging and simulations (Pre, Post, Follow Up). A short comment describes the status of the process in the simulation pipeline. In the patients where no PC-MRI data is available, a set of averaged BC is available retrieved from patients with complete data.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Pathology</th>
<th>Details</th>
<th>CT</th>
<th>MRI</th>
<th>CFD</th>
<th>Obs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P001</td>
<td>Aneurysm</td>
<td>Post-istmo in the inner curvature w/ max diam 55mm</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre and Post simulated w/PS boundary conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FU shows no changes in anatomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P002</td>
<td>Aneurysm</td>
<td>Tree separated saccular lesions</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre is done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FU Two different FU with no aneurysmal growth.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P003</td>
<td>Dissection</td>
<td>Acute scenario with patent TL and FL</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Dissection with complicated segmentation. Post done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P004</td>
<td>Dissection</td>
<td>Post-dissection aneurysm. Partially clotted, both lumen visible.</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P005</td>
<td>Dissection</td>
<td>Post-dissection aneurysm. Max diam 71mm.</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Dissection with complicated segmentation. Patient dead.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>P006</td>
<td>Aneurysm</td>
<td>Two dilations in the DA. Max diams 41mm and 100mm.</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Pre and post done with average boundary conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>P007</td>
<td>PAU</td>
<td>Ulcer of 17x27mm in the inner curvature of the arch</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>P008</td>
<td>Healthy</td>
<td>Patient to use as reference</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Done w/ average boundary conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>P009</td>
<td>Aneurysm</td>
<td>Aneurysm in the arch max dilation 49x47mm</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre and post done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>P010</td>
<td>Aneurysm</td>
<td>Fusiform aneurysm from the distal arch max diam 71mm</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Pre and post done PS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Pathology</td>
<td>Details</td>
<td>CT</td>
<td>MRI</td>
<td>CFD</td>
<td>Obs.</td>
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</tr>
<tr>
<td>P011</td>
<td>Dissection</td>
<td>Chronic dissection. FL partially patent</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>P012</td>
<td>Dissection</td>
<td>Acute dissection w/clear entry and exit tears.</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P013</td>
<td>Dissection</td>
<td>Post dissection aneurysm in a chronic set-up.</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>P014</td>
<td>Aneurysm</td>
<td>Post istmo fusiform aneurysm</td>
<td>Pre</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post istmo fusiform aneurysm</td>
<td>Post</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P015</td>
<td>Dissection</td>
<td>Both lumen have thrombus</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post istmo fusiform aneurysm</td>
<td>Post</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FU</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FU2</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>P016</td>
<td>Aneurysm</td>
<td>Aneurysm post-istmo</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>P017</td>
<td>Aneurysm</td>
<td>Pseudoaneurysm in the ascending aorta</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>P018</td>
<td>Aneurysm</td>
<td>Aneurysm post-istmo w/max diam 40mm</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>P019</td>
<td>Coarctation</td>
<td>Narrowing after LSA</td>
<td>Pre</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>
### Table 4.1: Current iCardioCloud database. Twenty one patients have been enrolled in the study following the acquisition protocol.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pathology Details</th>
<th>Obs.</th>
<th>CFD</th>
<th>MRI</th>
<th>CT</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>P020</td>
<td>Very angulated arch</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>since MRI data was incomplete.</td>
</tr>
<tr>
<td></td>
<td>Suspected coarctation but no ( \Delta P ) found w/ catheter</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Pre done w/ average boundary conditions</td>
</tr>
<tr>
<td></td>
<td>( \Delta P ) found w/ catheter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P021</td>
<td>&quot;Double&quot; bifurcated arch w/ two branches born in each side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre and two &quot;virtual&quot; scenarios for surgery done w/ averaged boundary conditions</td>
</tr>
<tr>
<td></td>
<td>&quot;Double&quot; aortic arch</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Twenty one patients have been enrolled in the study following the acquisition protocol.
4.1.5 Results

As an example, Figure 4.2 shows velocity, pressure and WSS in six patients from the iCardioCloud database. This representation is illustrated as exactly seen in the hospital where the doctor has the possibility to interact with the geometry.

![Velocity, WSS and pressure fields in six patients from the iCardioCloud database. Due to the enlargement, velocity is systematically lower in the zones where aneurysms are present.](image)

**Supercomputing in the medical environment**  CFD simulations usually take many hours (if not days) to run, often based on the dimension of the mesh used for the discretization of the domain, especially in geometries where flow is not organized (see Chapter 2). When patient images arrive to our server and are pre-processed, the main bottleneck is constituted by the delay on performing the numerical CFD simulation. Firstly, we have used our local cluster at University of Pavia, with simulations ranging from 2 days to 2 weeks based on the mesh refinement. These timings are not compatible with emergency procedures and
decision making, so to test our proof-of-concept, many simulations were performed in the Marconi cluster at CINECA \(^1\).

4.1.6 Discussion

The iCardioCloud project was proposed back when no solid collaboration existed between our Computational Mechanics and Advanced Materials Group and the Division of Vascular Surgery in IRCCS Policlinico San Donato. This work gave us the opportunity to interact with radiologists and surgeons to understand their needs and familiarize with the studies available to solve them. We successfully created a protocol for patient recruiting where PC-MRI was \textit{systematically} acquired even tough it does not constitute a routine exam for aortic diagnosis. As mentioned earlier, information was immediately sent to our server from the hospital without human interaction from the bioengineering side. By segmenting, meshing, imposing different boundary conditions and running CFD simulations with various parameters, we were able to learn-from-experience and refine the methods. This constituted the most valuable aspect of this project.

Feedback from surgeons was, fortunately, very heterogeneous. All the parameters extracted from CFD were appreciated and useful to understand hemodynamics in each single patient. Only by means of patient-specific simulations, the weaknesses of each morphology could be appreciated. iCardioCloud itself did not deliver results in which physical variables were associated univocally with evolution of disease (i.e. TAWSS related with aneurysm growth), but build the bases of all the projects reported herein.

4.2 Analysis of aortic hemodynamics with ageing

In this section we will discuss an application of CFD proposed by the University of Nebraska - Medical Center that aims at quantifying hemodynamic changes with ageing in a cohort of healthy subjects. The project focuses on understanding the role of hemodynamics in pathophysiology of the ageing human aorta. Ageing results in increased tortuosity and outward remodeling of the vasculature which entails drastic changes in fluid dynamics that can trigger vascular disease.

\(^1\)Marconi is a supercomputer consisting of 1512 nodes of 36 cores each connected by an OmniPath high speed network. This infrastructure became available to our group through the LISA 2017 initiative under the project B-BeST (Bringing Biomechanical Simulations to Clinical Target). Therefore, simulations were run with up to 2304 processors in parallel reducing the computational time to only a few hours.
4.2.1 Motivation and objectives

Human vasculature undergoes substantial changes with age (Virmani et al., 1991; Kamenskiy et al., 2015). These changes often include widening and elongation of the main elastic and muscular arteries (see Figure 4.3) resulting in increased tortuosity in senior subjects.

![Figure 4.3: Aortic geometry in individuals from different age groups. Aorta get wider and more tortuous with ageing. Reproduced from Kamenskiy et al., (2015).](image)

These geometric changes are likely associated with altered hemodynamics, which may include low and oscillatory shear - known to trigger biological pathways that lead to arterial stiffening and vascular disease (Reneman, Arts, and Hoeks, 2006; Ku, 1997). Furthermore, demographics and clinical risk factors have substantial influence on arterial remodelling and thereby can also influence blood flow. Understanding the role of hemodynamics in arterial remodelling in the context of age and risk factors would help better understand vascular pathophysiology in different populations of patients and develop new materials and devices for optimized repair.

We hypothesize that arterial remodelling that occurs as a result of ageing and the effect of risk factors, shifts hemodynamics from atheroprotective to atherogenic threshold resulting in arterial stiffening and vascular disease. We tested our hypothesis by performing CFD analysis in the anatomies representing subjects from each of the age groups described by Figure 4.3 and correlating hemodynamic variables, such as TAWSS and OSI, with tortuosity and arterial calcification, that will be used as a marker for vascular disease. Clinically, aortic calcification has been associated with higher incidence of cardiovascular events (Jayalath, Mangan, and Golledge, 2005; Harbaoui et al., 2016). Understanding the hemodynamic conditions associated with early onset of vascular disease in the context of demographics and
4.2. Analysis of aortic hemodynamics with ageing

Risk factors can allow early detection of disease-prone anatomy and would help understand the basic arterial pathophysiology.

4.2.2 Materials and Methods

A set of 122 healthy patients divided in nine age cohorts was included in the study (for demographics see Kamenskiy et al., (2015)). From CT imaging of the entire population, calcium was retrieved and mapped as illustrated in Figure 4.4. Furthermore, tortuosity of the entire aorta and the principal segments was calculated.

![Diagram](image)

**Figure 4.4:** Aortic geometry of a 68yo male showing different zones (left) to assess calcification burden (right). Areas of high calcification are observed in the abdominal aorta and in the arch that typically have abnormal hemodynamics. Substantial tortuosity of the vasculature in the regions can be appreciated.
A representative patient from each age group was chosen and aortas from the annulus to the iliacs, together with the proximal portions of all the surrounding vessels, were reconstructed into 3D geometries with Mimics (Materialise, Leuven, Belgium). Volume meshing for CFD was radius dependent due to the heterogeneity in the diameter of the vessels, yielding meshes with a mean of 8.5 million elements and average element size of 0.6mm. CFD simulations were run according to the procedure described in Chapter 2.

Regarding the set-up of the hemodynamic simulations, inflow wave was retrieved from Morbiducci et al., (2009) and then linearly scaled to match the stroke volume suggested by Simone et al., (1997) in each age group (see Table 4.2). Duration of each heart beat was kept always to 1s and time-step was 0.001s. All simulation conditions were kept as explained in Chapter 2 besides the number of simulated cycles that in this case was only three since pressure values were not the goal of this study.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Patient’s age</th>
<th>Stroke Volume [ml/beat]</th>
</tr>
</thead>
<tbody>
<tr>
<td>05-09</td>
<td>6</td>
<td>39.79</td>
</tr>
<tr>
<td>10-19</td>
<td>18</td>
<td>55.82</td>
</tr>
<tr>
<td>20-29</td>
<td>21</td>
<td>97.75</td>
</tr>
<tr>
<td>30-39</td>
<td>39</td>
<td>70.15</td>
</tr>
<tr>
<td>40-49</td>
<td>45</td>
<td>74.04</td>
</tr>
<tr>
<td>50-59</td>
<td>51</td>
<td>94.23</td>
</tr>
<tr>
<td>60-69</td>
<td>62</td>
<td>93.76</td>
</tr>
<tr>
<td>70-79</td>
<td>73</td>
<td>101.04</td>
</tr>
<tr>
<td>80-100</td>
<td>88</td>
<td>79.16</td>
</tr>
</tbody>
</table>

Table 4.2: Stroke volume used in each cohort of patients based on Simone et al., (1997).

In the outflow vessels, 3WK were attached following the tuning proposed in Chapter 3. The pressure wave for the calibration was, in all the cases, retrieved from Stergiopulos, Westerhof, and Westerhof, (1999). Regarding the flow waves needed for the minimization method, first the flow split to the main organs was calculated from Williams and Leggett, (1989). Then, for each branch (i.e. celiac trunk, mesenteric arteries, legs) flow was subsequently divided based on vessel diameters as in Zamir, Sinclair, and Wonnacott, (1992). Finally, with the coefficient retrieved as percentage of the inflow volume, the same waveform used in the ascending aortas was linearly scaled to match the target value.

Once the velocity field was retrieved from the numerical simulation, TAWSS and OSI were calculated in all the cohorts. Following Malek, Alper, and Izumo, (1999), regions with TAWSS lower than 0.4 Pa were considered atherogenic and zones with TAWSS above 1.5 Pa were considered atheroprotective. In the case of OSI, conditions were considered atherogenic above 0.3 (Morbiducci et al., 2010). Maps of these thresholds together with surfaces ratios of the disease zones to the overall areas were calculated as in Desyatova et al., (2017).
4.2.3 Results

Tables 4.3 and 4.4 show the calcification and tortuosity in the different segments of the aorta. Results are illustrated as average of each cohort in the dataset as well as for the nine geometries used for our CFD analysis.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pelvic arteries</th>
<th>Abdominal Aorta</th>
<th>Visceral Aorta</th>
<th>Thoracic Aorta</th>
<th>Aortic Arch</th>
<th>Total calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In individual anatomies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
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</tr>
<tr>
<td>21</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>39</td>
<td>0.01</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
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<td>0.07</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>73</td>
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<td>3.68</td>
<td>1.03</td>
<td>0.28</td>
<td>0.50</td>
<td>1.15</td>
</tr>
<tr>
<td>88</td>
<td>6.38</td>
<td>13.13</td>
<td>8.00</td>
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<td>7.29</td>
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<td>Average by age group</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>05-09</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>40-49</td>
<td>0.56</td>
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<td>0.13</td>
<td>0.19</td>
</tr>
<tr>
<td>50-59</td>
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<td>1.47</td>
<td>0.05</td>
<td>0.01</td>
<td>0.04</td>
<td>0.24</td>
</tr>
<tr>
<td>60-69</td>
<td>0.93</td>
<td>3.57</td>
<td>0.26</td>
<td>0.31</td>
<td>0.14</td>
<td>0.65</td>
</tr>
<tr>
<td>70-79</td>
<td>2.29</td>
<td>5.67</td>
<td>2.42</td>
<td>1.11</td>
<td>1.08</td>
<td>1.97</td>
</tr>
<tr>
<td>80-100</td>
<td>5.38</td>
<td>5.88</td>
<td>3.49</td>
<td>1.92</td>
<td>1.98</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Table 4.3: Calcification as % of the total volume of the arterial segments. A notorious increase can be seen from the age of 40.

Figure 4.5 depicts the TAWSS values in the nine selected patients ranging from 5 to 100yo. Furthermore, the area subject to a TAWSS below 0.4Pa and above 1.5Pa are highlighted in Figure 4.6. Figure 4.7 summarizes the evolution of the aforementioned TAWSS thresholds. Besides the presence of a few outliers, atheroprotective zones decrease whereas atheroprone zones increase homogeneously.

Since flow is also expected to become more oscillatory with age, Figure 4.8 illustrates the OSI in the selected patients. Similar to the analysis of the TAWSS, Figure 4.9 shows the areas where atheroprone flow is found (OSI > 0.3). To show the evolution, Figure 4.10 depicts the trend associated with age.
<table>
<thead>
<tr>
<th>Age group</th>
<th>Pelvic arteries</th>
<th>Aorta</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>In individual anatomies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>18</td>
<td>0.04</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>21</td>
<td>0.02</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>39</td>
<td>0.07</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>45</td>
<td>0.08</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>51</td>
<td>0.13</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>62</td>
<td>0.12</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>73</td>
<td>0.19</td>
<td>0.24</td>
<td>0.24</td>
</tr>
<tr>
<td>88</td>
<td>0.27</td>
<td>0.26</td>
<td>0.28</td>
</tr>
<tr>
<td>Average by age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05-09</td>
<td>0.03</td>
<td>0.11</td>
<td>0.10</td>
</tr>
<tr>
<td>10-19</td>
<td>0.03</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>20-29</td>
<td>0.03</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>30-39</td>
<td>0.05</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>40-49</td>
<td>0.07</td>
<td>0.16</td>
<td>0.14</td>
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<tr>
<td>50-59</td>
<td>0.09</td>
<td>0.18</td>
<td>0.17</td>
</tr>
<tr>
<td>60-69</td>
<td>0.10</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td>70-79</td>
<td>0.17</td>
<td>0.24</td>
<td>0.23</td>
</tr>
<tr>
<td>80-100</td>
<td>0.16</td>
<td>0.26</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 4.4: Tortuosity index in different sections of the aorta. Pelvic arteries: from the iliac bifurcation to the origin on profunda femoris. Aorta: origin of the LSA to iliac bifurcation

4.2.4 Discussion

Vascular remodelling with ageing is well known and described in literature. Large elastic and small muscular arteries remodel with age demonstrating increased diameter, length and tortuosity. These changes in vascular geometry are likely associated with changes in flow patterns which can push the artery towards an atherogenic pathway. Naturally, hemodynamics also change as we get older since two of its main drivers (namely shape of the aorta and boundary conditions) get modified. In this work, we wanted to quantify the evolution of blood flow indicators such as wall shear stress and oscillatory shear index with ageing and to correlate the results with the risk of calcification, the main consequence in terms of adverse medical outcomes. Associations with demographics and risk factors are currently incomplete. Previous studies have demonstrated correlation between calcium and older age, hypertension and smoking, but their respective contributions are not completely unveiled (Kamenskiy et al., 2015).

To test our hypothesis we used a group of 122 patients where tortuosity and calcium volume was calculated and stratified in five segments as shown in Figure 4.4. The rationale of this separation is that, anecdotally, calcification starts in the abdominal aorta, though
not yet demonstrated. In this way, we would be able to keep track of the evolution of calcium with more geometrical precision. Out of this numerous dataset, patients were divided in nine age cohorts from 5 to 100 year old where nine representative aortas were chosen for CFD simulation. Due to the lack of information on patient-specific, or cohort-specific, boundary conditions, we adapted current data on literature to calibrate 3WK circuits in all the outflows. From the simulations, velocity field was integrated in order to calculate TAWSS and OSI. Both indicators have been thoroughly described as mediators of atherosclerosis and consequent wall calcification.
Figure 4.6: Areas corresponding to low (red) and high (green) TAWSS as proposed by Malek, Alper, and Izumo, (1999).

Results show that mean TAWSS decreases with ageing and flow gets more oscillatory (see Figure 4.11). However, to establish a quantity that could be traceable along the patients, we proposed a protocol similar to our previous article (Desyatova et al., 2017). First, we defined TAWSS and OSI thresholds considered either atherogenic or atheroprotective and then we calculated the percentage of surface area covered by these type of flow characteristics. As depicted in Figure 4.7, atheroprotective zones decrease with ageing whereas atheroprone areas increase. A few outliers from a strictly decreasing/increasing trend are present since we are dealing with humans samples.
4.3 Embolic protection during TAVI: integration of in-vitro and in-silico analysis

4.3.1 Motivation and objectives

Stroke is a major complication of many procedures in cardiac surgery and invasive cardiology. New treatment options, such as transcatheter aortic valve implantation (TAVI), bear a high risk of stroke; in fact, the position paper on TAVI elaborated by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery acknowledges a clinically evident stroke rate between 3 and 9% for the transfemoral and 0-6% for...
the transapical approach (Vahanian et al., 2008). These relatively high stroke rates were re-confirmed in a more recent paper by Nuis et al., (2012).

Even more prevalent but more difficult to assess is the occurrence of sub-clinical brain damage due to micro-emboli that are released during the procedure and migrate to the brain: clinically silent but morphologically detectable perfusion deficits occur in 84% of the patients undergoing a TAVI (Kahlert et al., 2010). Even if the potential impact of these lesions to the neurocognitive function in the long term remains unknown, these numbers are worrisome.
4.3. Embolic protection during TAVI: integration of in-vitro and in-silico analysis

Several devices were introduced aiming at capturing or deflecting embolic material released during TAVI (Nietlispach et al., 2010; Carpenter et al., 2011; Naber et al., 2012). All of them, however, occupy significant space in the aortic arch, only capture large particles, are prone to dislodgement and bear an own risk for cerebral embolism by dislodging resident atherosclerotic material. Their real-world use is limited. Hence, prevention of periprocedural cerebral embolism remains a priority.
With all these considerations, the goal of this study is to have a set-up combining in-vitro and in-silico modelling of blood flow in order to assess the particle splitting within a thoracic aorta model. This first preliminary part aims at becoming familiar with the necessary techniques and have a first validation of a framework for particle tracking so as to design effective embodeviation strategies. The following step, not yet approached in this
thesis, will be to recreate possible flow diverting techniques only in silico so as to enter an optimization loop without the need of building devices in the lab.

In this first stage, embodeviation will be approached only by forcing an inflow volume from the right subclavian artery (RSA) into the BCT whereas the development of devices will be done afterwards.

Therefore, the steps were the following:

1. Set-up of the in-vitro circuit
2. Creation of the in-silico model
3. Finding the embodeviation threshold in silico
4. Comparison and validation of particle split

### 4.3.2 Materials and Methods

**Set-up of the in-vitro circuit**

A mock silicone model of an idealised aorta was built and connected to a circulatory loop driven by a centrifugal flow pump (Medtronic Bioconsole BIO-MEDICUS 550, Minneapolis, MN, USA). The supraortic branches were distally merged to one vessel in order to enable a flow quantification in two major directions: cranial (CRA), i.e., towards the cerebral circulation; caudal (CAU), i.e., towards the descending aorta. The CRA/CAU flow split ratio was kept constant during all the experiments at 35%/65%.

A bolus with a predefined distribution of particles with an average diameter of 0.5mm (Amberlite, Sigma-Aldrich) was injected at level of the aortic root by a syringe pump in less than 5 seconds (see Figure 4.12). The released particles were captured by two filter baskets, one for each direction, with the aim of evaluating the particle split.

The inflow rate was set at 4 L/min with a constant profile and, eventually, an inflow jet from the RSA is injected to test embodeviation. As a second variable, particles were released from the left and the right sides of the AA to evaluate the influence of the release location. Each combination of parameters was tested five times where the standard deviation for the particle collection resulted of ±6%, suggesting that the release and catch method is sufficiently consistent to draw conclusions for future testing of embolic protection devices.

Particles were counted from the filters in each experiment. It is important to note that some particles were kept in the surroundings of the AA and did not travel towards the peripheral circulation.
Creation of the in-silico model

Experiments were counterparted by in silico simulations with a replica of the aortic model used for the in-vitro experiments reproduced by Computer Aided Design software (Autodesk Inc., San Rafael, California, USA). In the computational model, supraaortic branches were already merged to represent exactly the filtering strategy (see Figure 4.13).

Volume meshing was performed according to the details in Chapter 2. As for the inflow boundary conditions, on the section slightly distal to the aortic root, we prescribed a constant flow rate of 4 L/min according to the in vitro series. The same Dirichlet strategy was used in the RSA from 0.0 to 0.5 L/min, with steps of 0.1 L/min. On the outflow sections, we prescribed the flow split conditions adopted for the experiments: 35% of the outflow in the cranial direction and 65% in the caudal direction.

The point-wise velocity field computed by CFD was post-processed with Paraview (Ahrens, Geveci, and Law, 2005) and a particle source was placed in the corresponding lateral inflow as proposed in the in vitro counterpart to perform particle tracking (particles were considered massless).

Comparison between models and quantities of interest

Finding the embodeviation threshold in silico By varying the inflow from the RSA in the in silico model, we aimed at finding the inflow threshold in that would refrain all the particles to enter the RCCA (cerebral circulation).

Comparison and validation of particle split Particles deposited in the CRA and CAU filters were quantified and compared with the corresponding in silico tracking at the outflow boundaries in two scenarios: without inflow from the RSA and with a flow equal to the
threshold defined in the previous step. We then hypothesized that particle diversion in all the supraortic vessels as measured in silico would resemble the in vitro experiments where we cannot retrieve the single values due to the absence of single-vessel filters.

4.3.3 Results

The RSA inflow that avoided all the particles to enter the RCCA was 0.5 L/min as shown in Figure 4.14.

Table 4.5 shows the particle split in vivo and in silico in both the experiments.
4.3.4 Preliminary conclusions

Even though this work is currently on a very early stage, some interesting conclusions can be drawn.

First of all, we had the chance to set-up the in vitro circuit and tune all the parameters needed for a reliable experiment. The inflow parameters, the number of particles and the overall organization in the laboratory is often cumbersome and requires a lot of manual work. In parallel, we created the CAD model for in silico simulations and also familiarized with the required mesh sizes, simulation times and particle tracing strategies.

One of our assumptions was that CFD particle distribution in the supraortic branches would imitate its in vitro counterpart, which we were not able to measure. Then, we first tested in silico the threshold that would avoid particles to enter the cerebral circulation, in our case assumed as the RCCA. Results showed that 0.5 L/min was the right choice for a 4 L/min aortic inflow. With more experiments, this threshold could vary among individuals.

When comparing the in silico against the in vitro results, particle split did not match in both experiments. Interestingly, mass-less particle distribution did not match completely the flow split as intuition would expect. We attribute this difference to the calibration of
the flow split in the in vitro set-up, which has a non-linear behaviour between input and output. This problem is currently being solved.

Further experiments will be focused (both in silico and in vitro) into understanding embodeviation with other inflow profiles. In particular, we will make further testing with other flow rates both with steady and unsteady profile. The goal will be to simulate other stroke volumes and, eventually, flow during heart pacing as in the real surgery.

Once hemodynamic scenarios will be validated, new flow combinations will be simulated in silico by introducing inflow jets in different parts of the aorta. Furthermore, the computational nature will give us also the possibility of simulating endovascular flow diverting devices.
Chapter 5

Advanced Applications: study of TEVAR

In this chapter we will expose three different topics in which numerical tools were used to give an insight into specific medical needs for TEVAR planning. The first project aims at using computational hemodynamics to identify hostile proximal landing zones for the endografts within the aortic arch. The second one, proposes a framework for virtually predicting blood flow after computationally deploying a stent-graft in patient-specific aortas. The last project intends at finding the right device for endografting the ascending aorta, a vascular district where open surgical repair is still the first-line treatment.

5.1 The Arch Project towards a better understanding of the arch landing zones

5.1.1 Current TEVAR planning

As mentioned in Chapter 2, TEVAR represents a well-established alternative to open repair in selected patients with both suitable anatomical features and adequate prognosis related to concomitant medical diseases. Endovascular procedures involving the aortic arch, however, are associated with higher rates of postoperative clinical failure (Böckler et al., 2016), and remain complex and challenging due the angulation and tortuosity of the arch and its peculiar biomechanical environment (Figueroa et al., 2009b). This represents a critical issue because patients with aortic arch pathologies account for up to 60% of TEVAR cases (Geisbüsch et al., 2010), and are in fact those that would benefit most from endovascular treatment.

Preoperative planning for TEVAR of the arch is based on Ishimaru’s classification (Ishimaru, 2004) that defines the proximal landing zones (0–4) as related to the origin of the
supra-aortic vessels, indicating the requirement of a prophylactic re-routing of the involved aortic branches (see Figure 5.1). Ishimaru’s aortic map, however, disregards landing zones angulation and tortuosity, that represent critical anatomical features associated with higher rates of endograft failure (Grabenwöger et al., 2012; Chen et al., 2014; Ueda et al., 2011).

![Figure 5.1: Ishimaru’s classification of the aortic arch. Reproduced from Leonard et al., (2004).](image)

5.1.2 The MALAN classification

In a recent article, Marrocco-Trischitta et al., (2017) proposed the Modified Arch Landing Areas Nomenclature (MALAN) as shown in Figure 5.2, that merges Ishimaru’s map with the Aortic Arch Classification in Type I to III, originally described by Madhwal et al., (2008) for predicting difficult carotid stenting. That study showed that arch types are associated with a consistent geometric pattern of Ishimaru’s zones that allows identifying specific proximal landing areas with suboptimal angulation and tortuosity for stent-graft deployment.
5.1. The Arch Project towards a better understanding of the arch landing zones

<table>
<thead>
<tr>
<th>Zone</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 0</td>
<td><img src="image1" alt="Type I Zone 0" /></td>
<td><img src="image2" alt="Type II Zone 0" /></td>
<td><img src="image3" alt="Type III Zone 0" /></td>
</tr>
<tr>
<td>MALAN</td>
<td>I/0</td>
<td>II/0</td>
<td>III/0</td>
</tr>
<tr>
<td>Zone 1</td>
<td><img src="image4" alt="Type I Zone 1" /></td>
<td><img src="image5" alt="Type II Zone 1" /></td>
<td><img src="image6" alt="Type III Zone 1" /></td>
</tr>
<tr>
<td>MALAN</td>
<td>I/1</td>
<td>II/1</td>
<td>III/1</td>
</tr>
<tr>
<td>Zone 2</td>
<td><img src="image7" alt="Type I Zone 2" /></td>
<td><img src="image8" alt="Type II Zone 2" /></td>
<td><img src="image9" alt="Type III Zone 2" /></td>
</tr>
<tr>
<td>MALAN</td>
<td>I/2</td>
<td>II/2</td>
<td>III/2</td>
</tr>
<tr>
<td>Zone 3</td>
<td><img src="image10" alt="Type I Zone 3" /></td>
<td><img src="image11" alt="Type II Zone 3" /></td>
<td><img src="image12" alt="Type III Zone 3" /></td>
</tr>
<tr>
<td>MALAN</td>
<td>I/3</td>
<td>II/3</td>
<td>III/3</td>
</tr>
</tbody>
</table>

TABLE 5.1: The newly proposed modified arch landing areas nomenclature (MALAN), which comprises the proximal landing zones according to the Ishimaru aortic arch map and types of arch according to the aortic arch classification. CCA, Common carotid artery. Reproduced from Marrocco-Trischitta et al., (2017).

5.1.3 Hypothesis of the Arch Project

Authors in Marrocco-Trischitta et al., (2017) conclude, as an example, that deploying and endograft in Zone 3 would not be the same in a patient with a Type I arch than a patient...
with a Type III arch because of angulation. Therefore, we hypothesize that the introduction of hemodynamic measurements into clinical practice, is expected to improve TEVAR planning and stent-graft design (Bogerijen et al., 2014b). In particular, we aimed to analyse Displacement Force (DF) magnitude and orientation in the aortic arch according to the MALAN classification by means of CFD modeling, in order to characterize also a consistent fluid dynamic pattern, and identify specific areas with a hostile hemodynamic environment.

5.1.4 The Displacement Force and its calculation

The concept of DF was early described by Lambert et al., (1999) and Resch et al., (2000) with ex vivo experiments that aimed at quantifying the force that would cause endograft migration. Later, Volodos et al., (2005) associated retrograde displacement of the stent-graft with the pulsatile pressure inside the aorta. The first computational study conducted by Howell et al., (2007) analyzed the DF in four patients that underwent EVAR and found that the main contributor of DF were pressure-related forces other than flow-related forces. More recently, the group of C.A. Figueroa reproduced these analyses in both thoracic and abdominal endografts in order to correlate DF with positional changes of the devices over time and suggested to use patient-specific analysis to foresee late device migration (Figueroa et al., 2009b; Figueroa et al., 2009a; Figueroa et al., 2010; Prasad et al., 2011).

We will herein calculate the DF exerted by the blood in a certain proximal landing zone (PLZ) as:

\[
\text{DF} = \int P n dA + \int \tau dA
\]

where \(P\) and \(\tau\) are the pressure and WSS at each surface cell respectively, \(n\) the local element normal and \(dA\) the area of the cell from the computational domain. The integration is then performed over each PLZ.

5.1.5 Methods

This study reviewed anonymized thoracic CT scans from patients undergoing diagnostic evaluation for various indications at IRCCS Policlinico San Donato in 2015 and was approved by the local Ethic Committee. The need for patient informed consent was waived because of the retrospective nature of the analysis and the use of anonymized data. For the purpose of the present analysis, we specifically reviewed 15 thoracic CTA scans, 5 per ToA (exclusion criteria followed Marrocco-Trischitta et al., 2017). Of note, only thin-cut (1.0 mm or 1.5 mm) CTs of patients with a healthy aortic arch with visible origins of the supra-aortic branches were considered. Aneurysmatic aortas were excluded because the original description of the aortic arch classification was based on healthy aortas.
5.1. The Arch Project towards a better understanding of the arch landing zones

Each CT scan was segmented using the software Mimics v18.0 (Materialise, Leuven, Belgium). The aortic tract between the aortic valve annulus and the diaphragm was considered, as also the proximal tract of brachiocephalic trunk, left common carotid artery, and left subclavian artery. Each 3D aortic model was then discretized by VMTK v1.3 to generate the computational mesh for CFD analysis (details as in Chapter 2). An average cut-off of 1.8 million of tetrahedral elements was considered for the simulations. This was based on a mesh convergence analysis that showed that further mesh refinement would have produced a difference of less than 1% in the computed DF. Figure 5.3 illustrates the 3D reconstructions of all the patients.

Given the retrospective nature of the study, no patient-specific hemodynamic information was available for the considered cohort of patients, and therefore the same flow boundary conditions were employed in all the cases. On the inflow section of the ascending aorta, a flow wave representing a cardiac output of 4.88 L/min was used as input, whereas in the outlets, 3-element Windkessel circuits were attached to mimic the distal vasculature. Table 5.1 summarizes the 3WK values used for the cohort. Both inflow and outflow boundary conditions were based on mean values from four patients that underwent PC-MRI and calibration as exposed in Chapter 3.

The results of the simulations were post-processed using a Python script and Paraview (Ahrens, Geveci, and Law, 2005) to isolate in each zone the wall pressure and the WSS at the systolic peak to calculate the DF. Given the purpose of the study, only the systolic peak instant was considered for the post-processing. Figure 5.4 shows the results of the simulation in one patient.
### Table 5.1: 3WK parameters used for the analysed patients. R1 and R2 \([\text{dyn} \cdot \text{s/cm}^5]\). C \([\text{cm}^5/\text{dyn}]\)

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCT</td>
<td>776</td>
<td>20251</td>
<td>9.32E-05</td>
</tr>
<tr>
<td>LCCA</td>
<td>3799</td>
<td>44982</td>
<td>3.35E-05</td>
</tr>
<tr>
<td>LSA</td>
<td>1394</td>
<td>32092</td>
<td>5.84E-05</td>
</tr>
<tr>
<td>DA</td>
<td>129</td>
<td>1512</td>
<td>1.09E-05</td>
</tr>
</tbody>
</table>

The magnitude and the direction of the DF for each landing zone (0-3) were computed for each patient. Equivalent Surface Traction (EST) of each zone were then computed by dividing the DF magnitude by the corresponding zone area in order to account for the impact of the geometrical differences only. Furthermore, the individual normalized components of each DF vector were compared among the landing areas to evaluate the change in orientation (upward vs. sideways) in the different Types of Arch (ToA).

Data were analysed using SPSS Statistics version 24 (SPSS Inc., Chicago, Illinois) to quantify statistical significance among the sample with a threshold of \(P<0.05\). Normality of the distribution of the data was tested using the Shapiro-Wilk test. Comparisons between the different outcome measures in the proximal landing zones and the ToA were made using the One-Way Anova followed by LSD post hoc for normally distributed data.

#### 5.1.6 Results

The 15 selected patients (73% male) were \(77\pm9\) years old. The three groups defined by the ToA were comparable in age (\(P=.595\)) and gender.

Comparison between ToA (Table 5.2), showed that DF magnitude was significantly different in Zone 3 (\(P=.007\)), with 3/II and 3/III \(^1\) having significantly greater values than 3/I (\(P=.004\) and \(P=.008\) respectively). Comparison within ToA, showed that DF magnitude was significantly different across landing zones in all the ToA, with Zone 0 having the highest magnitude regardless the ToA (\(P<.001\)). Furthermore, DF magnitude in 3/III was almost two times greater than in 2/III (\(P=.033\)), as also in 3/II compared to 2/II (\(P=.032\)).

As PLZ across the arch (0-3) are known to differ in terms of surface areas, EST were also computed to account for the impact of such a difference on the DF magnitude. Notably however, comparison of PLZ surface areas between ToA showed no statistical difference (\(P=.672\)). Comparison between ToA (Table 5.3), showed that EST was significantly different in Zone 3 (\(P=.009\)), with EST in 3/II and in 3/III being two times greater than in 3/I (\(P=.008\) and \(P=.006\)). Comparisons within ToA, showed no change in EST across PLZ within Type I arch (\(P=.297\)), and Type II arch (\(P=.054\)), whereas EST increased towards more distal PLZ.

\(^1\)Arabic number indicates the landing zone whereas the roman numeral indicate the Type of Arch.
5.1. The Arch Project towards a better understanding of the arch landing zones

**Figure 5.4:** Calculation of the DF in a patient. A: streamlines, B: pressure map and C: DF in each PLZ.

within Type III (P=.019). Between adjacent landing areas, EST was greater in 3/III than in 2/III (P=.016), and in 3/II than in 2/II (P=.016).

Analysis of the DF orientation (Tables 5.4 and 5.5), showed that the greater changes in
Chapter 5. Advanced Applications: study of TEVAR

### Table 5.2: Displacement Force in MALAN areas with comparisons across landing zone and Type of Arch

<table>
<thead>
<tr>
<th>Zone</th>
<th>Type I 0/I</th>
<th>Type II 0/II</th>
<th>Type III 0/III</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13.2±3.6</td>
<td>14.1±3.4</td>
<td>9.5±2.8</td>
<td>.090</td>
</tr>
<tr>
<td>Zone 1</td>
<td>1/I</td>
<td>1/II</td>
<td>1/III</td>
<td>.211</td>
</tr>
<tr>
<td>1.7±0.5</td>
<td>2.4±0.6</td>
<td>2.3±0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 2</td>
<td>2/I</td>
<td>2/II</td>
<td>2/III</td>
<td>.937</td>
</tr>
<tr>
<td>3.4±1.6</td>
<td>3.3±0.9</td>
<td>3.1±1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3</td>
<td>3/I</td>
<td>3/II</td>
<td>3/III</td>
<td>.007</td>
</tr>
<tr>
<td>2.6±0.9</td>
<td>6.1±1.5</td>
<td>5.8±2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5.3: Equivalent Surface Traction in MALAN areas with comparisons across landing zone and Type of Arch.

<table>
<thead>
<tr>
<th>Zone</th>
<th>Type I 0/I</th>
<th>Type II 0/II</th>
<th>Type III 0/III</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2265±382</td>
<td>2393±240</td>
<td>1807±420</td>
<td>.054</td>
</tr>
<tr>
<td>Zone 1</td>
<td>1/I</td>
<td>1/II</td>
<td>1/III</td>
<td>.460</td>
</tr>
<tr>
<td>2389±704</td>
<td>3134±1080</td>
<td>2765±919</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 2</td>
<td>2/I</td>
<td>2/II</td>
<td>2/III</td>
<td>.851</td>
</tr>
<tr>
<td>2195±453</td>
<td>1953±655</td>
<td>2138±912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3</td>
<td>3/I</td>
<td>3/II</td>
<td>3/III</td>
<td>.009</td>
</tr>
<tr>
<td>1725±641</td>
<td>3357±1019</td>
<td>3442±713</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.297</td>
<td>.054</td>
<td>.019</td>
<td></td>
</tr>
</tbody>
</table>

DF magnitude in 3/II and 3/III were related to the upward component, that was four times greater in 3/II compared to 2/II (P=.001), and five times greater in 3/III compared to 2/III (P<.001). On the contrary, in Type I arch the upward component did not differ through PLZ. Finally, sideways component did not change significantly between PLZ in any ToA.

#### 5.1.7 Discussion

The magnitude of the aortic arch DF depends on the blood pressure and the WSS. The pivotal study of Howell et al., (2007) belied the commonly held view that the main component of the DF is the shearing force of the flow and that, as a consequence, their main orientation is in the downstream direction of the flow. In fact, the primary contributor to the DF magnitude is the blood pressure, and their orientation depends on the geometry of the arch and is mainly in the upward direction (Howell et al., 2007; Figueroa et al., 2009b). Here, we described for the first time how the DF of the arch are distributed in the different proximal landing areas for TEVAR, defined according to the MALAN classification.
Our data showed that Zone 0, regardless the Type of arch (i.e. 0/I-III), presents the highest DF magnitude compared to the other arch zones, and that the DF vector in Zone 0 is oriented orthogonally to the aortic blood flood and to the vessel longitudinal axis in that area. Despite these unfavourable hemodynamic conditions, however, TEVAR in Zone 0 is less likely to be complicated by endoleak or stent-graft migration because it provides a longer neck length compared to the other zones (Melissano et al., 2007), and a moderate angulation and a negligible tortuosity, regardless the Type of arch. Also, computation of EST in each landing area showed that the higher DF magnitude in Zone 0 is due to its consistently greater surface area, a factor that positively correlates with DF magnitude.

DF with a greater magnitude and a vector orthogonal to the aortic flow and longitudinal axis were also found in 3/II and in 3/III, compared to the proximal adjacent areas.
(i.e., 2/II and 2/III respectively). These findings were even more evident when a comparison was made based on EST. Interestingly, we also found that the greater EST were related to changes in the upward component of the vector, while the sideways component remained unchanged. In contrast to 0/I-III landing areas, 3/II and 3/III are associated with suboptimal angulation and tortuosity, which require a longer proximal neck length (Altnji, Bou-Saïd, and Walter-Le Berre, 2015) often unavailable due to the anatomical restraint of the origin of left subclavian. As a consequence, the resulting biomechanical environment of 3/II and 3/III appears unfavourable for endograft deployment. In addition to the relevance for TEVAR planning, our findings regarding DF magnitude and orientation in Zone 0, and in Zone 3 of Type II and Type III arches, may have implications also in the development of proximal entry tears in spontaneous Type A and Type B aortic dissections.

Indeed, we recognize some limitations of our study. First, healthy aortas were employed, as we conceived it as a proof-of-concept regarding the definition of ToA, which was based on non-aneurysmatic aortas. Second, due to the lack of information on patient-specific hemodynamic environment, the same flow boundary conditions were employed in all cases. However, these limitations did not hinder the comparison between the hemodynamic patterns of the different landing zones, being related to their consistent geometric features. Finally, the limitations inherent to the computational methods, namely the assumptions of a Newtonian fluid and of a rigid arterial wall, should be also considered.

We are well aware that the clinical relevance of our finding remains to be validated in a dedicated postoperative outcome analysis of patients treated with TEVAR of the arch. Nevertheless, our work showed that the MALAN classification is associated with consistent hemodynamic features that, in addition to the geometric pattern previously reported (Marrocco-Trischitta et al., 2017), further improve its predictive value to identify hostile proximal landing zones for TEVAR of the arch. Finally, we believe that our findings support further studies to introduce fluid dynamics parameters among the criteria employed for TEVAR planning.

5.2 Virtual Endografting as a Predictor of Endovascular Intervention

5.2.1 Why numerical simulations before TEVAR?

TEVAR is a consolidated procedure to treat thoracic aortic diseases such as aneurysms and dissections, especially in those patients who are unsuitable for standard open surgery. However, it is not exempt of complications as previously described in Chapter 2. Many of these
5.2. Virtual Endografting as a Predictor of Endovascular Intervention

drawbacks are associated to the biomechanics of stent-graft apposition and hemodynamics. Consequently, the clinical outcome of such a minimally invasive technique is strictly related to an appropriate patient/stent-graft selection, stent-graft/aorta mechanical interaction, and operator skills. In this context, a quantitative assessment of the biomechanical actions induced in the aortic anatomy due to the stent-graft, and vice versa, may support the planning of the procedure, improving its clinical outcomes. Unfortunately, planning is currently based on geometrical measurements performed on static images (Erbel et al., 2014), discharging the aforementioned biomechanical aspects. For this reason, in the last decade, the bioengineering community has promoted the use of numerical simulations to assess in a non-invasive manner the aortic biomechanics, and in particular, the aortic hemodynamics before and after TEVAR (Zarins and Taylor, 2009).

5.2.2 State of the art and objectives

In 2006, Frauenfelder et al., (2006) analysed hemodynamic changes in AAA after stent-graft placement by CFD in eleven patients. Both pre-operative and post-operative fluid-dynamic simulations are based on CT datasets. Similarly, Karmonik et al., (2010) used CFD to provide quantitative assessment of hemodynamic wall forces in Type B dissection before and after the treatment using pre- and post-operative CT scan and MRI data. Midulla et al., (2012) further combined aortic anatomy derived from CT with MRI, used to obtain boundary conditions of the aortic wall movement during the cardiac cycle, performing CFD analysis as an evaluation of post-TEVAR aortic blood flow in twenty patients. The mentioned studies are just few examples of the extensive and constant effort to bring aortic fluid-dynamics simulations to the bedside (Figueroa and Zarins, 2011; Guzzetti et al., 2017).

Although these studies accurately describe post-operative hemodynamics, since based on actual post-operative images and measurements, they lack the predictive capability of the simulations, i.e., quantify aortic hemodynamics after the intervention based on pre-operative images and stent-graft design characteristics. To this aim, two major ingredients are necessary: 1) an accurate modelling of both the prosthesis mechanics and its deployment mechanism; 2) a reliable modelling of the aortic lumen after the stent-graft apposition.

While progress has also been done in modeling the stent-graft mechanics and its deployment in (patient-specific) aortic models by structural finite element analysis (Roy et al., 2016; Altnji, Bou-Saïd, and Walter-Le Berre, 2015; Perrin et al., 2015; Auricchio et al., 2013; De Bock et al., 2012), the integration of a stent-graft model after the deployment with the aortic fluid domain is still an open issue in the field of predictive fluid-dynamics simulations of TEVAR. As an example, Filipovic et al., (2011) examined the hemodynamic velocity field and shear stress in the thoracic aorta with and without aneurysm, based on an individual patient case and virtual surgical intervention, performed by a simple local resection
of the aneurysm where it was supposed to be bridged by the real endograft. Analogously, Alimohammadi et al., 2014b analysed the hemodynamic effectiveness of aortic dissection treatment by simply simulating the stented domain sealing the entry tear and removing the intimal flap.

Other studies, such as Xiong, Choi, and Taylor, (2012) and Neugebauer et al., (2016), proposed to create the virtual post-operative model manipulating the pre-operative surface of the aortic wall exploiting the centerline of the vessel and design parameters of the prosthesis. Although their approach creates a more accurate representation of the surface compared to previous studies (Filipovic et al., 2011; Alimohammadi et al., 2014b), it has a limited capability of capturing undesired protrusions of the stent-graft into the lumen, as in the case of the bird beak (Bogerijen et al., 2014a; Ueda et al., 2010). Furthermore, comparison of virtual surgery with actual post-operative data is missing in both cases.

Combination of virtual stent-graft deployment and CFD analysis has been addressed in 2009 by the group of Figueroa, who compared CFD in a virtually implanted endograft geometry with the actual post-operative one (Figueroa et al., 2009b); however, details on how the stent-graft is placed are not extensively described. A similar approach is used in Figueroa et al., (2009a) to measure the displacement forces based on follow-up imaging after endovascular repair of an AAA. Subsequently, Prasad et al., (2013) proposed a computational framework for investigating the positional stability of aortic endografts combining Computational Solid Mechanics and Computational Fluid Dynamics. Such a study focuses on abdominal aneurysm investigating in a parametric manner several factors that are clinically known to affect stent-graft stability. Although it is certainly one of the most comprehensive works performed in the field of virtual endografting, it considers an idealised model of AAA, neglecting the modeling of the actual endograft deployment as well.

Given all these premises, the present study aims at providing a realistic and robust computational framework to support TEVAR planning in clinical practice by predicting the post-operative haemodynamics, given a selected stent-graft model to be implanted and the target pre-operative aortic model. In particular, we propose a novel technique based on distance images for the integration of stent-graft and aortic model to generate a CFD-suitable volumetric mesh following the simulation of stent-graft deployment. The study focuses on TAA, presenting two clinical cases as illustrative examples of the framework application, which consists of three main steps: patient-specific simulation of the stent-graft deployment by structural FEA (Auricchio et al., 2013), creation of CFD-suitable domain with FEA outcomes based on signed distance functions (Osher and Fedkiw, 2001) and CFD analysis to compute post-TEVAR hemodynamics (Auricchio et al., 2014). Moreover, for one of the two clinical cases, a comparison of the predicted hemodynamics with the actual one computed using real post-operative images is presented.
5.2.3 Materials and Methods

Figure 5.5 illustrates the main steps of the proposed framework: 1) realistic simulation of stent-graft deployment; 2) creation of CFD analysis-suitable domain; 3) CFD simulations.

**STEP 1: Realistic simulation of stent-graft deployment**

The first step consists on the patient-specific structural analysis of the TEVAR implant, which combines all the different sub-steps depicted in Figure 5.5-step 1: a) medical image processing; b) stent-graft modelling; c) simulation of stent-graft deployment.

**Clinical cases and medical image processing** As illustrative examples of the clinical use of the proposed framework, we refer in the following to two patients, who were admitted to IRCCS Policlinico San Donato (San Donato Milanese, Milan, Italy) with episodes of chest pain. In both cases, contrast enhanced multislice CT was acquired on a Siemens SOMATOM Definition AS scanner (Siemens Medical Solutions, Erlangen, Germany), with a slice thickness of 1mm, a reconstruction matrix of 512 × 512 pixels, and a final resolution of 0.8mm × 0.8mm × 1mm.

Patient 1 (P1) presented a saccular aneurysm having a maximum diameter of 55 mm just below the aortic arch, whereas Patient 2 (P2) had a maximum diameter of 40mm in the same position. The length of the proximal landing zone is 24mm and 18mm for P1 and P2, respectively. The arch inner radius is 37mm and 19mm for P1 and P2, respectively. TEVAR was performed in P1 with the deployment of one stent-graft Medtronic Valiant 28-24-150 (Medtronic, Santa Rosa, CA, USA), consisting of 8 nitinol rings covering a polyester skirt to limit blood flow into the sac plus a proximal uncovered ring to improve stability without
occluding the LCCA (El-Sayed and Ramlawi, 2011). A post-operative CT confirmed the correct placement of the prosthesis and the absence of neither migration nor endoleak. Due to the complicated morphology of P2 arch, characterised by a short proximal aneurysm neck and high arch angulation, decision to undergo TEVAR was not taken immediately, considering the case as a borderline patient not suited for TEVAR. Need of patients’ consent for using their images was waived due to the retrospective nature of the study and the use of anonymized data.

Three scans (pre-operative scan of P1, pre-operative scan of P2 and post-operative scan of P1) were segmented with VMTK as described in Chapter 2. The first two segmentations were used as starting point of the simulation framework for virtual TEVAR, while the latter was used as a reference in the comparative analysis between the virtual prediction and the actual surgical outcome.

**Stent-graft and aortic wall modeling** Following the procedure described in Auricchio et al., (2013) stent-graft models were created to define meshes suitable for structural FEA using Abaqus/Explicit v. 6.16 (Simulia, Dassault Systèmes, Providence, RI, USA). In the case of P1, the stent-graft model resembles the size of the implanted actual device, i.e., a Medtronic Valiant 28-24-150; the mesh consists of 81449 nodes which are connected by two sets of elements: one composed by 22937 linear brick elements with reduced integration (C3D8R) representing the struts and one of 76942 triangular membrane elements (M3D3) representing the fabric coverage. In case of P2, who did not undergo surgery, we hypothesized to implant a Medtronic Valiant 26-26-100 stent-graft, sized by the analysis of the diameter of the proximal neck and aneurysm extension. The mesh of the stent-graft model consisted of 66698 nodes, 19759 brick elements and 60361 membrane elements. Struts were made of Nitinol whereas the fabric was made of woven polyester adopting the material properties reported in Kleinstreuer et al., (2008).

Following a preliminary analysis aimed at evaluating the impact of rigid-wall hypothesis on the final stent-graft configuration after the deployment, we consider the aorta as a rigid surface resembling its pre-operative lumen \(^2\). Moreover, in order to reduce the computational cost of the simulation, we performed a surface remeshing, using the corresponding VMTK module, to minimize the number of elements and describe the surface without losing geometrical accuracy; the remeshed triangular surface was then imported in Abaqus. Final aortic model consists in a mesh of 6926 nodes connected by 13698 triangular elements (type R3D3) and 3470 nodes connected with 6396 elements for patient P1 and P2, respectively.

\(^2\)Rigid vs. deformable wall analysis is reported later in this section
5.2. Virtual Endografting as a Predictor of Endovascular Intervention

**Virtual stent-graft deployment** Set-up of the input file for the structural FEA was supported by an in-house developed Python script allowing the user to select the given stent-graft model and the proximal landing point within the diseased vessel. The selection of the landing point in case of P1 is based on the actual post-operative images, while in case of P2 the choice was based on surgeon’s advice supported based on visual inspection of the pre-operative surface reconstruction. Numerical analysis of stent-graft deployment in the aortic model is a non-linear problem involving large deformations and contact; Abaqus/Explicit was used as finite element solver. To avoid spurious inertial effects, all the simulations are run under quasi-stati regime: the ratio of kinetic energy (ALLKE) to internal energy (AL-LIE) is monitored along the whole simulation to be below the threshold of 10% following the recommendations of the software manual. The steps of the deployment for the case of patient P1 are depicted in Figure 5.6: following the approach proposed by Auricchio et al., (2013), the stent-graft is first crimped by a catheter and curved from a straight position to the vessel centerline; in this step, the catheter and the struts of the prosthesis have a frictionless contact interaction. Once the stent is in place, a uniform enlargement of the catheter surface along its length allows the stent-graft re-expansion to simulate its deployment. To do so, a contact pair between the stent-graft struts and the luminal surface of the artery is activated. All the simulations were run on a multicore Intel Xeon E5-4620-2.20 GHz processor.

![Figure 5.6: Successive steps of the virtual deployment procedure in P1. A: the landing point is selected from surgeon’s choice. B and C: stent-graft is simultaneously crimped and bent to match the vessel centerline. D: the catheter is enlarged until the prosthesis contacts the inner vessel wall.](image)

To assess the quality of the virtually created geometry, the portions of the aorta where the stent-graft was placed were compared between the real post-operative reconstruction and the virtual one in P1. Both surfaces were clipped and the prosthesis surface was then
registered with the iterative closest point algorithm (Zhang, 1994). Once the geometries were superposed, point-wise distances were calculated between each of the points of the surface and a colormap created to illustrate the differences using the corresponding VMTK modules.

The post-deployment configuration of the stent-graft fabric, resulting from the numerical analysis, is then exported in stereolithographic format as an input for the second step of the framework described in the following.

**STEP 2: creation of CFD analysis-suitable domain**

CFD analyses require the definition of a suitable mesh describing the fluid-domain. Meshing vessel-like geometries is sometimes a cumbersome operation, specially if the shape of the artery can not be straightforwardly associated to a conforming, cylinder-like geometry as in our cases and in most of the actual clinical cases of TEVAR (Patterson et al., 2010). In fact, the fluid-domain is now bounded partially by the native aortic lumen, partially by the stent-graft and potentially by both of them in case of prosthesis malapposition. Boundaries are obviously not known a priori in the case of a predictive simulation of a stent-graft implant; for this reason, the structural analysis of the deployment, as described in the previous section, serves as input of this second step of the framework (see Figure 5.5, step 2).

**Cylinder mapping on the stent-graft**  As a preliminary stage of the construction of a CFD analysis-suitable domain from the structural apposition results, we worked with classical CAD functions and perform a mapping procedure in order to obtain a smooth description of the implanted device much easier to manipulate in subsequent steps, which may be potentially even very detailed. A generic surface can be described adopting a NURBS representation as follows:

\[
J(\xi, \eta) = \frac{\sum_{i=1}^{n} \sum_{j=1}^{m} N_{i,p}(\xi) M_{j,q}(\eta) B_{i,j} W_{ij}}{\sum_{i=1}^{n} \sum_{j=1}^{m} N_{i,p}(\xi) M_{j,q}(\eta) W_{ij}} \tag{5.2}
\]

where \(N_{i,p}(\xi)\) and \(M_{j,q}(\eta)\) are B-spline basis functions of order \(p\) and \(q\) respectively, while \(n\) and \(m\) are the number of control points in the orthogonal directions and \(W_{ij}\) are proper weights.

Following Morganti et al., (2015) the idea is to start from a simple primitive NURBS geometry resembling the shape to be mapped: in our case, a cylinder-like shape is swept along the centerline of the implanted device (see Figure 5.7, A). Then, keeping fixed the number of control points \(n\) and \(m\), the B-spline functions \(N_{i,p}(\xi)\) and \(M_{j,q}(\eta)\) and the weights of the
primitive geometry, the mapping procedure consists in finding the optimal position of the control points $B_{i,j}$, in a least square sense, such that the distance between the target surface and the mapped one are minimized. The target surface (i.e., the implanted prosthesis) is evaluated at a set of $n_s$ sampling points (with $n_s > n \cdot m$) as depicted in Figure 5.7, B. Increasing the number of control points ($n$ and $m$) of the primitive geometry through simple refinement procedures (Cottrell, Hughes, and Bazilevs, 2009) allows a more accurate representation of the implanted device geometry. Then, the cylindrical surface representing the stent-graft is extruded along the internal normal to the surface of a quantity equal to 0.4 mm following the strut diameter and a thin volumetric annular stent was generated (see Figure 5.7, C and D).

![Figure 5.7](image_url)

**Figure 5.7**: Mapping of the stent-graft surface into a cylinder. A: primitive NURBS cylinder following the stent-graft centerline. B: original deployed geometry with its sample points. C: extrusion of the NURBS cylinder representing the skirt. D: slice from C showing the annular stent (blue) together with the final position of the skirt (green) and the struts (black). S: superior, I: inferior, R: right and L: left.
Chapter 5. Advanced Applications: study of TEVAR

**CFD mesh generation**  The creation of a single conforming surface mesh representing the volume where the blood flows after the stent-graft deployment is one of the main innovations of the present study. We used the concept of signed distance function (Osher and Fedkiw, 2001). Given a surface $S : \mathbb{R}^2 \rightarrow \mathbb{R}^3$ a signed distance function to the surface $S$ is defined as the scalar function $f_S(x) : \mathbb{R}^3 \rightarrow \mathbb{R}$ representing the distance from $x$ to the nearest point on the surface $S$, assuming negative values for $x$ inside the space bounded by the surface and positive outside. On the surface, the signed distance function assumes zero values. From the signed distance function is always possible to reconstruct the original surface extracting its zero values i.e. $S = \{x \in \mathbb{R}^3 : f_S(x) = 0\}$. We call distance image a discretization of the signed distance function over a set of voxels, i.e., each voxel of the distance image assumes the value of the signed distance function in the voxel location. Our idea is to construct two distance images with same coincident voxels, representing the annular stent and the vessel, and to appropriately merge them in order to obtain a combined distance image from which the final surface can be extracted. The two distance images were constructed with a voxel resolution of $0.4\text{mm} \times 0.4\text{mm} \times 0.4\text{mm}$ in order to have enough spacial resolution to capture the thickness of the annular stent. For the aorta, the distance image assumed the standard convention with negative values inside the aorta and positive outside as seen in Figure 5.8, A. For the stent, we inverted standard signs and the distance image was computed with positive values inside the thickness of the stent and negative outside (see Figure 5.8, B). The two images were then combined using the maximum operator in order to obtain a final image with negative values inside the lumen and positive values both outside the lumen and inside the volume of the stent (see Figure 5.8, C). As it can be seen in Figure 5.8, C, the negative values of the combined distance image represent the union of vessel and stent but are not the area we are searching for. Indeed, also the left subclavian artery, which is closed by the implant, and the aneurysmatic sac, which is excluded by the implant, assume negative values although they should be excluded from the final surface. The final surfaces were then constructed extracting the negative values from the inside of the lumen with a region growing method with a starting seed inside the lumen (Yushkevich et al., 2006). With this technique, the front proceeds as long as it bumps into a zero value on which it stops; in this way, only the regions in which the blood can flow (starting from an inside seed) are included in the final surface geometry (see Figure 5.8, D).

**STEP 3: CFD simulations**

Three CFD simulations were performed, one for each of the following cases: 1) analysis of virtual post-TEVAR for patient P1; 2) analysis of actual post-TEVAR for patient P1; 3) analysis of virtual post-TEVAR for patient P2. For the sake of simplicity, the simulations are labelled in the following as P1-virtual, P1-actual, and P2-virtual, respectively.
Meshing was performed according to the details described in Chapter 2. Mesh granularity was defined after a sensitivity analysis for velocity and pressure convergence and ranged from 1.2 to 7 million elements.

CFD simulations were also carried out as explained in Chapter 2. Time step was chosen equal to 0.75ms and 6 cycles were simulated to let both velocity and pressure converge. Average Reynolds number was 1554, 1347, 1670 for P1-virtual, P1-actual, and P2-virtual, respectively. Womersley number was 25 in all the three cases. The same inlet/outlet boundary conditions are used in all the three simulations; such conditions are derived from post-operative medical images regarding P1. In particular, post-operative PC-MRI was acquired from P1 after TEVAR using a Siemens MAGNETOM Aera scanner (Siemens Medical Solutions, Erlangen, Germany). Five oblique image slices were positioned in the mid-ascending aorta, the descending aorta at the height of the diaphragm, and in the proximal sections of the three supraortic vessels. Temporal resolution was 30 samples/beat with pixel resolution of 2.08mm × 2.08mm. Venc was chosen equal to 150 cm/s; TR/TE: 37.1/2.5ms. Flow rate from PC-MRI was imposed as boundary condition in the ascending aorta with a peak flow of 423 ml/s and a stroke volume of 83 ml assuming a flat velocity profile. Outflow boundaries consisted of 3WK tuned as described in Chapter 3.
5.2.4 Results

STEP 1: Realistic simulation of stent-graft deployment

The simulation of stent-graft deployment was successfully performed in both of the cases under investigation in an average time of 6.5 hours. As shown in Figure 5.9 - A, the simulation of stent-graft deployment in the pre-operative model of the aorta for P1 is able to capture the main aspects of the actual post-operative configuration. In fact, the simulation shows that the device membrane totally covers the left subclavian artery ostium, which is indeed excluded by the circulation, calling for a surgical bypass as part of the clinical procedure. At the same time, the simulation is also able to predict the actual position of proximal uncovered ring of the stent-graft which allows to keep the patency of the LCCA, while increasing the stability of the implant in the landing zone. Moreover, in the inner curvature of the arch, it is possible to visualise that the numerical results appropriately capture the localised kinking of the stent-graft (Figure 5.9 - B); such a stent-graft kink is also present in the distal zone of the implant.

![Figure 5.9: A. Geometrical comparison of the post-operative stent-graft configuration predicted by the structural FEA (left) and the actual one obtained by image segmentation (right). B. Zoom view at the level of in the inner curvature of the aortic arch highlighting the localised kinking of the prosthesis predicted by the simulation (left) and present also in the actual post-operative image elaboration. The results refers to the case of P1.](image)

Results of stent-graft deployment in P2, similarly to what was observed in P1, shows that the LSA was completely covered by the stent-graft fabric while the LCCA is patent. Unfortunately, the simulation revealed a non optimal apposition of the proximal part of the prosthesis to the aortic wall which is particularly remarkable in the inner curvature of the arch, immediately at the proximal neck of the aneurysm sac as highlighted by Figure 5.10.
5.2. Virtual Endografting as a Predictor of Endovascular Intervention

**Figure 5.10:** Results of the simulation of stent-graft deployment in P2. Left: final configuration of the stent-graft released in the pre-operative aortic model; Right: Zoom view of the proximal part of the endovascular implant emphasizing the bird-beak; the contour-plot of the point-wise distance between the stent-graft proximal ring and the aortic wall shows the malapposition of the device specially in the inner curvature of the aorta.

**STEP 2: creation of CFD analysis-suitable domain**

Simplification of the stent was straightforward and there is an agreement between the shape and coverage of the virtually deployed graft and the reconstructed cylinder as appreciated in Figure 5.7 - D. The quantitative comparison of the virtual post-operative lumen shape (P1-virtual) with the actual one, reconstructed from the real post-operative images (P1-actual), is reported in Figure 5.11 as pointwise distances between the the surfaces. The magnitude of such a distance ranged from 0mm to 5mm with an average of 1.31mm; the highest discrepancy is located near the distal sealing zone, in the posterior side, where the aorta tapers significantly. As previously discussed, the structural simulation has shown that P2 is an example of stent-graft malapposition suggesting a high risk of bird-beak effect. Indeed, this case presents a device protrusion inside the lumen that the proposed approach is able to capture, reconstructing at the same time a conforming surface ready for fluid simulations (see Figure 5.8 - C and D).
STEP 3: CFD simulations

Figure 5.12 depicts the magnitude of the flow velocity and the pressure distribution along the aorta for P1 at the systolic peak (20% of the cardiac cycle) for both P1-virtual and P1-actual analysis. Results on both cases show that the magnitude of the blood flow velocity is higher in the supra-aortic branches, in the inner portion of arch, and distal part of the aorta covered by the stent-graft. Velocity in those regions is higher in the virtual model, having a larger extension as well, when compared to the actual one. The maximum value computed by P1-virtual analysis in the proximal zone of the endografting is 168 cm/s whereas P1-actual indicates a value of 146 cm/s; regarding the distal endografting zone, P1-virtual indicates 185 cm/s as maximum, while in the case P1-actual the computed value is 161 cm/s. Pressure ranges from 99 to 122 mmHg in the virtual domain at the systolic peak and from 100 to 120 mmHg in the real one; a gradient is seen from the ascending to the descending aorta with sound values in both cases.

A further comparison of the computed blood flow profile between the virtual and the actual model is reported in Figure 5.13, where the contour plots of the velocity magnitude at the systolic peak in the proximal, middle, and distal cross-sectional planes normal to the stent-graft rings are depicted. In the proximal slice, velocity profiles are in both cases skewed towards the inner curvature of the arch. Due to the different shape of the predicted and the post-operative geometry, velocity peaks are on the inferior-right and inferior-left
5.2. Virtual Endografting as a Predictor of Endovascular Intervention

Figure 5.12: Volume rendering of the velocity magnitude and contour plot of the pressure resulting from P1-virtual and P1-actual. The reported values refer to the systolic peak.

parts of the aorta, respectively. At the middle plane, flow is mostly flat across the slice with an acceleration zone in the outer curvature and a small deceleration zone in the inner curvature; the latter effect is more remarkable in the CFD results of P1-actual due to the uneven profile of the lumen cross-section. Finally, the distal slice matches the recirculation zone of the distal ring and lower velocity magnitudes are seen towards the inner curvature. Acceleration has a C-like shape that surrounds the posterior part of the vessel. Obviously, a comparative analysis is limited to patient P1 because patient P2 did not undergo TEVAR.

In order to compare the hemodynamic conditions of the two clinical cases, streamlines of the velocity in the region of interest are shown in Figure 5.14. In the ascending and descending parts of both aortas, streamlines follow an organized pattern suggesting that the presence of the stent-graft does not disturb the flow neither proximally nor distally to the implant. In both cases, the LSA is excluded from the analysis because entirely covered by the stent-graft membrane, while the BCT and LCCA are characterized by high blood speed. Furthermore, velocity is significantly higher in P2 along all the aortic region covered by the stent-graft, whereas P1 only has higher velocity areas in the proximal and distal curves of the prosthesis. Flow is fairly organized inside P1 stent-graft whereas bulging in P2 creates recirculation at the inner curvature. Interestingly, vortical structures are seen on the distal landing zone of the stent-graft, with much more intensity in P2. Following the streamlines, this secondary flow seems to be originated by the portion of blood impinging the outer wall of the vessel. It worth noting that the proximal stent-graft protrusion present
Figure 5.13: Velocity at the systolic peak in different slices of the stent-graft in P1. Cutting planes corresponded to the proximal plane of the first ring, the proximal plane of the fifth ring, and the distal plane of the eighth ring. The magnitude of the velocity, normalized to its maximum value, is reported for each slice. Directions of the slice with respect to its position in the aortic lumen is indicated as well; S: superior, I: inferior, L: left, R: right, A: anterior and P: posterior.

In the case P2 is not leading to evident flow disturbance near the inner curvature of the arch.

5.2.5 Discussion

In the present study we introduce a computational framework to support the planning of TEVAR for thoracic aortic aneurysms; such a simulation tool computes the post-operative hemodynamics relying on pre-operative images, accounting also for the simulation of the stent-graft deployment. In particular, two clinical cases are discussed emphasising the flexibility of the proposed tool to tackle actual patient-specific scenarios.

The framework integrates three main steps: 1) simulation of stent-graft deployment by
5.2. Virtual Endografting as a Predictor of Endovascular Intervention

Figure 5.14: Velocity field in the predicted aortas at the systolic peak.

Figure 5.14: Velocity field in the predicted aortas at the systolic peak.

The potential use of structural FEA as a preoperative planning tool of endovascular repair has been proven by several publications, which validate the simulation outcomes comparing the numerical results with in-vitro experiments (De Bock et al., 2012) or with the actual geometry of the deployed stent-graft(s), retrieved from post-operative images. Most of these studies deal with the ascending thoracic aorta (Auricchio et al., 2013) and the abdominal aorta (Perrin et al., 2015), while the descending thoracic aorta and the arch are not extensively investigated (Altnji, Bou-Saïd, and Walter-Le Berre, 2015).

Our study fills this gap further confirming the predictive capability of this type of simulations also in the descending thoracic aorta, discussing two clinical cases of saccular aneurysm. The comparison of the stent-graft configuration after the virtual deployment correctly matches the actual shape of the prosthesis implanted in the real clinical case. In particular, the simulations were able to highlight the risk of bird-beak in P2, which was considered a borderline patient for endovascular repair due to the short proximal aneurysm neck, limiting the landing zone, and the acute arch angulation, challenging the stent-graft conformability.

We presented also an approach based on distance image method to merge the vessel and stent-graft geometries to create CFD-suitable meshes. Such a technique is the main
novelty of the present study because it allows overcoming the limitations of other simplistic approaches proposed in literature, where a direct modification of the aortic surface is performed to simulate endografting (Filipovic et al., 2011; Xiong, Choi, and Taylor, 2012; Neugebauer et al., 2016). Indeed, we achieve a description of the aorta/endograft configuration which would be difficult to obtain using simple boolean operations such as union, intersection or difference between surfaces; a feature which is particularly important when dealing with bird beaks or occluded arterial branches.

To reach our proposed goal, we transformed the stent-graft final geometry into an annular cylinder-like structure, able, if required, to follow even wrinkles and geometric details of the implanted device. This would create a much smoother geometry compatible with a fitting mesh.

The quantitative comparison of the virtual post-operative lumen and the actual one retrieved from the medical images presents differences of up to 5mm in few zones of the endograft, which may be caused by the displacement of the aorta during the surgical procedure making a perfect registration of the surfaces difficult, while the overall mean value of the absolute difference was 1.31mm which is just above the spatial resolution of the CT scan. Flow patterns resulting from the predictive analysis are in close agreement with the post-operative simulation in P1. The velocity field in the whole aortic geometry in the systolic phase is qualitatively similar, but velocity is higher in the virtually reconstructed domain; such a difference may be caused by the artefact in the post-operative CT created by the stent-graft, which may lead to an overestimation of the luminal size. Such an agreement is also confirmed when the cross-sectional flow profile within the stent-graft body is analysed.

Combining the geometries with our strategy can create a virtual surgery domain in which details such as bird beak configuration, mostly in angulated arches, can be represented in the final mesh (see for example Figure 5.8, D). Flow patterns in the virtual vessel show differences between the patients, even though they have similar morphologies. Recirculation areas observed in P2 within the body of the stent-graft might be due to the arch angulation. However, this pattern has not yet proved to be prejudicial in a long term basis. Curiously, even though P2 mesh captured correctly the kinking of the bird beak in the proximal fixation point, this does not create particular flow disturbances. Conversely, low velocity is seen in the distal fixation zone which can be explained by the diameter mismatch between the tapered aorta and the uniform endoprosthesis. Though it is not yet proven, this can be a hint on the reason for which endografts often migrate proximally rather than distally (Prasad et al., 2011). Results also underline the value of using the proposed framework to highlight and to avoid potential drawbacks of TEVAR, even if in the distal part of the stent-graft, limiting the need for secondary surgical intervention (Dumfarth et al., 2011).

The following limitations are important to be addressed when interpreting the results. In
the present study, we exploited post-operative PC-MRI data to set both the inflow rate and to calibrate the outlet boundary conditions of the CFD analysis in a patient-specific manner, despite the tool aims at predicting the post-operative hemodynamics relying ideally on the sole pre-operative data. Further developments of the present study should overcome this limitation modelling the whole systemic circulation as proposed by Balossino et al., (2009), who addressed this topic for the analysis of carotid hemodynamics describing how the peripheral arterial model should be adapted to predict hemodynamic impact of vascular surgery. Moreover, we use the same boundary conditions in all the three CFD simulations; such a limitation is leading to an overestimation of the velocity magnitude in P2. Future studies should systematically include acquisition of patient-specific flow data from medical images (Nauta et al., 2016). Although the present study tackles a real clinical problem and based on the analysis of patient-specific data, the investigation of two specific cases limits the extension of our medical conclusions to a more general scenario. Regarding the validation of the hemodynamics, a bigger cohort of patients have to be analyzed before getting the tool to the bedside. Sensitivity analysis with variations in the boundary conditions should be also performed to give further significance to the differences between the predicted and the post-operative values. Moreover, a blood flow simulation including FSI would improve the results, specially if considering both vessel and prosthesis stiffness in the model (Molony et al., 2009). Although the computational costs of the simulations proposed in the present study is still not compatible to emergency clinical requiring quick decisions, it is suitable for elective case of TEVAR or to further investigate borderline patients where the sole geometric analysis of the aorta morphology based on CTA is not enough.

In conclusion, we used structural FEA for the simulation of the prosthesis deployment integrated with CFD to predict patient-specific TEVAR hemodynamics in a realistic, post-operative model of the aorta. Considering our results, we demonstrated that stent-graft and vessel surfaces could be accurately merged for an appropriate predictive reconstruction of the fluid-domain suitable for CFD analysis. This framework can thus constitute another tool to provide information to the surgeon about borderline patients during the pre-operative planning in elective setting. As a future development, the framework will be benchmarked with a larger number of clinical cases; in particular, special attention will be payed to the impact of landing zone angulation (Marrocco-Trischitta et al., 2017) on the final stent-graft apposition.

5.2.6 Preliminary analysis on rigid vs. deformable wall models

It worth noting in this context that endovascular surgeons choose prostheses with a 10%-15% of radial oversizing to improve fixation by pushing the aorta eccentrically (Erbel et al.,
It is therefore important to analyze whether the use of a rigid vessel constitutes a significant difference both in the deployment and the fluid-domain reconstruction phases of our simulation procedure. To this aim, we have compared the outcome of deployment simulation using a rigid wall model of the aorta and a deformable one. Following the workflow discussed in the present paper, the same device used in P1 was deployed in a hyper-elastic vessel (Mooney-Rivlin form) where material properties were retrieved from the study by Prendergast et al., (2003) and 3D triangular shell with reduced integration (S3R) elements were used; the mesh consists of 6926 nodes and 13698 elements. Then, the cylinder-like structure and the fluid-domain were created for the new geometry following the procedure discussed in Section 5.2.3. The displacement of the aortic annulus, the terminal sections of the supra-aortic branches, and the distal end of the descending aorta were set to zero as boundary condition for the structural FEA analysis in the case of deformable wall. Results of the two simulations are reported in Figure 5.15, where the final configuration of the stent-graft within the aorta is shown.

![Rigid and Deformable Stent-Graft](image)

**Figure 5.15:** Configuration of the stent-graft virtually deployed in a rigid-wall model of the aorta (left) and in a deformable one (right). The results refer to the case of patient P1.

The qualitative analysis of such results already indicates a negligible difference, which has been further illustrated in Figure 5.16, where both the membrane and struts of the stent-graft computed in the two cases are respectively superimposed.

Finally, the spatial difference results to be negligible also from a quantitative point of view as shown in Figure 5.17. In the skirt, maximum distance between the results of the two approaches was 3.6mm with an average of 0.8mm. The difference is also negligible in the
5.3 TEVAR in the ascending aorta: a case study

5.3.1 Introduction

We have earlier described the benefits and complications of TEVAR. In general, the more angulated the arch, the lower the mechanical long term stability of the prosthesis (Ueda et al., 2011; Chen et al., 2014). Current guidelines recommend deploying the prosthesis with at least 2cm of healthy neck proximal to the aneurysmal sac in order to ensure a safe landing zone where the stentgraft can be correctly apposed. Accomplishing this requirement is not straightforward along the thoracic aorta. For example, if the aneurysm is located in proximity of the supraaortic arteries, one or more of them have to be surgically bypassed in order to create the appropriate 2cm healthy landing zone.

Another mechanically complicated zone for TEVAR deployment is the ascending portion of the aorta. When an aneurysm or a type A dissection is present here, open surgery for
partial/total replacement of the hemiarch is performed. Drawbacks for using and endovascular approach are evident: in the proximal side, the proximity to the aortic valve mitigates any possible landing zone for the stent wires whereas in the distal side, the supraaortic vessels may have to be bypassed so as to create an appropriate landing zone.

Furthermore, it is known that the ascending aorta is the most distensible part of the vessel and is subject to the continuous mechanical effort of the heart (Prehn et al., 2007; Lu et al., 2009). There are only few documented case studies in which TEVAR was successfully performed in the ascending aorta. Authors such as Lin et al., (2007), Senay et al., (2007) and Vaughan-Huxley et al., (2011) were among the first to report cases with good outcomes of TEVAR deployment in the ascending aorta. In all the cases, endoprostheses were not available in the market and they adapted other endovascular devices to the anatomy of each of the patients. Metcalfe et al., (2012) reported the first case in which an endovascular approach for a type A dissection was used in an acute scenario with positive clinical outcomes. Larger population studies were informed by Joyce et al., (2012) and Vallabhajosyula et al., (2015) with in-hospital and long-term success. Both studies were motivated by the difficulty, if not impossibility, of their patients to undergo open surgical repair.

Based on current success cases and the need of assessing clinical feasibility of TEVAR in the ascending aorta, computational tools can be of major help to clinicians when making the
choice of surgery and device. Many aspects of TEVAR and EVAR have been addressed by the computational mechanics community as informed earlier in this chapter but, to the best of our knowledge, stent-graft deployment simulations in the ascending aorta has only been reported, and validated, in a previous work of our group (Auricchio et al., 2013). The aim of this work is to present a computational tool that can help decision-making process by virtually placing an endograft in the ascending portion of the aorta. If computational tools succeed on making the right choice of device, the medical community will have a further decision-making instrument to pursue TEVAR in the ascending aorta.

### 5.3.2 Materials and Methods

A 72yo patient was admitted at IRCCS Policlinico San Donato with chest pain following a previous ascending aorta replacement. Contrast enhanced CT was performed as described in 5.2.3. Images confirmed a 47mm pseudoaneurysm in the ascending aorta. 3D reconstruction of the aorta from the annulus to to the diaphragm and the root of the 3 supraortic vessels was performed with VMTK. Figure 5.18 shows the patient’s aorta. The vascular surgeon rejected the possibility of an open-chest surgery due to the overall condition of the patient.

#### Device selection

Three devices with various dimensions and materials were tested. The first one was a Cook CMD TBE (device A herein) with three stainless steel rings and a polyester (PET) skirt of a length of 60mm. The second tested endograft was a Cook CMD ZTLP (device B) with three Nitinol rings plus an extra proximal ring to improve fixation. Again the skirt was made of PET and the total covered length was 70mm. The third prosthesis was a CMD ZTLP (device C) similar to the former with a further ring added for distal fixation and a covered area of 75mm. Material properties for Nitinol and PET were reproduced according to Kleinstreuer et al., (2008) whereas stainless steel was characterized as in Demanget et al., (2013). Figure 5.19 shows the three CAD models of the devices in their undeployed state.

A finite element mesh was created for each of the prostheses as described in 5.2.3. Table 5.6 shows the element configuration in each case.

<table>
<thead>
<tr>
<th>Stent-graft</th>
<th># of nodes</th>
<th># of membrane elements</th>
<th># of brick elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>96740</td>
<td>99280</td>
<td>28080</td>
</tr>
<tr>
<td>B</td>
<td>118874</td>
<td>111118</td>
<td>37296</td>
</tr>
<tr>
<td>C</td>
<td>156520</td>
<td>137060</td>
<td>51534</td>
</tr>
</tbody>
</table>

**Table 5.6:** Finite element components of the three devices.
FIGURE 5.18: Aorta showing a pseudoaneurysm enlargement in the ascending section. Top: sagittal CT slice, bottom: 3D reconstruction.

Endograft deployment

The virtual deployment of the stent-grafts was performed within a rigid wall vessel according to the procedure described in 5.2.3. For the prostheses A and B, the expansion phase was
uniform along the whole length of the device. This means that all the zones of the catheter were radially expanded simultaneously.

In the case of C, five different strategies were used for the expansion of the catheter to account for the mechanical impact of the sequence. With the vicinity of the aortic valve, proximally, and the supraaortic vessels, distally, the deployment sequence is of utmost importance since it conditions the overall fixation of the device and thus particular accuracy is needed. Deployments were made: by uniformly expanding the catheter or uniform, with a distal to proximal expansion or backward, with a proximal to distal expansion forward, starting by the central ring and propagating to the sides center to sides and finally reproducing a ring expansion resembling the multi-stage deployment of commercially available delivery systems, herein vendor. The latter sequence is shown in Figure 5.20.

Figure 5.21 depicts the intermediate release step of all the deployment strategies.

Distance comparison

In order to account for the impact of the different deployment strategies, the average and maximum pointwise distances between the position of the struts were compared among the 5 deployment procedures in prosthesis C with VMTK. This choice was made since there was no baseline or gold standard to be used as a reference.
5.3.3 Results

Figure 5.22, shows the final positioning of the three prostheses after the deployment.
5.3. TEVAR in the ascending aorta: a case study

In order to assess the proximity of the fabric coverage to the vessel wall, Figure 5.23 shows slices normal to the most proximal and distal planes of the skirt for each endograft.

Figure 5.24 is an example of the surface distance quantification between the Uniform and the Vendor strategies used for prosthesis C.

Table 5.7 reports the mean and max distances within the struts of the 5 deployment methods used only for stentgraft C.
Chapter 5. Advanced Applications: study of TEVAR

5.3.3 Discussion

Ascending aortic pathologies are complicated to approach with TEVAR due to the anatomical difficulties that this zone of the aorta represents. Even though many cases have been reported about successful outcomes of endografting procedures, as in the recent review of Muetterties, Menon, and Wheatley, (2017), the technique is not yet consolidated. In this study, we showed a computational tool that can predict the positioning of an enoprosthesis and assess the geometrical characteristics which will conclude in an optimal deployment in a patient-specific scheme.

![Figure 5.24: 3D representation of the wires in the Uniform deployment and the unsigned distance to the Vendor strategy.](image)

<table>
<thead>
<tr>
<th>Uniform</th>
<th>Backward</th>
<th>Forward</th>
<th>Center to sides</th>
<th>Vendor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.10/4.9</td>
<td>0.36/2.6</td>
<td>0.37/1.8</td>
<td>0.95/3.2</td>
</tr>
<tr>
<td>Backward</td>
<td>NA</td>
<td>1.18/8.6</td>
<td>0.98/4.9</td>
<td>1.28/6.8</td>
</tr>
<tr>
<td>Forward</td>
<td>NA</td>
<td>NA</td>
<td>0.36/2.7</td>
<td>0.92/4.6</td>
</tr>
<tr>
<td>Center to sides</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.77/3.2</td>
</tr>
</tbody>
</table>

Table 5.7: Distances among the struts in the different deployment techniques, average/maximum in mm.

Finally, in order to ensure that simulations were performed in a quasi static regime (see 5.2.3), Figure 5.25
During the course of this research, production of ascending aortic endografts by the companies seemed underestimated due to the heterogeneity of geometries and lack of population studies that guarantee stability of the prosthesis and treatment success. If results prove to be concludent, further knowledge would be available to produce off-the-shelf devices with more confidence or even a new product adjusting for some of the most common cases.

From the results of the three endograft deployment in their final position, we can see...
that device A lacks an appropriate apposition to the wall both in the proximal and distal sites. Even though the length of the device should be enough if the aneurysm would be in another part of the aorta, it fails to cover the aneurysmatic region appropriately due to the angulation of the arch. A bird beak configuration is seen in the distal ring. When compared to the rest of the prosthesis, this behaviour is also assumed to be caused by the Stainless Steel which is more rigid than Nitinol. The second device, prosthesis B, was another model suggested by a company to treat this case. The proximal ring was added in order to improve proximal stability in the proximity of the aortic valve leaflets without disturbing its opening. The presence of this extra ring improved proximal apposition as shown in Figure 5.23. The choice of increasing the length of the covered region by 10mm in comparison with device A should have improved the distal apposition as well, however this was not completely achieved. Based on the results from the two earlier devices, we designed prosthesis C by extending further the covered area and adding another ring distally in order to improve fixation in the vicinity of the BCT without covering the supraortic branches. In this case, the aneurysm is completely covered and both proximal and distal sealing have considerably improved.

The other goal of this study was to prove if different deployment sequences would have an impact on the final positioning of the endograft. As mentioned in the earlier paragraph, the extreme angulation of the ascending hemiarch makes deployment complicated. We ranged from an uniform expansion, which is computationally the easiest and most intuitive to sequential patterns of different complexity such as backward, forward and centre to sides which cover firstly the distal, proximal and central zones of the aneurysm respectively. The sequence used in commercial devices was also evaluated to test its impact on the final apposition. Results from Table 5.7 show that mean differences were at most above 1mm whereas considerable maximum displacements were mostly found the proximal side of the first two rings (see Figure 5.24). The lack of a reference technique makes us impossible to conclude which of them is the best one to use in the patient as far as the overall apposition of the endoprosthesis is appropriate. Intuitively, forward and vendor strategies could be the easiest to apply in a clinical setting.

Some limitations of the work should be recognized when analysing the results. Firstly, a better standard for assessing the quality of the apposition should be adopted. We currently base our conclusions on simple inspection of the different slices of the stent-graft. Then, to have a better appraisal of the results and the subsequent validation, the same deployments should be made in-vitro.

Based on the positive results of our experience we can then conclude that the use of these computational techniques, which nowadays are available in the research community, can give endovascular surgeons a tool to choose their device and predict complications in the endovascular treatment of the ascending aorta. On the other hand, successful simulations
might encourage companies to develop ad-hoc products for these pathologies, if not in a next future, on the shelf prosthesis.

5.4 Conclusion

Given the positive results of these three projects developed in close collaboration with vascular surgeons, we can conclude from this chapter that FEA and CFD can strongly help the clinical decision making process when planning TEVAR.
Chapter 6

Conclusions and future directions

6.1 Conclusions

The biggest effort of the present thesis has been done for pushing already available computational technologies towards the bedside, facilitating their use in clinical practise. With this concept in mind, three main goals have been achieved during the PhD program:

- Improve the collaboration between engineers and physicians, making them comfortable in working within a bioengineering environment. This first goal should not be underestimated since interactions with clinicians are usually very complex due to huge differences in the methodologies, approached and even in the terminology and technical language. Through periodic (often monthly) meetings and frequent discussions, we succeeded in achieving the goal, on one side, of making them capable of interpreting simulation results and, on the other side, of improving engineers knowledge on disease aetiology, possible evolutions and therapeutic strategies.

- Fit computational times of FEA both for solids and fluids to the needs of clinical practise. Aortic CFD is nothing but simple and by becoming familiar with all its details, we were able to adapt the methodology for each project. Performing simulations seems like a systematic procedure, however each of the projects in which we worked required a different quantity to be retrieved from the numerical analysis. We successfully adapted the meshes, boundary conditions and post-processing options to the medical needs and further worked in an High Performance Computing environment so as to reduce computational times to a few hours. If all the projects are put together, more than 50 patients underwent CFD, something not seen yet in literature.

- Propose a new simulation framework that integrates different, well known, computational tools. We further succeeded on creating the ingredients that would integrate more complex computational methods so as to make the whole biomedical pipelines
easier to use. A clear example of this is the Virtual Endografting framework discussed in Chapter 5, where FEA for solids and CFD were already consolidated technologies that, up to date, were unlinked to solve a concrete medical question. By programming a simple interface for choosing the endoprosthesis, a fast simulation with Abaqus suite, a robust stent-vessel integration method and a quick, application-oriented, CFD simulation, we translated biomedical tools to the bedside.

In the following, specific conclusions are drawn for each presented chapter. In Chapter 2 we started with a background on the medical conditions (aortic disease) that support the project, highlighting the work motivations based on a real clinical need. Then, all the ingredients needed to perform numerical CFD simulations were exposed with a strong focus on aortic blood flow by referring only to tools made for this purpose. The goal was to make the reader familiar with the set of dedicated instruments and the usual complications that are found when performing hemodynamic simulations in the aorta. Even though it is important to know the origin of the numerical methods behind the tools in order to understand how they work, a simple yet robust methodology was exposed. We can then conclude that the second chapter succeeded on transmitting the origin, methods and tools necessary for a correct approach to CFD in the human aorta.

Chapter 3 constituted the main novelty of this work which intended to answer one of the longest standing doubts on vascular CFD: the choice and tuning of the boundary conditions. Most of the other constituents of numerical analysis in this field have been tested, validated and consolidated in the biomedical community such as reliable image reconstruction, discretization of Navier-Stokes equations, blood rheology modelling and powerful numerical methods. However, choosing the right boundary conditions seem far to be a solved issue for researchers and is still being extensively investigated. A systematic and robust approach has not been proposed yet. Our method stems from the experience gained by collaborating with radiologists and surgeons where we learnt that complete data needed for the numerical solution are not always, or strictly speaking never, present. Sometimes this is due to the invasiveness of the study whereas, other times it becomes too time-consuming. The minimization approach for finding the 3WK parameters acknowledges its flaws in terms of precision, but more importantly, it is flexible enough to accommodate available data. At this point, we can conclude that the BC tuning method fills the missing gap in order to perform CFD simulations in a big cohort of patients, each of them having heterogeneous boundary data.

Once a rigorous methodology including reliable boundary conditions was proposed for the simulation of blood flow in pathological vessels, it was applied within three projects, as
explained in Chapter 4. The first one was iCardioCloud, a database of imaging and CFD data on thoracic vascular disease. As patients were enrolled, imaging became immediately available in our servers without previous interaction of an engineer. We consider this the first milestone on making a cloud-oriented, engineering project, simple for physicians. Being patients and diseases very heterogeneous, this gave us the opportunity of testing and refining all the ingredients of the simulations (such as meshing, CFD parameter tuning, etc.) aiming at making the procedure systematic and robust. Thanks to this acquired experience we reached a database close to 20 simulated patients. On the other end, doctors can use post-processed and ready-to-watch images and reconstructions, as well as videos representing the hemodynamics that do not require further elaborations.

The second project, in collaboration with Dr. Alexey Kamenskiy from University of Nebraska - Medical Center, also exploited the capabilities of the developed systematic approach to CFD analysis. In this case, the goal was to track the evolution of atherogenic hemodynamics (in particular TAWSS and OSI) with ageing by analysing nine representative aortas from cohorts ranging from 5 to 100 year old. Meshing was straightforward and tuning BC based on very little information, such as the age and geometrical parameters. CFD simulations involved the use of a large number of cores, since they required very fine meshes to (i) resolve the velocity field both in wide (central) and narrow (peripheral) vessels and (ii) achieve mesh independence in the quantification of TAWSS. Results statistically satisfied the hypothesis suggesting that morphological changes with ageing switch hemodynamics from atheroprotective to atherogenic. TAWSS decreased with ageing and flow became more oscillatory, with a few exceptions among cohorts which are natural when analysing human samples. The work is still in progress and to the date, we are trying to correlate hemodynamic results with calcification burden.

The third project, in collaboration with Cardiocentro Ticino (Lugano, Switzerland) focused on a simpler application of CFD, aimed at predicting particle splitting within an aorta phantom. Simulations were validated against an in-vitro counterpart with the goal of estimating direction of emboli when performing TAVI and test methodologies for embodeviation. Computational simulations did not match our preliminary in-vitro analyses, which suggests that further tuning needs to be done in both sides. Furthermore, as an alternative to ad-hoc designed commercial devices, we proposed to inject saline solution from the right subclavian artery at a certain rate that would avoid emboli to go to the brain circulation. In this case, with the subsequent steps, CFD will allow us to test the flow threshold needed in patient-specific analysis to avoid stroke in surgery planning.

More advanced applications of computational tools for vascular disease were approached in Chapter 5, with a special focus on TEVAR and its possible complications. We first applied the developed framework for CFD simulations in the thoracic aorta for simulating
blood flow in 15 healthy subjects. These were divided in three equal groups having different arch angulation with the aim of identifying the Displacement Forces in each landing zone for TEVAR. The rationale, based on a previous article that measured proximal landing zone angulation, was that more angulated arches yield more hostile landing zones. Results confirmed our hypothesis that hemodynamics are influenced by arch angulation and this created particularly adverse biomechanical conditions in certain types of arch. To the date, results are being validated in eight aneurysmatic patients.

In Chapter 5 we also presented a complete framework for TEVAR planning, starting from the virtual deployment of an endograft within a patient-specific aortic model by means of FEA. The key development of this framework was to merge in a reliable and robust, yet computationally simple way, the 3D vessel with the virtually deployed stent-graft. We first improved the state-of-art of structural simulations of TEVAR intervention making the already existing procedure much more automatic: the operator now simply has to select the landing point in any vessel and choose the desired prosthesis from a predefined library, while model construction step, simulation strategy definition and analysis are all automatic procedures. From the structural simulation outcomes, the CFD domain (taking into account the patient-specific vessel and the implanted device) is obtained and discretized in two steps: the surface of the stent-graft is converted into a cylinder-like structure needed to build a conforming 3D tetrahedral mesh; then a distance-image technique is implemented for merging the vessel and the cylinder-like prosthesis representation. Finally, a validation step was carried out with the post-operative simulation of one of the analysed patients. We also tested the framework in a patient with a borderline morphology in terms of angulation and healthy neck length to undergo TEVAR. Simulation results confirmed the expected bird beak configuration as a result of the hostile morphology. With these results available, we can conclude that our proposed framework succeeded in both deploying an endoprosthesis in a reliable, flexible and computationally cheap way and also post-operative CFD was well represented.

Finally, the last part of Chapter 5, we evaluated another TEVAR environment where endoprostheses are not currently a first-line treatment, the region of implementation being the ascending aorta. This work was born from the need vascular surgeons to operate a pseudoaneurysm just distal to the annulus in a patient not suitable for open surgery. We then proposed to deploy three different stent-grafts by a trial and error approach. The first two devices were suggested by a vendor dedicated to this particular cases, whereas the third one was proposed by us after carefully analysing the particular morphological characteristics of the patient. Due to the proximity to the aortic valve and the obvious differences in length between the inner and outer curvature of the ascending arch, we further tested different deployment strategies by enlarging the catheter surrounding the rings with various opening sequences. Even though it is still a work in progress, results showed that the last device had
improved proximal and distal apposition to the vessel wall. Given the results, we could
gladly confirm that FEA for the simulation of endovascular surgery in the ascending aorta
could help on selecting the right prosthesis even in the case in which it has to be constructed
ad-hoc.

Considering all the results and discussions, we can successfully conclude that new tools
for Moving Computational Tools for Aortic Disease from the Bench to the Bedsidewere
constructed and now we have more available, easy-to-use and robust computational tools
for the evaluation, diagnosis and treatment of thoracic aortic diseases.

6.2 Future directions

We are currently working on bringing new and improved technologies in all the steps of
the work we have already done. Most of the directions proposed in this section were born
by analysing current literature on the topic and see other state-of-the-art methods on aortic
CFD.

4D-MRI A technology created in the last few years, the 4-dimensional Phase Contrast
MRI, has been battling the use of CFD in the medical environment. In short, this new MRI
sequence allows the operator to retrieve the velocity field of the blood inside a region of
interest (which can be the entire aorta) along a cardiac cycle. This means than NSE are not
to be solved any more by tedious computations and, instead, the MRI workstation retrieves
the velocity and pressure fields directly. The recent article by Stalder et al., (2011) exposed
the pros and cons of each methodology and finally concluded that the combination of both
could be the best approach for having a fast and reliable representation of blood flow. In
our work, we are currently giving the first steps on processing 4D-MRI images and evalu-
ating how to introduce its results into CFD for TEVAR. As an example, we are evaluating
the role of stent-graft artefact into reconstructing the flow inside the aorta and also using
through-planes as input for our boundary conditions (with the previous PC-MRI technique
the operator had to specify a priori the through plane where he wanted to measure flow,
whereas now it is done a posteriori).

4D-CT Another device that can give a new insight into CFD simulations is the 4D CT
scanner. This device adds to the regular CT the registration of the aortic anatomy in many
steps along the cardiac cycle. Such a study lets us reconstruct the 3D surface and volume
meshes in many instants of the beat. By doing so, we can build a CT-driven FSI simulation
in which neither coupling equations of the fluid and the structure nor the mechanics of the
vessel have to be solved. The same rigid vessel approach would be used by updating the position of the nodes in every iteration. Currently, this work has been performed by some of our collaborators with promising results in carotid anatomies, whereas the main issue to be solved for translating the method to the aorta are the big deformations that it undergoes.

**LES** Large Eddy Simulation is a technique used frequently in aerospace engineering when simulating flow with high Reynolds numbers (usually above 10000). This technique does not resolve all the scales of the fluid and a coarser mesh can be used (see Wilcox et al., 1998). In the medical environment, more particular for acute aortic syndromes, Reynolds number in diseased patients usually rises up to 6000 or 7000 in the worst case scenarios. Stabilization is made by adding numerical viscosity. However, in the case of the aortic dissection, Reynolds can climb up to 14000 in the entry/exit tears, making the simulation unstable under any means. For this, Bertagna, Quaini, and Veneziani, (2016) created a CFD algorithm based on a deconvolution filter that was later validated in a benchmark suitable with cardiovascular simulations. To the date, we are improving tuning the last details of the code in order to simulate blood flow in dissected patients.

**Computational time** We mentioned many times that a low computational time is a must when dealing with the medical environment. The finite element method, used by the library lifeV has intrinsic limitations not discussed in this thesis. However, many updates on the library can be done in order to improve its performance. Some of them include further vectorization of the code, the use of TPetra matrices and other preconditioner tools by Trilinos and time adaptivity.

**User interfaces and merging other databases** We have already created a friendly environment in which physicians can upload images and then download processed data from CFD. However, a more powerful user interface is missing. We are evaluating the possibility of merging other databases from projects that have a similar approach within cloud-computing in medicine, such as the i2b2 database (Murphy et al., 2010).
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