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Mathematical Modelling of Thrombus Formation in Type B Aortic Dissection

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February 13, 2018

Claudia Menichini

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Abstract

Type B aortic dissection is a critical clinical emergency caused by the rupture of the inner wall of the aorta. The formation of a tear allows blood to flow into the aortic wall layers, leading to the formation of a second blood-filled region known as the “false lumen”. This disease compromises blood supplies to organs in the abdomen and can lead to complications such as aortic aneurysm, rupture or malperfusion syndromes, resulting in a high mortality risk.

Although Type B aortic dissections are generally associated with high in-hospital survival, post-discharge prognosis is poor and highly variable. Significant predictors for long term outcomes include the formation and extent of thrombosis in the false lumen. Partial false lumen thrombosis has been identified as a significant predictor for late complications due to increased false lumen pressure and hence a high risk for aneurysm growth and rupture. On the other hand, improved outcomes are associated with complete false lumen thrombosis, which can be achieved through endovascular repair. If it was possible to predict which patients would develop false lumen thrombosis and to what extent and how to improve the chances for complete thrombosis, treatments could be significantly improved.

The main purpose of this thesis is to develop a computationally efficient approach to predict thrombus formation in patients affected by Type B aortic dissection. A hemodynamics-based computational model has been developed, which employs shear rates, fluid residence time, and platelet distribution to evaluate the likelihood for thrombosis and to simulate the growth of thrombus and its effects on blood flow over time. The computational approach has been applied to idealised and patient-specific geometries to (i) assess the accuracy of model predictions, and (ii) identify geometric features that favour false lumen thrombosis. Finally, data acquired as part of the ADSORB trial have been used to further validate the model and to identify potential predictors of true and false lumen volume changes. It has been demonstrated that the model is capable of predicting which patients are most likely to develop thrombosis of the false lumen and to what extent, for both medically treated patients and those following TEVAR. This information can potentially help clinicians to select the most appropriate treatment or surgical strategy for individual patients.

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List of Symbols and Abbreviations

AD	Aortic dissection
TL	True lumen
FL	False lumen
BMT	Best medical therapy
$TEVAR$	Thoracic endovascular repair
$SINE$	Stent graft-induced new entry
CT	Computed tomography
MRI	Magnetic resonance imaging
$TAWSS$	Time-averaged shear stress
OSI	Oscillatory shear index
ρ	Blood density
$\mathbf{u}$	Blood velocity
p	Pressure
μ	Blood viscosity
H_t	Hematocrit
RT	Residence time
RRT	Relative residence time
D_{RT}	Self-diffusivity of blood
RP	Resting platelets
AP	Activated platelets
D_p	Diffusivity of platelets
D_{pt}	Thermal diffusivity of platelets
$\dot{\gamma}$	Shear rate
C	Coagulant
D_{ceff}	Effective coagulant diffusivity
BP	Bound platelets

ϕ	Switching coefficients
BP_t	Bound platelets threshold
C_t	Coagulant threshold
RRT_t	Relative residence time threshold
$\phi\dot{\gamma}$	Shear-rate switching coefficient
$\dot{\gamma}_t$	Shear-rate threshold
$\dot{\gamma}_t$	Momentum source term
$3 - EW$	3-Element Windkessel model
R_t	Total resistance
R_c	Characteristic impedance
R_p	Peripheral resistance
C	Vessel compliance
τ	Time constant
c	Pulse-wave velocity
BFS	Backward facing step
TF	Tissue factor
TB	Thrombin
PT	Prothrombin
X_a	Factor X_a
V_a	Factor V_a
$X_a - V_a$	Complex $X_a - V_a$
AT	Anti-thrombin
$INACT$	Inactivated product
PT	Proximal tear
MT	Middle tear
DT	Distal tear
ϵ	Clot porosity
PAS	Platelet activation state

Introduction

“On the 25th of October he [King George II] rose as usual at six, and drank his chocolate; for all his actions were invariably methodic. A quarter after seven he went into a little closet. His German valet de chambre in waiting heard a noise, and running in, found the King dead on the floor. Nichols was directed to open and embalm the royal body. What he found (and meticulously described) was the first clear account of the condition we now know (after Laennec) as aortic dissection (AD): ...the pericardium was found distended with a quantity of coagulated blood, nearly a pint...; the whole heart was so compressed as to prevent any blood contained in the veins from being forced into the auricles; therefore the ventricles were found absolutely void of blood...; and in the trunk of the aorta we found a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed under its external coat and formed an elevated ecchymosis. The King passed away at Kensington Palace while straining on the toilet. His death was caused by cardiac tamponade from an acute dissection of the ascending aorta that ruptured into the pericardial sac. He had reigned for 33 years. Such was the well-documented beginning of the storied chronicle of AD, the most lethal and most frequent of all aortic catastrophes.”

The text cited above presented by Criado [1] reports one of the first written testimonies of aortic dissection, dated back to the 1760 [2]. Aortic dissection is a critical medical condition caused by the rupture of the inner wall of the aorta. This event leads to the formation of a tear which allows blood to flow between the inner and outer layers of the aortic wall in the so called “false lumen” (Fig. 1.1). This aortic catastrophe affects 3-4 people per 100,000 per year [3] and compromises the normal function of the whole circulatory system, possibly causing severe complications such as rupture, enlarging aneurysm, aortic insufficiency, or malperfusion syndromes [4, 5]. The mortality rate associated with aortic dissection is high, and it increases by 1-2% per hour in early stages after symptom onset [6], with a ten-year survival rate ranging between 30%

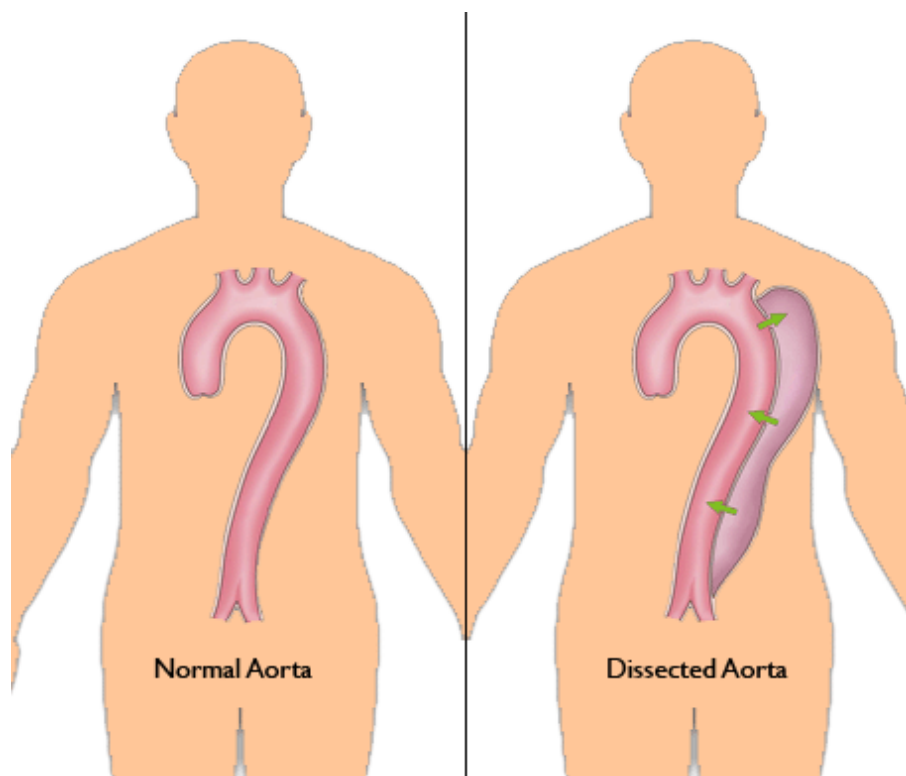


Figure 1.1: “Normal aorta and dissected aorta”. Available at: <http://www.iradonline.org> [7].

to 60% for patients discharged from the hospital [3]. Urgent surgical intervention is necessary when the entry tear is located in the ascending aorta (Stanford Type A dissection), as more complications can arise from this specific morphology. Medical treatments or endovascular repairs are typically adopted when the entry tear is situated in the descending aorta (Type B dissections), depending on the level of complication of the patient.

Geometric features and hemodynamic parameters such as flow patterns, wall shear stress (WSS), and pressure distribution have been widely recognised to affect the formation and advancement of aortic dissection. Extensive computational and experimental studies have been performed in order to improve our understanding of this disease and to predict its evolution [8, 9, 10]. The influence of geometric parameters, such as tear configuration, position, and number, aortic diameter, true lumen/false lumen radius ratio on the progression of aortic dissection has been analysed in different studies [11, 5, 12]. For both medically and endovascularly treated patients, outcomes have been found to be affected by the degree of thrombosis developed in the false lumen. Patients with partial thrombosis of the false lumen have exhibited a higher mortality risk as compared to those with a patent false lumen, and complete thrombosis has been shown to have beneficial effects

on patients' recovery as it promotes with re-absorption of the dissected area [13, 5]. However, the dynamic process leading to thrombus formation is still not well understood, and it is not possible to predict which patients will develop false lumen thrombosis and to what extent.

1.1 Research Objectives and Thesis Outline

The main purpose of this thesis is to develop a computationally efficient approach to predict thrombus formation and potential complications in patients affected by Type B aortic dissection. Several studies have been found in the literature to predict thrombosis in different circumstances, however, most of these applications are limited to simplified geometries and neglect the effects of thrombus growth on fluid flow due to high computational costs. To overcome these limitations, a hemodynamics-based model was developed in order to improve our understanding of the mechanisms involved in the development and progression of aortic dissection. The computational approach proposed has been applied to patient-specific geometries to predict which patients are most likely to develop thrombosis of the false lumen and to what extent, and the risk for complications such as enlargement and development of stent-induced new entry tears (SINE). This information could potentially help clinicians to define guidelines for selecting the optimal treatment strategy for a given patient.

In the next chapter an overview of the clinical features of aortic dissection, classification, diagnosis, and treatments is given. The chapter also presents a review of the applications of Computational Fluid Dynamics (CFD) to the study of aortic dissection. Also included are the relationship between thrombosis and dissection and previous mathematical models found in the literature to predict blood clotting. Chapter 3 provides an overview of the numerical procedures and mathematical models used in this thesis to simulate thrombus formation, including the hemodynamic-based model developed for the predictions of false lumen thrombosis in aortic dissection. In Chapter 4, the model is first validated against experimental data in a backward facing step geometry, then thrombus predictions and computational costs are compared with those of a kinetics-based model. This is followed by the application of the model to idealised dissection geometries in order to evaluate the effect of geometric features on thrombus growth (Chapter 4). Following the application to idealised dissection models, the model is further validated in patient-specific geometries by comparing predictions with actual clinical outcomes, and these results are presented in Chapter 5 and

Chapter 6. The methodology presented in Chapter 3 and validated in Chapters 5 and 6 is extended to more complex patient-specific geometries in Chapter 7, where anatomical data analyses were carried out in order to identify the main features associated with changes in false and true lumen volume. Chapter 8 presents a pilot study on the prediction of stent-induced complications such as the formation of new tears. Finally, conclusions and future directions are provided in Chapter 9.

Literature Review

2.1 Background on the Cardiovascular System

The circulatory system has a vital role in sustaining human life, as it is responsible for providing oxygen and nutrients to the cells and for removing waste products and CO_2 . Two major elements compose the circulatory system: the cardiovascular system, responsible for circulating blood to the major organs and tissues, and the lymphatic system, which removes toxins and wastes from the body.

The cardiovascular system consists of the heart, blood vessels, and blood. The heart is a muscular organ which pumps blood into two separate circuits, the pulmonary circulation and the systemic circulation. The pumping system is sustained by the periodic contraction and relaxation of the cardiac muscle, an involuntary striated muscle which represents the main component of the heart, together with connective tissue. A double-walled sac called the pericardium encloses the human heart, and the main blood vessels branch off this sac. The left and right side of the heart fulfill different functions: while the left side is responsible for the systemic circulation and pumps oxygenated blood and nutrients to the main organs, the right side regulates pulmonary circulation and blood oxygenation. Each of the two sides is composed of two parts, an atrium, where blood enters, and a ventricle, from which blood is pumped into blood vessels.

Blood flow within the cardiovascular system is driven by a pressure gradient generated by the periodic contractions of the cardiac muscle. In normal resting conditions the human heart beats approximately 60 to 80 times per minute, and the duration of a heartbeat defines a complete cardiac cycle. During this period, the pressure inside the arteries varies between a highest value defined as peak systolic pressure, and a minimum value identified as diastolic pressure. Normal ranges in healthy individuals are between 60-80 *mmHg* in diastole and 90-120 *mmHg* in systole.

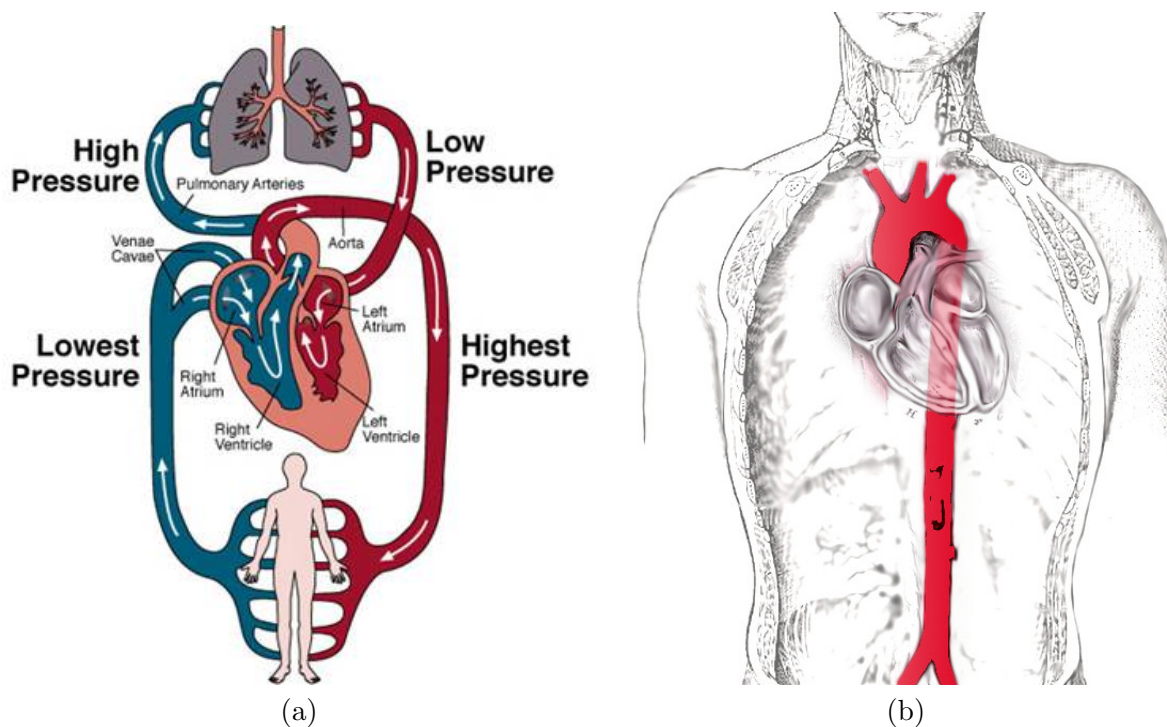


Figure 2.1: (a) Schematic diagram of the cardiovascular system [14]. (b) The aorta. Available at: <http://www.iradonline.org> [7].

At the same time, the volume of blood ejected into the arteries varies during the different phases of a cardiac cycle, and the velocity magnitude ranges from very low values close to zero to a maximum velocity of up to 1.5 m/s in a normal aorta. There is usually a phase shift between the flow and pressure waves due to the viscoelastic nature of blood and the compliant nature of vessel walls.

2.1.1 Blood Vessels and The Aorta

Blood and nutrients are transported to organs and tissues through a complex network of blood vessels composed of arteries, veins, and capillaries. Arteries are responsible for carrying blood away from the heart and generally carry oxygenated blood, with the exception of pulmonary and umbilical arteries. The role of the venous system is to transport blood, generally de-oxygenated, towards the heart. Once again, pulmonary and umbilical veins make an exception, as they carry oxygenated blood. Capillaries are microvessels responsible for the exchange of oxygen, nutrients, waste products, and interstitial fluids between blood and tissues. Their diameters are in the order of $5\text{-}10 \text{ }\mu\text{m}$ and are lined by thin walls which allow efficient exchange between the blood and interstitium. These microvessels are connected to arterioles and venules and provide a bridge between the arterial and venous systems.

The aorta is the largest artery, it branches off the left ventricle and extends into the abdomen until it bifurcates into the iliac arteries (Fig. 2.1). Typical classifications distinguish the thoracic aorta, the upper part which is placed in the thoracic cavity, from the abdominal aorta, which extends into the abdomen. The thoracic aorta is itself subdivided into ascending aorta, arch of aorta, and descending aorta. The aorta is responsible for providing oxygen and nutrient supplies to the entire body, except for the pulmonary circulation. Several arteries branch off the aorta; these include the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery, which start from the aortic arch and are responsible for delivering oxygenated blood to the neck and the head. The descending part of the aorta has a number of branches, which deliver oxygenated blood and nutrients to the chest and the abdomen, before bifurcating into the common iliac arteries, which supply the lower part of the body.

The aortic wall is divided into three layers (Fig. 2.2). The tunica intima is the most inner layer and is mainly composed of endothelial cells and subendothelial connective tissue which are in direct contact with blood and form a smooth surface. The middle layer is the largest part of the aortic wall and it is known as tunica media, consisting of muscles and elastic fibers, which provide elastic properties to the aortic wall, and allow the wall to stretch in response to pressure variations. The outermost layer is the adventitia and it is mainly composed of collagen-rich connective tissue, which provides structural support to the vessel wall.

The aorta can be affected by a variety of conditions and diseases. The elastic properties of the aortic wall can be compromised by the formation of atherosclerotic plaques or atheromas due to the accumulation of fatty substances such as cholesterol. Atherosclerotic plaques increase the stiffness of the walls and can cause local narrowings, thereby obstructing blood flow. The plaque rupture can cause thromboembolism, which may trigger the onset of heart attacks or strokes. The aortic walls can also dilate, narrow, or even rupture, due to pathological conditions such as aneurysms, coarctations, and dissections. While coarctations are generally related to congenital defects, aneurysms and dissections can be provoked by high blood pressure (hypertension), atherosclerosis, genetic conditions such as Marfan's syndrome, connective tissue disorders, and injuries.

2.2 Aortic Dissection

Aortic dissection (AD) is generally considered one of the most catastrophic diseases that can affect the aorta. This critical pathological condition originates from the formation of a tear in the inner-

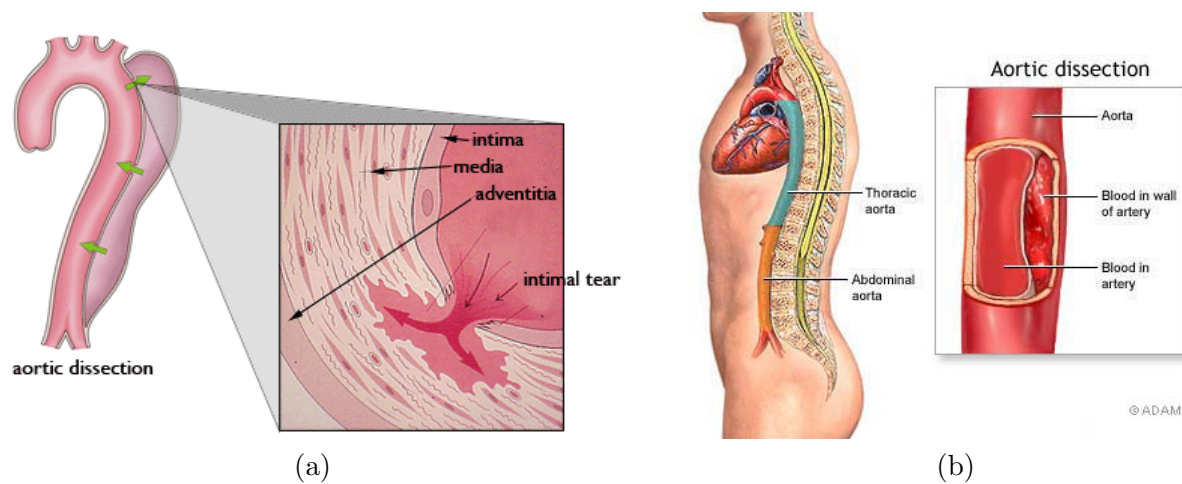


Figure 2.2: (a) Model of aortic dissection and aortic wall layers. Available at: <http://www.iradonline.org> [7] and (b) Aortic dissection as seen from sagittal plane. Available online at AorticDissection.com [15].

most layer of the aortic wall, the intima. Blood starts flowing between the wall layers driven by the aortic pressure, causing the formation of a false lumen (FL) which propagates between the intima and the media. An intimal septum, commonly defined as flap, separates the true lumen (TL) from the false lumen. This disruptive event affects the operation of the whole cardiovascular system, and can lead to severe complications such as rupture, enlarging aneurysm, aortic insufficiency, or malperfusion syndromes [4, 5].

Aortic dissection was first defined as “anvrisme dissquant” by Rene’ Laennec in 1819, but this definition proved to be not suitable for this disease, as dissection is not associated with chronic dilation, and it created the still persisting confusion between thoracic aneurysm and dissection. Development and progression of aortic dissection can be related to a number of risk factors. Hypertension is generally considered as the most common predisposing factor, followed by a history of atherosclerosis and pre-existing cardiovascular diseases, such as aneurysms and defects of the aortic valve [16]. Other possible risk factors reported by the International Registry of Acute Aortic Dissection (IRAD) [16] include prior cardiac surgery, genetic diseases such as Marfan’s, Ehlers-Danlos, and Turner’s syndromes, age, sex, as men have been found to be more prone to develop dissections, and ethnicity. Statistical analyses report incidence ranges between 3-4 per 100,000 in the United Kingdom and United States [3]. However, the annual incidence of aortic dissection is not well known, as it is strongly dependent on the occurrence of risk factors, and not all dissections are diagnosed as the disease is often detected only at necropsy [17].

The mortality rate associated with aortic dissection is high, and varies depending on anatomi-

cal features of the dissection. When the entry tear is formed in proximity of the aortic valve, the risk for complications is higher, and the patient status is considered more critical. For all dissections, the mortality risk increases by 1-2% per hour in early hours after symptom onset [6], which implies a 50% death chance in the first 48 hours if the disease is left untreated. The ten-year survival rate ranges between 30% to 60% for patients discharged from the hospital [3], but long-term survival rates are still not well known.

In the first two weeks from the onset of the symptoms, patients are generally referred as in acute conditions. After the initial acute period, the condition is classified as chronic. Multiple classification systems have been proposed to describe the different types of aortic dissection. Among these, the most commonly used are the DeBakey system and the Stanford system, which are based on anatomical features (extent of the dissection and location of the entry tear, Fig. 2.3). The DeBakey system classifies aortic dissections into three main groups, depending on the site of intimal rupture and the propagation area. Type I DeBakey patients present the first tear in the ascending aorta and a false lumen which generally propagates towards and often beyond the aortic arch. This condition is generally considered the most lethal of all as it carries a high risk of rupture, and accounts for an in-hospital mortality rate as high as 34% [16]. When the false lumen propagation zone is confined to the ascending aorta, the condition is classified as Type II DeBakey dissection. The third group, DeBakey Type III, encompasses patients presenting the entry tear in the descending aorta.

The Stanford classification system is based on similar features and subdivides aortic dissection types into two groups, Type A and Type B, depending on where the false lumen is located. Type A dissections involves the ascending aorta and can extend to the aortic arch, or distally to the descending aorta. Type B Stanford aortic dissections can involve the aortic arch or the descending aorta and do not affect the ascending aorta.

A further characterization for Type B dissections involves the distinction between complicated and uncomplicated cases. Patients showing clear evidence of malperfusion, rupture, or rapid enlargement of the aortic diameter are defined as complicated, whilst stable conditions are observed for uncomplicated patients [19].

2.2.1 Diagnosis and Imaging Techniques

The diagnosis of aortic dissection is rather challenging, as similar symptoms can be presented for a variety of medical conditions. Most patients generally report a “sudden tearing or ripping

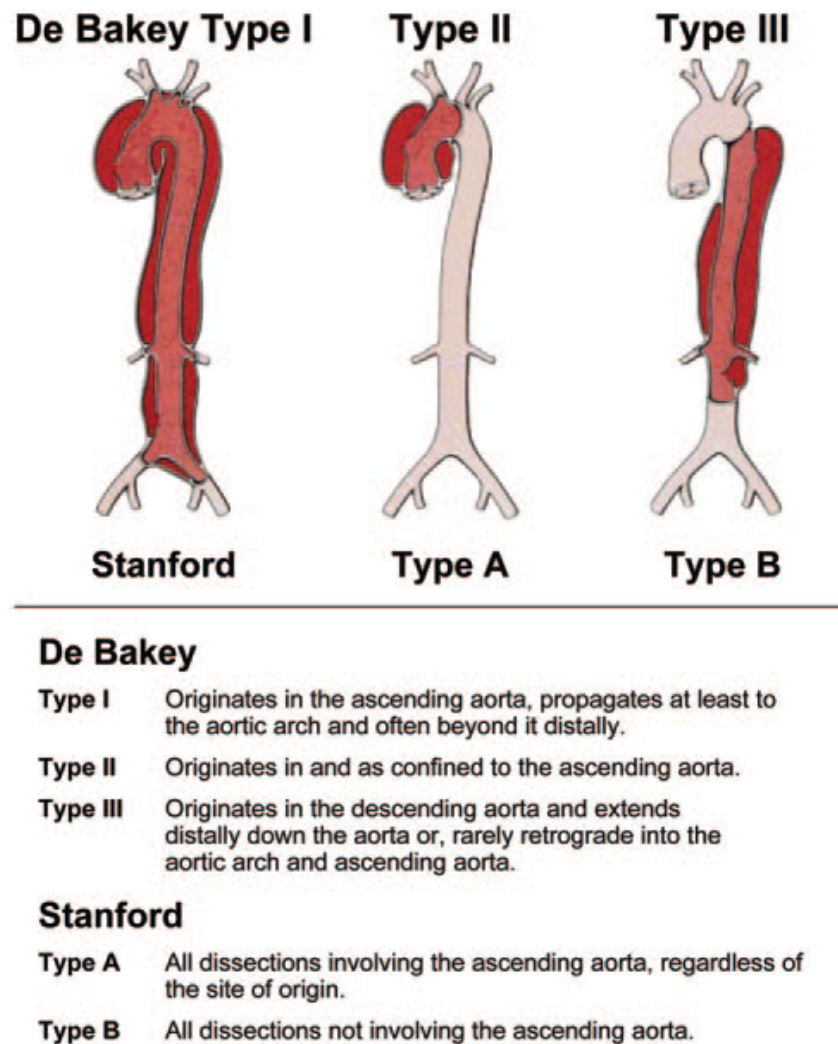


Figure 2.3: “The most common classification systems of thoracic aortic dissection: Stanford and DeBakey.”. Reproduced from Nienaber and Eagle [18] with permission from Copyright © 2003 Wolters Kluwer Health, Inc.

chest pain” which may propagate in different regions including the back and the abdomen, but different symptoms can be manifested at first medical inspection [16]. Specific tests and imaging techniques are generally required to confirm the diagnosis. The most commonly used methods involve Aortography, Echocardiogram, Computed Tomography scans, and Magnetic Resonance Imaging. The effectiveness of these diagnostic techniques is generally asserted on the basis of two statistical parameters, sensitivity and specificity. Sensitivity represents the percentage of true positives, effectively identified as such. Specificity quantifies the percentage of patients correctly identified as true negatives out of the negative signals.

- **Aortography.** Aortography consists in a x-ray examination of the aorta, and requires the placement of a catheter and the injection of a contrast agent. Retrograde aortography has been historically considered as the standard method to diagnose aortic dissection, and presents high specificity (above 95%), but lower sensitivity, below 80% [20]. This technique has recently been replaced by newly developed imaging methods, which are more rapid and less invasive and have proven greater reliability for diagnosing aortic dissection [21].

- **Echocardiography.** Echocardiography makes use of ultrasound waves to produce images of the heart. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) represent valuable methods for diagnosis, and have shown respectively a sensitivity of 78.3% and 98%, and a specificity of 83% and 95% for diagnosing dissection in the ascending aorta [22, 3]. Nonetheless, the application of echocardiography to diagnose aortic dissection is often limited by the scarce capability to visualize the descending section of the aorta, and often requires further investigation to confirm the diagnosis.

- **Computed Tomography.** Computed Tomography (CT), also referred as Computerised Axial Tomography (CAT), is a powerful imaging technique which involves the use of x-rays and allows the generation of 3D tomographies of the human body based on cross-sectional images obtained through a penetrating wave (Fig. 2.4 and Fig. 2.6a). Computed Tomography imaging has been commonly used in medical diagnosis since its introduction in 1971, and the application of CT scanning has been extended to many clinical purposes, including the diagnosis of tumors, vascular diseases and internal injuries, and heart scans.

Helical CT scanners have shown high potential in the diagnosis of many diseases, and high sensitivity (93%) and specificity (98%) have been reported for diagnosing aortic dissection [20].

- **Magnetic Resonance Imaging.** Magnetic Resonance Imaging (MRI) is a medical imaging technique based on the use of strong magnetic fields and radio waves to produce accurate scans of specific parts of the body. MRI scans are generally used to diagnose different medical conditions, to analyse the evolution of diseases, and to assess the effectiveness of medical treatments. Magnetic Resonance Angiography is a MR protocol for the examination of blood vessels.

MRI has shown high sensitivity (above 90%) and specificity (above 85%) for aortic dissection and allows doctors to accurately visualize the extent of the dissection and the location of the tears, permitting to easily classify the disease [20]. Due to time delays, lack of availability, and other complications, MR is not commonly used as the first method for dissection diagnosis [22].

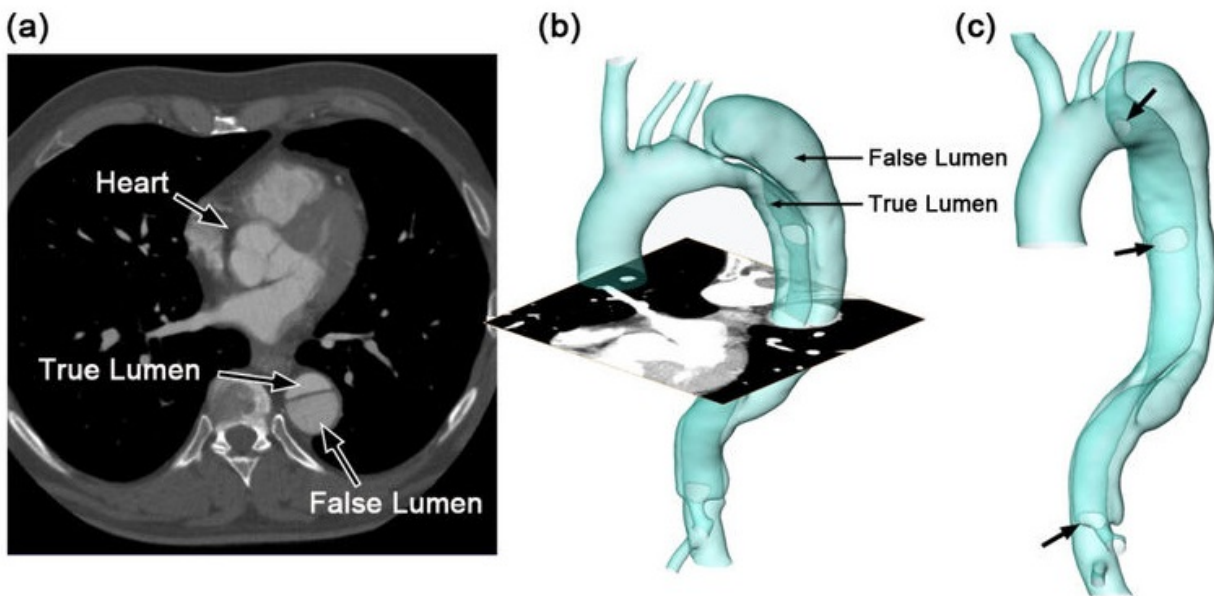


Figure 2.4: “The reconstructed surface of the aortic dissection. (a) is one axial slice of the CT scan; (b) is the reconstructed surface of the aortic dissection; (c) shows the positions of the entries along the flap (indicated by arrows)”. Reproduced from Chen et al. [23] with permission from Copyright © Chen et al. [23] licensee BioMed Central Ltd. 2013.

In addition to providing anatomical images, phase-contrast magnetic resonance imaging (PC-MRI) can be applied to measure local velocities. This is obtained by applying a gradient pulse which causes phase shifts in moving protons proportional to their velocity. PC-MRI offers a useful tool for obtaining realistic boundary conditions required for patient-specific computational modelling.

2.2.2 Medical and Surgical Treatments for Aortic Dissection

The management of aortic dissection is generally based on the anatomical features of the dissection. The selection of optimal treatment procedures is controversial [24] and the choice is generally entrusted to the surgeons’ expertise and consultation of data from international registries, surveys, and reviews [25]. For both Type A and Type B, opiates are usually administered to reduce pain and initial pharmacological therapy is generally provided in order to stabilize the patient’s conditions and prevent further propagation of the dissection [26]. Medical treatments are immediately provided for hypertensive patients to reduce the pressure on the walls and maintain systolic pressure below 120 mmHg and mean pressure below 80 mmHg [24]. An initial treatment with β -blockers can be further integrated with calcium-channel blockers, nitroglycerin, and sodium nitroprusside depending on the patient’s response to reduce the variation of pressure over a cardiac cycle (“impulse

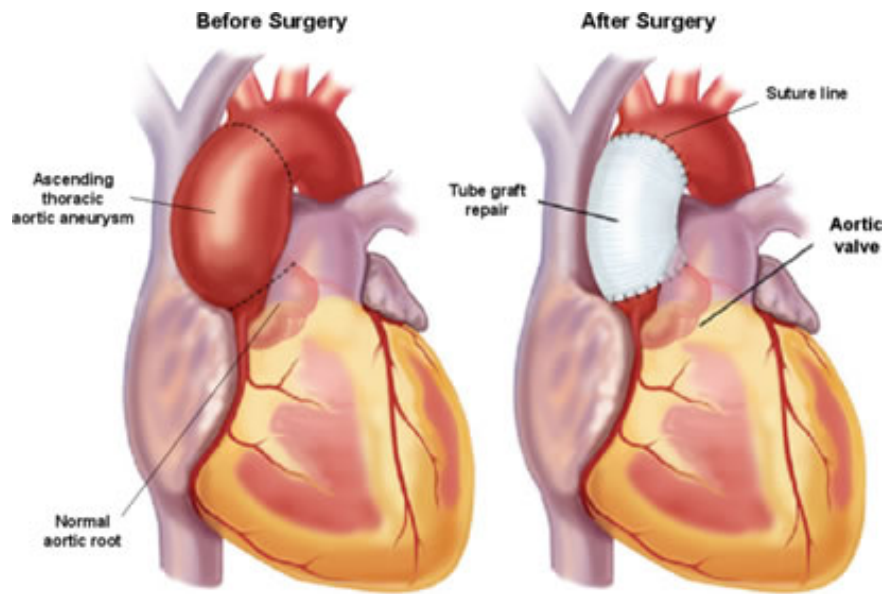


Figure 2.5: Dacron graft for surgical repair. Available online at: <http://www.iradonline.org> [7].

force”). This can be controlled by prolonging the diastolic filling time and consequently reducing the heart rate [24, 26].

Urgent surgical intervention is common practice for Stanford Type A dissection due to the high risk for complications. The rupture of the aortic wall can in fact extend to the aortic valve, coronary arteries and branches, compromising brain perfusion and leading to aortic regurgitation and cardiac failure. Aortic rupture, cardiac tamponade, stroke, visceral ischemia, and myocardial infarction are commonly reported complications for Type A dissection. The surgical treatment involves the reinforcement or replacement of the injured tract of the ascending aorta with a synthetic Dacron graft (Fig. 2.5). The possible involvement of aortic valve or coronary arteries may require replacement of the valve and reattachment of the coronary arteries. Data from the International Registry of Acute Aortic Dissection (IRAD) concerning surgical operations for Type A dissection report an in-hospital mortality of 26% [16].

Depending on the conditions of the patient and the possible outbreak of complications, medical treatments (best medical therapy or BMT), surgery, or endovascular repairs can be adopted for patients with Type B dissections. Uncomplicated patients are normally treated with antihypertensive therapies in order to regulate aortic pressure and reduce the stress on the walls. The use of thoracic endovascular aortic repair (TEVAR) has become increasingly popular in the last two decades as a promising alternative to open surgical treatments for complicated acute Type B

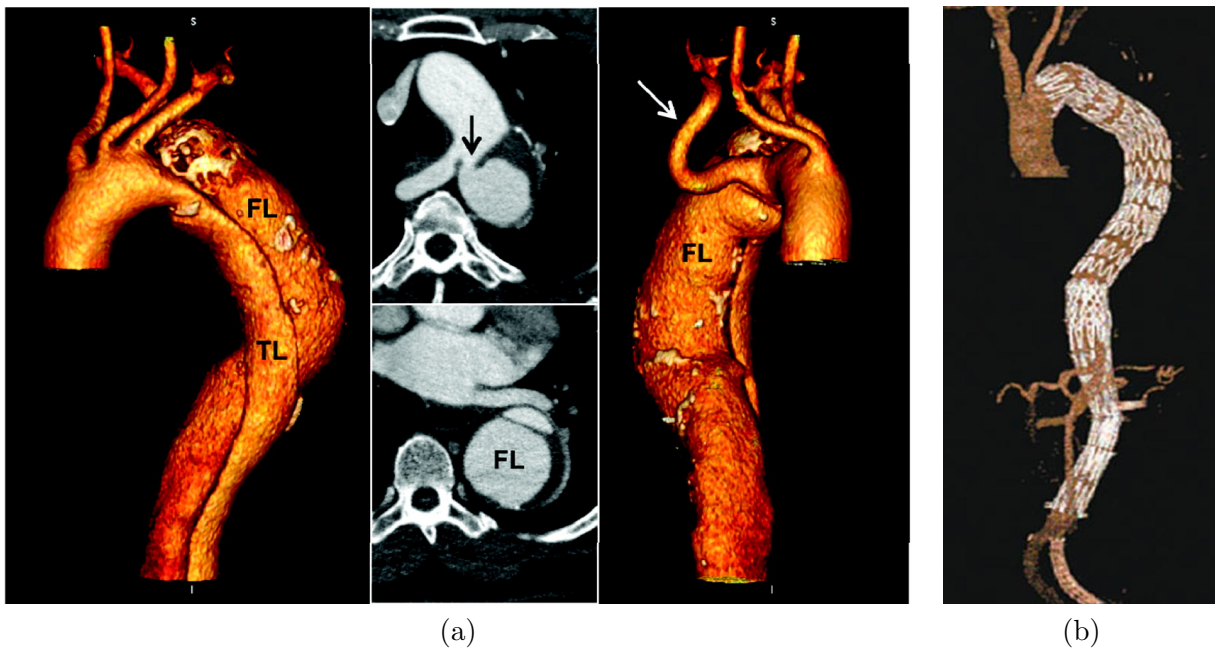


Figure 2.6: (a). “Stanford Type B aortic dissection on volume-rendered 64-slice multidetector CTA with compressed true lumen (TL) and expanded false lumen (FL). Axial slices are displayed between 3D reconstruction from 2 views.” Adapted from Nienaber et al. [27] with permission from Copyright © 2009 Wolters Kluwer Health, Inc. (b). “Example of the use of fenestrated stent grafts in the setting of chronic distal aortic dissection with side branch stent-graft in left renal artery and separate stent-graft in left common iliac artery.” Adapted from Nienaber et al. [28] with permission from Copyright © 2014 BMJ Publishing Group Ltd.

dissections [29, 30]. This minimally invasive procedure involves the placement of an endovascular stent-graft in the diseased section of the aorta (Fig 2.6b) in order to seal the entry tears, reduce pressure in the false lumen, promote remodelling of the aorta (i.e. increase TL volume and decrease FL volume), and induce complete thrombosis of the false lumen. Furthermore, recent results from two randomized trials of respectively 140 (INSTEAD trial) and 61 patients (ADSORB trial) in stable conditions selected for TEVAR have shown positive results of TEVAR for the treatment of chronic and acute uncomplicated dissections [31, 28]. The 5-year follow-up from the INSTEAD study has shown favorable aortic remodelling rates and beneficial effects of endovascular repair for the treatment of chronic dissections in the reduction of aorta-specific mortality rates and in the delay of disease progression [28]. The 1-year results from the ADSORB trial have also shown higher rates of positive aortic remodelling and false lumen thrombosis following TEVAR as compared to patients only treated medically [31], demonstrating that acute uncomplicated dissections can be treated effectively with the device used.

2.3 Computational Studies of Aortic Dissection

The evaluation of hemodynamic parameters and the analysis of morphological features and biomechanical properties of blood vessels play an important role in understanding the pathogenesis of vascular diseases. The development of Computational Fluid Dynamics (CFD) software and high performance hardware has allowed the analysis of complicated flow fields in three-dimensional domains through the use of computational simulations, providing a powerful tool for process analysis in different engineering applications. In the last few decades, the application of CFD has been extended to biomedical research to study how fluid dynamics affects the development and progression of cardiovascular diseases, such as aneurysms, dissections, and atherosclerosis, and to analyse the performance of medical devices such as stent-grafts, wall supports, and prosthetic valves. Numerical solutions of partial differential equations describing the flow field have allowed medics and engineers to capture the complex features of blood flow, providing better insight into the function of the cardiovascular system.

In the last decade, CFD models have been used to gain more insight into the development and progression of different diseases including aortic dissection. The numerical resolution of flow fields in idealized and patient-specific geometries has allowed researchers to develop a better understanding of the fluid dynamics related to this disease and analyse the distribution of key variables such as pressure and wall shear stress. Computational models have also been applied to study the likelihood for thrombus formation and the effectiveness of endovascular and surgical treatments, such as fenestrations and by-passes [32, 33].

Several authors have proposed idealized models to assess the effects of different parameters on the flow field and to quantify the forces acting on the walls, including tear size and location [32, 12], extent of dissection and tear distance [34], and number of tears [11]. Different hypothetical “phantom” models have been developed as benchmark platforms to predict possible outcomes, including tear and false lumen enlargement, collapse, thrombosis, and rupture [35, 36, 34]. These simplified geometries have generally been based on patient-specific features and are easily reproducible in lab-scale, allowing comparison and validation with experimental data, like the experimental analysis proposed by Rudenick et al. [11] to assess how tear size and configuration affect flow patterns and hemodynamics, cross-validated by the computational work of Soudah et al. [37]. On the other hand, the idealized phantoms employed in most studies present extremely simplified features which

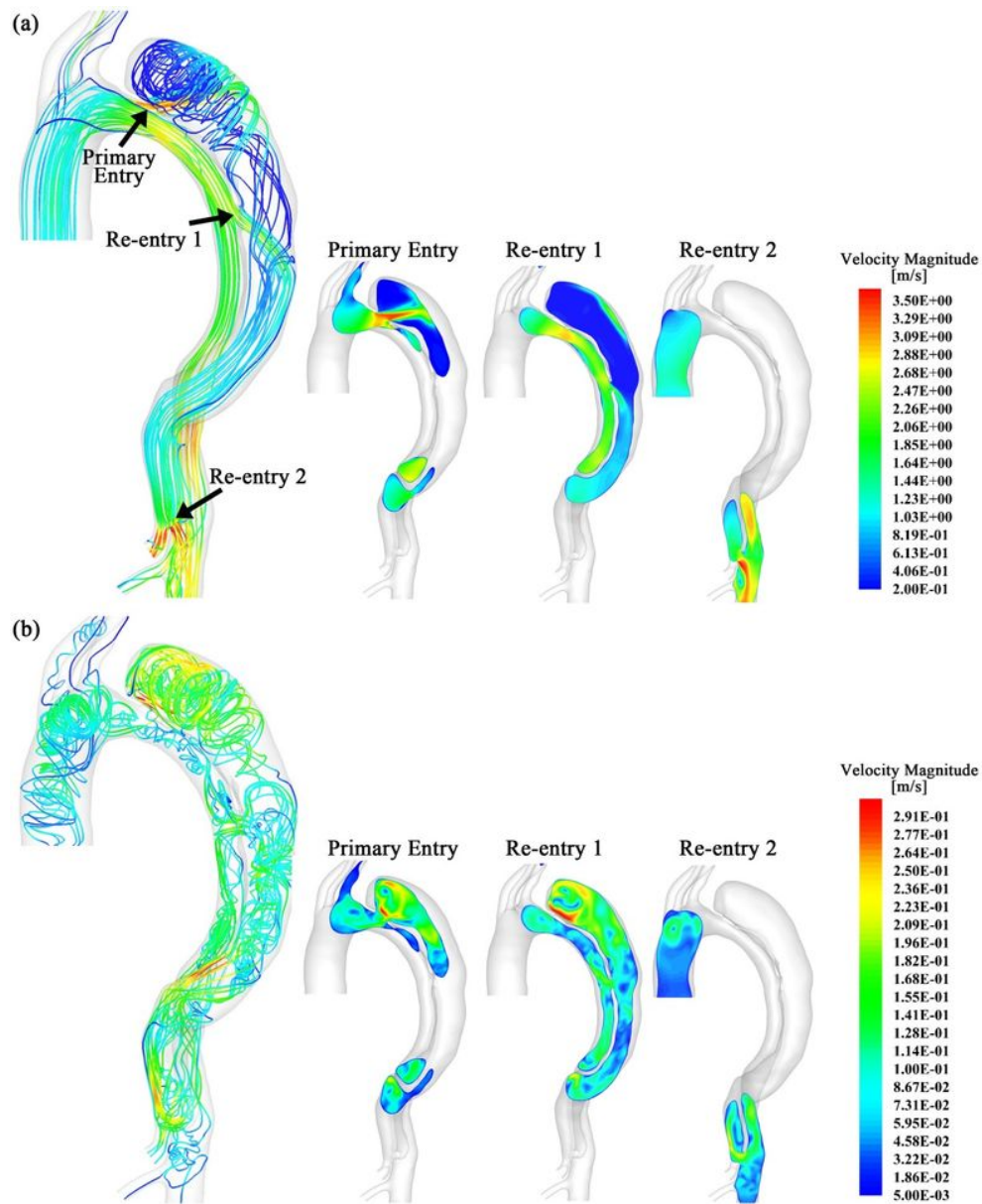


Figure 2.7: “Flow pattern within the dissected aorta. The larger pictures on the left in (a) and (b) display the flow pattern at systolic peak and in the middle of diastole, respectively, by drawing lines that are tangential to the instantaneous velocity vectors. These lines are contoured by velocity magnitude. The smaller pictures on the right show the flow distribution by drawing the velocity magnitude contour at three slices, each of which crosses the entries that connect true and false lumen. Arrows in (a) indicates the positions and numbers of those entries.” Reproduced from Chen et al. [23] with permission from Copyright © Chen et al. [23] licensee BioMed Central Ltd. 2013.

cannot fully capture the complexity of real geometries related to tortuosity and bents, which affect the flow patterns and cause disturbances and helical flow [38].

Realistic geometries have been used in several studies to gain better insight into the relation-

ship between morphological features and fluid mechanics in aortic dissection, and patient-specific geometries have been reconstructed from CT, MRI, and MRA scans [8, 39, 40, 41]. Highly disturbed flow, with secondary motion and strong recirculation in the false lumen and near the tears has been generally observed in all the computational studies (Fig. 2.7) [38]. As Tse et al. [42] reported, the complicated flow patterns and pronounced helicity observed might have an effect on the wrapping of the false lumen around the true lumen [43]. The highly disturbed flow patterns are generally accompanied by high values of local and time-averaged shear stress near the tears [39], which increase the risk for tear dilation and dysfunction of endothelial cells.

Pressure distribution is a key variable to understand the causes of collapse and rupture of false lumen, growth of the aortic diameter, and expansion of the dissected area. Non-uniform pressure distribution has been generally observed, with higher pressure in the true lumen than in the false lumen in the proximal region and inverted trend in the distal region [8, 9, 42]. The pressure difference between true and false lumen drives the propagation of the dissected zone, and it has been found to be dependent on number, size, and location of tears [12, 41], and mainly on the accumulated size of the proximal and distal connections [11].

The lack of information regarding wall properties and the complexity of the system, where each part is bounded by heterogeneous walls characterized by different thickness and biomechanical properties, has driven most authors to assume rigid wall behaviour [9]. This assumption is likely to influence the predicted pressure and shear stress distribution, as the viscoelastic behaviour of arterial walls has an effect on damping pulse pressure and would reduce the observed peaks. The numerical validation of *in vitro* phantom measurements carried out by Soudah et al. [37] highlighted significant differences in pressure distribution observed between the computational model with rigid walls and the elastic *in vitro* phantom for small tear diameters due to the compliant effect of the elastic models, which resulted in lower systolic peaks. For larger tear diameters true and false lumen pressures were equalized [11], and this reduced the differences between elastic and rigid-wall models. Similar findings highlighting the influence of wall-elasticity on FL flow and pressure were reported by Rudenick et al. [44], who analysed the impact of wall elasticity on intraluminal hemodynamics in AD through a lumped-parameter model. Fluid-structure interaction (FSI) simulations of aortic dissections are rare due to the complex geometry and unknown wall properties. Alimohammadi et al. [45] performed FSI simulations on patient-specific dissection assuming hyperelastic wall behaviour and uniform wall thickness. Their results showed that while

wall shear stress is not significantly affected by the rigid wall assumption, FSI simulations are needed to better quantify other parameters such as oscillatory shear index (OSI).

2.4 Thrombosis in Aortic Dissection

The evolution of aortic dissection introduces significant morphological changes in the aorta. The formation of intimal tears and a false lumen causes highly disturbed flow conditions, including turbulence, recirculation zones, and high variability in wall shear stress levels. All these parameters have a major influence on thrombus formation within the false lumen. In fact, the tearing of the aortic wall and the high shear stress levels detected in the proximity of tears can promote the initial activation of platelets. The formation of recirculation zones within the false lumen characterized by stasis, long residence times, and low shear stress creates an ideal environment for platelet aggregation and deposition, leading to thrombus formation on the walls. More details about pathogenesis of thrombus formation and its association with aortic dissection can be found in Sections 2.4.1 and 2.4.2.

The progression of false lumen thrombosis has been found to have a major influence on patients' survival and therapeutic outcomes. Bernard et al. [13] and Tsai et al. [46] identified false lumen patency as a key factor to predict the progression of aortic dissection and underlined the link between the evolution of aortic diameter and false lumen patency and thrombosis. The study carried out by Tsai et al. [46] highlighted the determining role of partial thrombosis in the false lumen as a warning for higher mortality risk (Fig. 2.8). The authors compared mortality rates for 201 patients with acute Type B aortic dissection, and observed the highest 3-year mortality rate (31.6%) for patients with a partially thrombosed false lumen, followed by patients with complete thrombosis (22.6%), and patent false lumen (13.7%). The follow-up study carried out by Trimarchi et al. [5] investigated the effect of false lumen thrombosis on growth rate of the aorta. A positive correlation was found by the authors between partial thrombosis and higher aortic growth, justified by the higher false lumen pressure caused by the formation of thrombi, which could possibly lead to occlusion of the distal tear thereby increasing the risk for enlargement and rupture.

On the other hand, complete thrombosis of the false lumen is generally considered as a positive sign for improved outcomes as it increases the likelihood of healing of the dissection [5, 46], and the effectiveness of endovascular and medical treatments is strongly related to successful thrombosis of the false lumen.

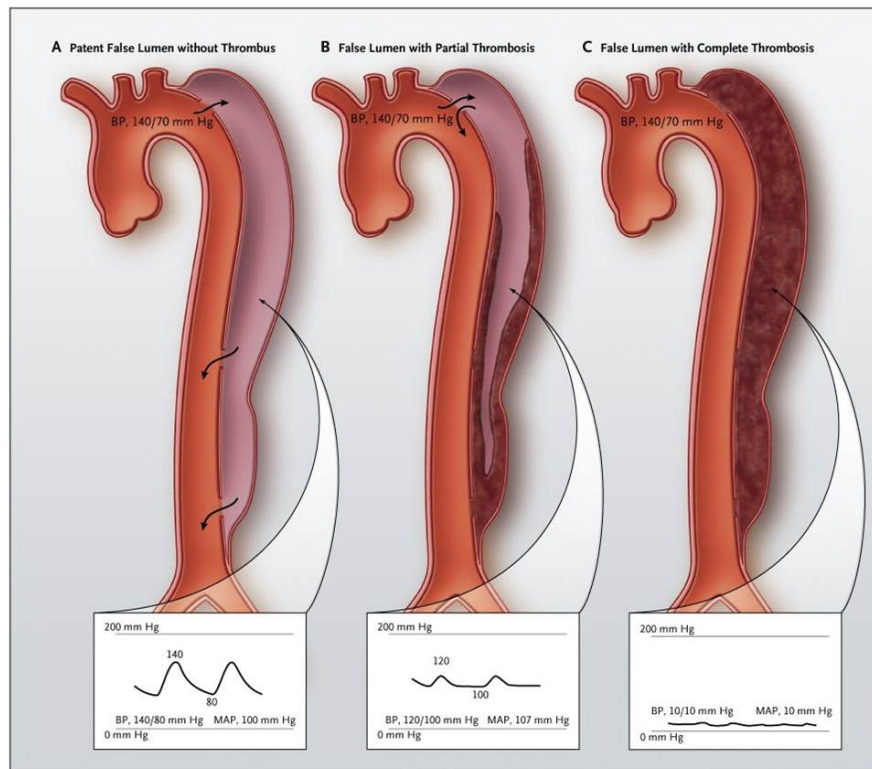


Figure 2.8: “Conceptual Model of Risk According to the Status of the False Lumen. The figure shows a proposed model of the physiological consequences of false-lumen patency or thrombosis, based on hemodynamic studies in ex vivo models and in patients with aortic dissection. Panel A shows Type B aortic dissection with patent proximal and patent distal re-entry tears in the absence of thrombus. The blood-pressure tracing shows systolic, diastolic, and mean arterial pressures in the false lumen similar to the pressures in the true lumen. Panel B shows Type B aortic dissection with a patent entry tear and partial thrombosis that occupies the inner circumference of the false lumen and obstructs the re-entry tears, forming a blind sac. The blood-pressure tracing shows diastolic and mean arterial pressures in the false lumen that exceed the pressures seen in Panel A, with identical pressures in the true lumen. Panel C shows Type B aortic dissection with a false lumen filled with thrombus and no longer communicating with the true lumen. The pressure within the false lumen is likely to be low and non-pulsatile. BP denotes blood pressure, and MAP mean arterial pressure.” Reproduced with permission from Tsai et al. [46], Copyright © 2007 Massachusetts Medical Society.

2.4.1 Hemostasis and Thrombosis

The major components of blood are plasma, the fluid part of the extracellular fluid, and formed elements, mainly red blood cells (RBCs), white blood cells (WBCs), and platelets. Platelets, or thrombocytes, play a fundamental role in the phenomenon of hemostasis, the natural mechanism through which our body stops bleeding and starts healing wounds. This inborn mechanism consists in the formation of blood clots, or thrombi, within diseased blood vessels in order to seal the wounds and promote tissue repair. These cell aggregates are mainly composed of platelets, red blood cells, and white blood cells, packaged in a cross-linked network of fibrin, a fibrous protein

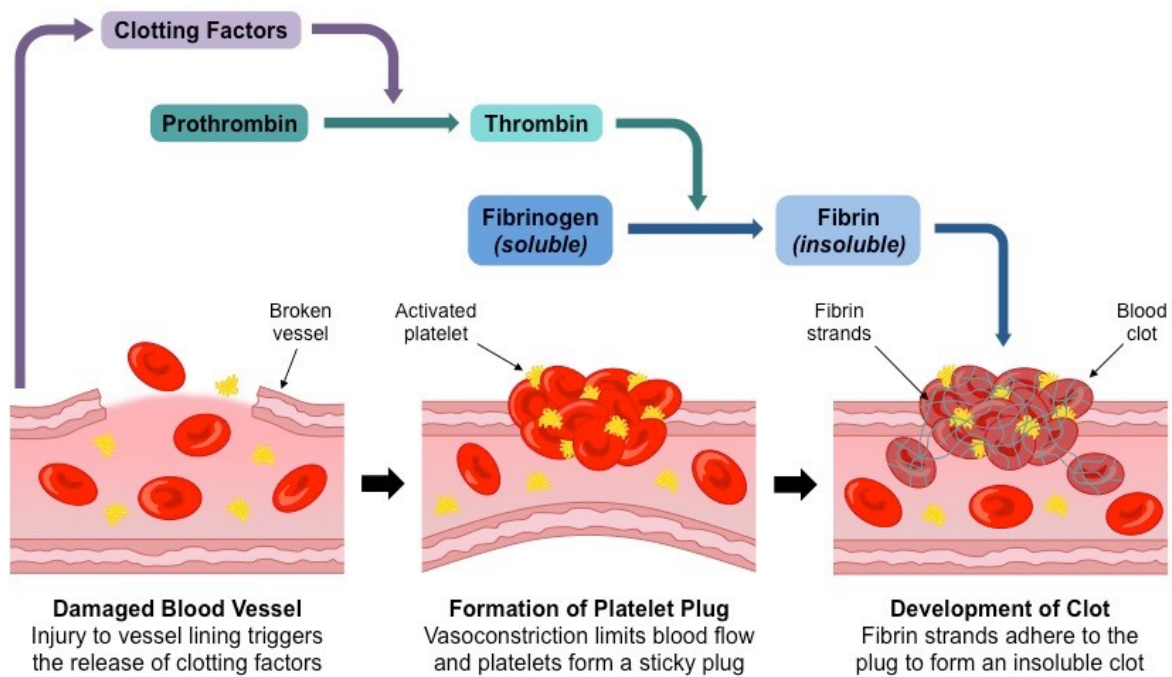


Figure 2.9: Simplified coagulation cascade. Available online at BioNinja [47].

produced from the glycoprotein fibrinogen during the coagulation process. Among all the chemical and biochemical species involved in the formation of blood clots, the enzyme thrombin plays a key role in the coagulation process. Thrombin is not only directly responsible for fibrin formation from fibrinogen, but it's also involved in the activation of platelets and other coagulation factors, and at the same time acts as an antithrombotic agent by promoting the production of inhibitors that regulate the coagulation process.

In both normal and abnormal conditions, the formation of thrombi involves a complex network of chemical and biochemical processes (Figure 2.9) coupled with transport mechanisms. During the phenomenon of hemostasis, platelets are sensitized and activated by chemical and physical agonists that promote a conformational change. Activated platelets adhere to the injured section of blood vessels and can stick together forming aggregates, and release more agonists, establishing a feed-back mechanism which promotes the activation of more platelets. The last step in the hemostatic process is the coagulation cascade, which involves complex biochemical processes that lead to the formation of blood clots. The whole mechanism can be summarised into three major phases:

- **Platelet adhesion and activation:** Thrombocytes can exist in two different forms: resting and active. In normal conditions, platelets circulate as discoidal cell fragments. In the presence

of an injury, platelets undergo a conformational change and switch from their resting to an active state, assuming a spherical shape with pseudopodia (filamentous projection of the cell cytoplasm, Fig. 2.10) in order to adhere to the damaged tissue and form a platelet plug. When platelets enter into contact with injured sections of the vascular wall, specific glycoprotein receptors interact and bind with different components of the extracellular matrix, such as von Willebrand factor (vWF) and collagen. The contact with these surface chemicals triggers the initial activation of platelets. Once this process has started, a complex chain of feedback mechanism stimulates the production of other chemicals, such as ADP, thromboxane A_2 , and thrombin, which promote further activation of platelets. Other factors can also trigger the initial activation of platelets. Among these, shear stress is considered to play an important role in abnormal thrombus formation as it can affect endothelial function and phenotype [48]. The effect of shear stress on platelets activation will be discussed in more detail in the next section.

- **Aggregation:** The release of chemical agonists triggers the activation of specific receptors, which promotes platelet-to-platelet adhesion and leads to the formation of the primary platelet plug (primary hemostasis). This platelet plug temporarily seals the injured section of the wall, reducing minor bleeding.

- **Coagulation cascade:** The coagulation process (or secondary hemostasis) leads to the production of fibrin, a non-globular protein which is responsible for the cross-linking of the platelet plug and the formation of stable clots. This complex mechanism is highly regulated and involves the action of coagulation factors and cofactors, calcium, and platelets (Fig. 2.11). Three major pathways can be identified in the coagulation process: extrinsic, intrinsic, and common pathways. The extrinsic pathway, also defined as tissue factor pathway, triggers the activation of the coagulation cascade through the action of tissue factor (coagulation factor III), a protein expressed by subendothelial cells. Tissue factor exposure promotes the activation of coagulation factors VII, VIII, IX, X, XI, and the conversion of prothrombin to thrombin ($II \rightarrow II_a$). The coagulation cascade is amplified by the intrinsic pathway, or contact activation pathway, which is initiated by collagen exposure and the conversion of factor XII to its activated form XII_a . This pathway leads to the activation of factors IX, X, XI, and finally factor II, and converges with the extrinsic pathway into the common pathway at the activation of factor X. The final step in the coagulation cascade involves the production of fibrin from fibrinogen ($I \rightarrow I_a$) promoted by the action of thrombin.

The abnormal formation of blood clots within a blood vessel can cause obstruction or in

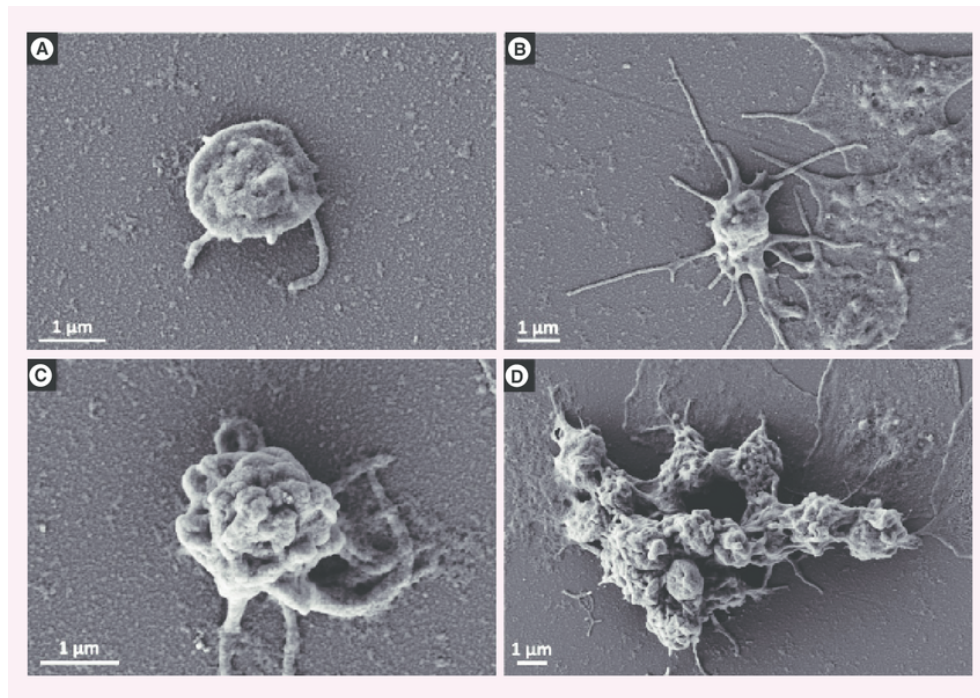


Figure 2.10: “The ultrastructural features of human platelet activation on polyvinyl chloride surface as shown by scanning electron microscopy. Platelet shape changes after activation: (A) discoid platelet with short pseudopodia; (B) platelet with long pseudopodia interacting with platelets adhering to the surface and showing a 'fried egg' structure; (C) small platelet aggregate; and (D) platelet aggregate.” Reproduced from Tomaszewski et al. [49] with permission from Copyright © 2015 Future Medicine Ltd.

extreme cases blockage of blood flow in the circulatory system. This phenomenon is defined as thrombosis, and causes reduced oxygen supplies to tissues, which can degenerate in hypoxia or anoxia, bringing cells to lactic acid production through anaerobic metabolism, and possibly leading to infarction or tissue death. The detachment of thrombi from the wall can additionally cause the formation of emboli (embolization) which can obstruct other blood vessels. If the formation of thrombi occurs in one of the coronary arteries, the reduced supply can compromise the operation of the heart, causing it to stop beating, and lead to heart attacks. Likewise, the occlusion of cerebral arteries caused by thrombi or emboli can reduce the supply of oxygen and nutrients to brain cells, possibly leading to ischemic strokes and cell death.

2.4.2 Causes of Thrombus Formation: The Virchow's Triad

Variations of local hemodynamic conditions and rheology play a major role in the formation of thrombi within the circulatory system. The factors involved in abnormal coagulation of blood can be classified into three categories, namely: variation in the constituents of blood, endothelial

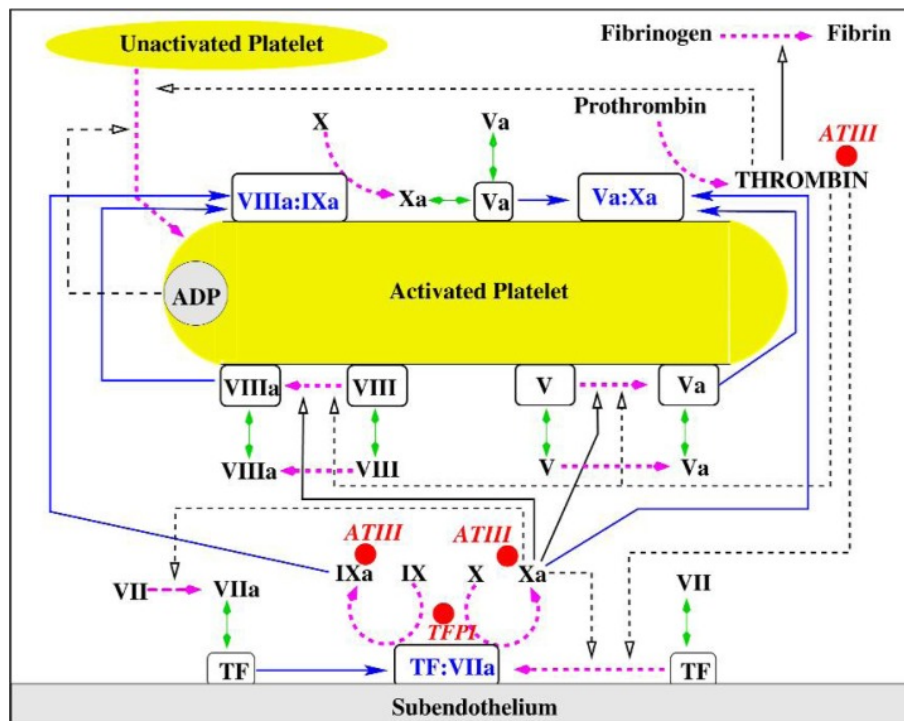


Figure 2.11: “Schematic of coagulation reactions. Dashed magenta arrows show cellular or chemical activation processes. Blue arrows indicate chemical transport in the fluid or on a surface. Green segments with two arrowheads depict binding and unbinding from a surface. Rectangular boxes indicate surface-bound species. Solid black lines with open arrows show enzyme action in a forward direction, while dashed black lines with open arrows show feedback action of enzymes. Red disks indicate chemical inhibitors.” Reproduced from Leiderman and Fogelson [50] with permission from Copyright © 2010 Oxford University Press.

injury, and altered flow conditions (stasis or turbulence). The combination of these factors is commonly defined as the Virchow’s triad, which is named after the German doctor and physician Rudolf Virchow, who extensively studied thrombosis and venous thromboembolism [51]. Each of the three elements of the Virchow’s triad can act independently or simultaneously on the formation of thrombi. As more risk factors arise, patients are more likely to develop thrombosis.

Changes in Blood Constituents

The change in blood constituents can involve both variations in rheological properties of blood and in concentration of clotting factors. Patients presenting hypercoagulable states (or thrombophilia) are exposed to an increased risk of thromboembolism due to an abnormal tendency of blood to clot. Hypercoagulability can arise from genetic or acquired disorders, including cancer, liver diseases, obesity, smoking, and birth control, and can be possibly related to increased concentrations of procoagulants (fibrinogen and Factor VII), low values of anticoagulants (like antithrombin and

protein-C), or high viscosities caused by changes in composition or local hemodynamic conditions [52].

The complex and tortuous geometry of aortic dissection will give rise to areas of flow separation and stagnation where shear rates are lower than normal physiological values, causing an increase in local viscosity, which can promote the adhesion of platelets on the vessel walls [53].

Endothelial Damage and Shear Effects

Trauma, rupture of atherosclerotic plaques, and high shear stress levels can cause for endothelial injuries and tissue factor exposure, which will stimulate immune responses, induce platelet activation, and initiate the coagulation cascade. Multiple studies have focused on understanding the effects of shear rates and shear stress on the activation of platelets [54]. These parameters act as a physical agonist on the activation of platelets, promoting morphological changes in platelets structure by applying elongational stresses [55] and at the same time affecting endothelial function and causing hemolysis of RBCs with consequent release of ADP (adenosine diphosphate), a known chemical agonist for platelet activation [56]. The action of shear stress on the activation of platelets is dependent on exposure time, as it can be clearly observed from the results collected by Hellums [57] shown in Fig. 2.12. At low shear stress levels long exposure times are required to promote platelet activation, but these values are dramatically reduced for increasing shear stress. The critical shear stress-exposure time combinations are far from the normal levels found in the cardiovascular systems, but can be caused by local disturbances and deformations related to cardiovascular pathologies. On the other hand, both Suter et al. [58] and more recently Yin et al. [59] highlighted that exposure to pulsatile shear stress produced a much stronger response and significantly higher levels of platelet activation, suggesting a positive relationship between velocity, shear rates, and thrombogenesis. In particular, Sheriff et al. [60] observed that high shear stress sensitizes platelets to further activation, with 20-fold faster activation rates in low-shear zones for platelets briefly exposed to elevated shear stress. Nesbitt et al. [61] also investigated the relationship between shear variations and thrombus growth, and showed platelet aggregation to be stimulated by shear microgradients. The authors demonstrated that adhesion preferentially occurred in low-shear regions at the downstream side of the growing clot characterized by decelerating shear, and that shear-induced aggregation appeared to be independent of local concentrations of soluble agonists.

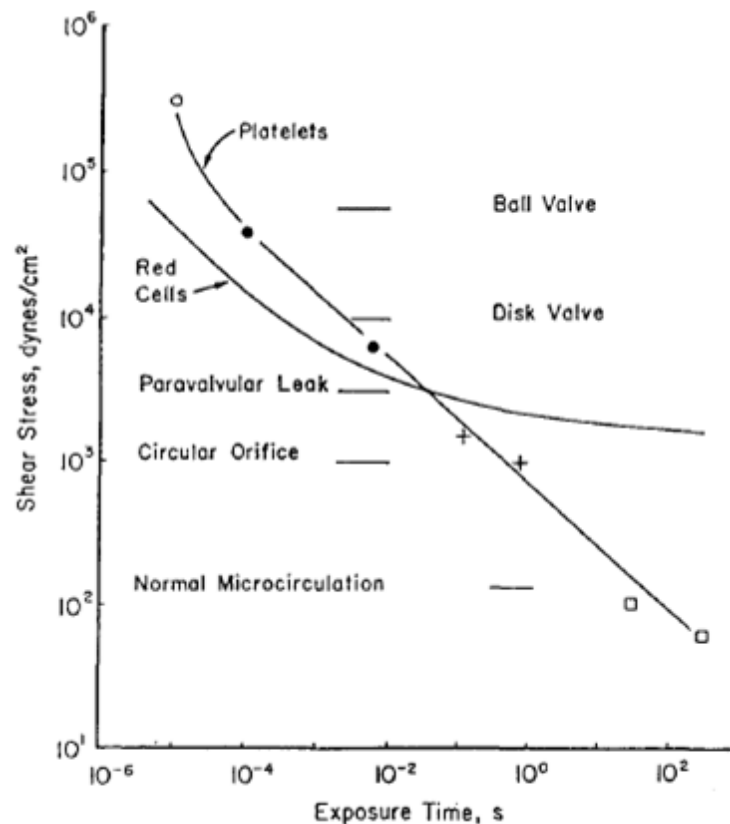


Figure 2.12: “Estimates of stress levels in cardiac valves and the normal circulation. Results are from several workers using various devices appropriate for the desired exposure.” Adapted from Hellums [57] with permission from Copyright © 1993 Springer.

Patients affected by aortic dissection are exposed to endothelial injuries in different ways. Following the intimal rupture, blood cells are likely to be in direct contact with a different and potentially thrombogenic surface between the first two wall layers and exposed to high periodical peaks of shear stress, which can potentially promote the activation of platelets. At the same time, the flow field will oppose the local aggregation of platelets and will carry the cells towards regions of stasis and recirculation, where high residence times offer favourable conditions for adhesion on the walls and aggregation.

Variation of Hemodynamic Conditions

Development of atherosclerotic plaques, aneurysms, dissections, and other diseases that can cause local changes in the geometry of blood vessels are the main causes for variations in hemodynamic conditions. Deviations of flow patterns from a well organised laminar flow may involve local areas of stasis or turbulence, which can influence thrombogenesis. The association between local

hemodynamic parameters and the risk for thrombus formation has long been studied [55, 54]. The experimental study on canine arteries performed by Stein et al. [62] clearly showed a relationship between turbulent flow and thrombus formation. As several authors have reported, turbulence has multiple effects on thrombus formation and acts by enhancing mass transfer and local mixing of coagulation factors, allowing platelets to come into close proximity of the vessel walls, and affecting endothelial cell functions [52]. On the other hand, areas of recirculation and stasis are normally associated with long residence times that permit local build-up of coagulation factors and prevent dilution. Such areas are typically exposed to low shear rates (below 100 s^{-1}). Shear rates below physiological values have been reported to stimulate atherogenic and thrombogenic phenotypes [48, 63]. Under these low shear conditions, cell-cell interactions are enhanced causing a local increase in blood viscosity, and sedimentation is promoted by the action of fibrinogen, as opposed to high shear conditions where the process becomes more dependent on VWF and fibronectin [53, 64]. The composition of thrombi formed under low shear conditions is usually rich in red blood cells and fibrin (red thrombi), unlike arterial thrombi that are generally formed near high shear regions and appear as white clots due to a high concentration of platelets.

2.5 Modelling of Thrombus Formation

Thrombus formation is a complex biological process which involves a large number of chemical and biological species, transport phenomena, and kinetic processes acting on different time scales. Different approaches based on statistical, discrete, and continuum models have been proposed in the literature in order to predict thrombosis and describe the different biochemical and physical mechanisms involved in the formation of blood clots. These models can be generally subdivided into macroscopic, microscopic, and mesoscopic. While macroscopic models tend to describe variations in macroscopic properties (rheology, changes in flow field), microscopic models are focused on changes in cellular entities and processes acting on much smaller time and spatial scales [65]. This section presents a review of the models and methods available in the literature for thrombus formation, highlighting the strengths and deficiencies of previous models. Three main categories have been identified: models based on hemodynamics, discrete and statistical approaches, and kinetics-based continuum models.

2.5.1 Models Based on Hemodynamic Parameters

Local fluid dynamics affect the formation of thrombi and their growth rates, and the shape and size of blood clots [61, 66]. Numerous experimental and computational studies have been conducted in order to examine the link between thrombus formation and local flow features. The experimental work carried out by Stein et al. [62] analysed the effect of turbulence on thrombus formation in canine femoral arteries and veins by establishing arteriovenous shunts, and showed positive correlation between Reynolds numbers and the weight of thrombus. Karino and Goldsmith [67] measured the adhesion of platelets to collagen fibers in annular vortex formed from a sudden expansion at low Reynolds numbers, and found adhesion rate and location of peaks to be dependent on geometrical features. The effects of local geometry and corresponding fluid dynamics on platelet deposition were also studied by Schoephoerster et al. [68], who examined the platelet density in idealised stenosis and aneurysms and observed maximum depositions in areas of high recirculation and reattachment. Schoephoerster et al.'s [68] study was extended by Bluestein et al. [55], who developed a computational model to analyse the corresponding fluid dynamics in laminar and turbulent conditions and introduced a level of activation parameter defined as $\Sigma\tau \times \Delta t$ to quantify the cumulative effect of shear stress variations and exposure time on platelet activation. A similar approach was proposed by Raz et al. [69], who validated numerical results with an experimental Digital Particle Image Velocimetry (DPIV) technique, and proposed an algorithm to quantify stress history by tracking lagrangian trajectories.

The relations between shear stress and platelet activation in stenotic vessels at different occlusion levels were also investigated by Bark and Ku [70], who compared the activation parameter proposed for shear history by Bluestein et al. [55] with the one proposed by Goodman et al. [71] $\tau^{2.3}t$ calculated by fitting Hellums's [57] data. A following study by Bark et al. [72] showed positive correlation between thrombus accumulation rates and wall shear rates up to 6000 s^{-1} , and measured in the throat of the stenosis higher growth rates for pathological shear rates than for physiological shear. It is interesting to notice that several studies observed deposition in the recirculation areas, while others measured higher growth rates upstream and in the throat of the stenosis. These contrasting results were thought to be attributed to differences in surface chemistry, geometry, flow conditions, and biomechanical properties of the walls [68].

Other fluid dynamics-motivated approaches include the studies of Biasetti et al. [73], who investigated the relationship between coherent vortical structures and intra-luminal thrombus forma-

tion in fusiform and saccular aneurysms using the λ_2 method [74], then integrated with convection-diffusion-reaction equations to model the coagulation cascade and inspected the distribution of chemical agonists [75], although neglecting cellular species and thrombus growth.

A hemodynamics-based shape optimization method to predict thrombus growth was proposed by Di Achille et al. [76] who showed good agreement between predicted intra-luminal thrombus formation in abdominal aortic aneurysm and *in vivo* data. The model proposed by Di Achille et al. [76] is based on two hemodynamic parameters, namely thrombus formation potential (TFP) and thrombus deposition potential (TDP). These parameters are defined as a function of oscillatory shear index (OSI), time-averaged wall shear stress (TAWSS), and accumulated shear history (PLAP). Nauta et al. [77] also adopted the PLAP indicator to evaluate the probability of thrombus formation in aortic dissection, finding that regions of high PLAP were associated with thrombosis.

The fluid dynamics-related studies presented above are capable of describing the role of fluid dynamics in thrombus formation, but neglect the complex network of biochemical mechanisms involved in the process. As a consequence, the models are not able to predict growth rates, thrombus composition, and possible embolization [78]. More comprehensive models have been proposed in the literature by coupling fluid flow with chemical processes and including transport of different species by means of continuum and Lagrangian approaches.

2.5.2 Discrete and Statistical Models

Several efforts have been made to describe platelet motion with a discrete approach. Of particular relevance is the computational model developed by Fogelson [79] and revisited by Fogelson [80], which analyses the process of thrombosis making use of two different spatial scales, a macroscopic scale for the fluid domain and a microscopic scale for cell aggregation. The model describes platelet-platelet and fluid-platelet interactions in a micro-vessel, where platelets are treated as discrete corpuscles flowing in a viscous incompressible fluid, and resting platelets are assumed to be activated by exposure to a general chemical agonist. The model was then extended by Fogelson and Guy [81] who introduced interaction with vessel walls and adhesion by adopting an immersed boundary approach.

The approach proposed by Worth Longest and Kleinstreuer [82] for platelet adhesion also relied on Lagrangian particle tracking method. Their model included convective-diffusive transport

of particles, mass, and inertia, and a near wall residence time parameter positively correlating with particle deposition in a stagnation point flow cell and a stenosis with rapid expansion.

A hybrid approach for a multiscale model was proposed by Xu et al. [83], who developed a 2D model where the macroscale dynamics of blood flow are described with a continuum approach, while the microscale processes involving particle-particle and surface-particle interactions are represented through an extended stochastic discrete cellular Potts model capable of reproducing aggregation and thrombus growth. The model initially accounted only for thrombin and fibrin generation, but was then extended to reproduce the full tissue factor pathway [84], showing acceptable agreement with experimental measurements but limited to two-dimensional simple geometries because of high computational costs.

2.5.3 Kinetics-Based Continuum Models

The main limitation of discrete and statistical models is their high computational costs, which limit the analysis to small domains and allow the simulation of a limited number of particles, much smaller than the real population. A large number of continuum models have been proposed to address this issue as they appear to be more suitable for large scale simulations. The models proposed are generally described by a set of convection-diffusion-reaction (CDR) processes expressed through a system of ordinary or partial differential equations (ODEs or PDEs) and coupled with Navier-Stokes and continuity equations to describe fluid flow, and in most cases focus only on a section of the coagulation cascade, given the large number of processes involved.

The first comprehensive model for transport, adhesion, agonist generation, and coagulation was the one presented by Sorensen et al. [78]. The model accounts for two types of platelets, resting and activated, platelet-granule-released and platelet-synthesised agonists and inhibition processes, prothrombin, thrombin, and ATIII. All the chemical species including platelets are assumed to be passively transported by the fluid, and surface mechanisms are modelled through a flux boundary condition. The diffusivity of platelets is assumed to be shear-enhanced to consider the shear-dependent diffusion-augmenting effect of RBCs on transport of platelets. The model was in agreement with previous experimental measurements, but significant discrepancies were found as the model neglected the interaction between blood flow and the species described.

A simpler model was presented by Wootton et al. [85] describing platelet flow near a stenosis. The model implemented in Fluent v4.2 only accounts for platelets, and considers convective

transport, shear-enhanced diffusion and accumulation on the walls through a first order reaction model with a surface-flux boundary condition. The large number of assumptions made, including a constant adhesion rate and neglect of chemical agonist transport, caused significant differences from experimental measurements. A similar approach was adopted by David et al. [86], who compared a constant adhesion rate with shear-dependent kinetics, and found better agreement with experimental results by taking into consideration wall shear stress.

An exhaustive model for the extrinsic pathway was presented by Kuharsky and Fogelson [87] whose system of ODEs take into account plasma-phase and surface-bound enzymes and zymogens, coagulation inhibitors, and convective and diffusive transport of resting and activated platelets by assuming the existence of a thin near-wall well mixed fluid layer whose thickness is dependent on flow. However, this assumption limited the applicability of the model to the study of small injuries, and fluid-thrombus interactions were neglected [50].

A model for the extrinsic coagulation pathway was also designed by Anand et al. [88], who introduced a viscoelastic rheological model for blood and blood clots, a shear activation mechanism, and CDR mechanisms for platelets and most chemicals involved in the coagulation process. Clots are assumed to be more than 16 times more viscous than blood and are supposed to be formed at fibrin concentrations above a given threshold, while clot dissolution takes place at low fibrin values. The model showed good agreement with experimental data, but was limited to the study of a single coagulation pathway in unidirectional flow, and assumed a sharp transition at the blood-clot interface.

The models presented above are limited to the analysis of simple geometries based on straight channels. A more complex system was analysed by Bedekar et al. [89] who applied a CDR model incorporating platelet activation, adhesion, and thrombin generation and inhibition in a patient-specific carotid artery model with two saccular aneurysms. Kinetic processes were inspired by the models proposed by Sorensen et al. [78] and Kuharsky and Fogelson [87], and a fluidics resolved approach previously introduced by Jenkins et al. [90] was used for surface reactions, based on a quasi-steady state balance of reactive and diffusive fluxes at the walls. A build up of thrombin and high surface adhesion rates were observed in the aneurysm sacs due to high residence time. The model represented the first attempt to predict thrombus formation in a clinically relevant geometry, but it lacked the ability to describe the effects of thrombus growth on fluid flow [65].

Thrombus growth causes major changes in fluid flow, and the discrepancies between previous models and experimental data highlighted the need to consider thrombus-fluid interactions to reliably describe the process. Goodman et al. [71] tried to address this major problem by developing a continuum model for thrombus formation, growth, and embolization. The model was based on a set of PDEs describing transport of chemical species and surface and near-wall reactions to predict device-induced thrombosis, and introduced a shear activation parameter calculated by fitting the results of Hellums [57] with a shear-stress/exposure-time dependent equation. Regions with high concentration of adherent platelets were identified as thrombus, described as producing activation factors, and the local viscosity was increased 100,000-fold to model the effects of growth on fluid flow. Acceptable agreement was found with experimental measurements by the authors.

Probably the most detailed continuum model developed to date for thrombus formation is the one proposed by Leiderman and Fogelson [50]. The model includes four types of platelets (mobile-unactivated, mobile-activated, bound-activated, and subendothelium-bound), accurately describes biochemical pathways involved in the coagulation cascade, and accounts for the interaction between the growing thrombus and fluid flow. Transport and chemical processes are represented through a set of partial differential equations discretised with a finite-difference method. The growth of thrombus is simulated through a negative momentum source proportional to the local concentration of platelets which permits the analysis of fluid motion inside the solid clot, treated as a porous medium.

2.6 Summary and Research Objectives

Aortic dissection is a critical medical condition affecting the aorta characterized by high mortality and morbidity risk. Development and progression of aortic dissection cause pronounced morphological changes which impact blood flow and hemodynamic parameters such as shear stress and pressure, and create local conditions which are likely to promote thrombogenesis. Previous research shows that patient outcomes are strongly dependent on the level of thrombosis in the false lumen, which increases the risk for mortality if partial, but improves the effectiveness of medical and endovascular treatments and survival chances if complete.

The growth of thrombi alters hemodynamic conditions and flow patterns, making it difficult to predict the progression of false lumen thrombosis. Although several computational models have

been proposed in the literature to predict thrombus formation, the application of such models has been mostly limited to simplified geometries and has required a number of assumptions to reduce computational costs, such as constant velocity, Newtonian behaviour of blood, and the existence of a well mixed near-wall layer where reactions take place. These assumptions limit the applicability of these models to clinically relevant studies, and, to the best of the author's knowledge, no attempts have been made prior to this work to predict the evolution of thrombosis in aortic dissection. It was therefore the interest of this PhD project to formulate a reliable computational model to predict the formation of thrombi within the false lumen and its effects on fluid flow. The application of such model on patient-specific geometries will potentially offer better insight into the evolution of aortic dissection, and might provide valuable information for patient-specific treatment planning.

Mathematical Models and Numerical Procedures[†]

The literature review presented in the previous chapter has highlighted that flow features and hemorheology play an essential role in thrombus formation in aortic dissection, motivating the use of hemodynamic parameters to identify areas of high probability for thrombogenesis. The approach proposed in this thesis is based on a combined analysis of blood flow performed by means of Computational Fluid Dynamics and transport mechanisms to model the distribution of biological and chemical species and thrombus growth.

This chapter presents the mathematical models developed in this thesis for the simulation of thrombus formation in Type B aortic dissection. First, the general governing equations for fluid flow and species transport are described. This is followed by details of a novel computational model developed for the prediction of thrombus formation in Type B aortic dissection and its effects on blood flow. Lastly, numerical methods used to solve the system are given, along with geometry reconstruction, mesh generation and boundary conditions required for numerical solution of the system of equations.

3.1 General Governing Equations

The formulation of mathematical models for problems related to transport phenomena is based on the application of conservation laws. When modelling blood flow in large arteries, blood can be assumed to be a continuum medium and it can be described through the use of macroscopic

[†]The content of this chapter is partially adapted from: *Menichini, C and Xu, XY (2016). Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications. Journal of mathematical biology, 73(5), 1205-1226. [91]*

properties: velocity, temperature, pressure, and their time derivatives. A control volume approach can be adopted to quantify the rate of change of a given variable by applying simple balances through the boundaries and within the system. This approach is based on the analysis of a small fluid element with a differential volume of dimensions $\partial x, \partial y$, and ∂z , where all the variables of interest are defined as a function of space and time. The general formulation of conservation laws in this system dictates that the rate of increase of a given variable is equal to the net flow crossing the system's boundaries plus the net amount of that variable generated. The rate of change of a generic quantity ϕ can be analysed by either tracking fluid particles (Lagrangian approach), or by analysing how the flow changes in a fixed region of space (Eulerian approach). The Eulerian method is generally preferred in engineering applications as it is easier to measure fluid properties in a given point of space rather than following fluid particles.

The mass conservation law is referred to as *continuity equation*. A mass balance around a control volume yields the following formulation:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0 \quad (3.1)$$

which is valid for both compressible and incompressible fluids. For an incompressible fluid, the time and space derivatives of the density are null, and the continuity equation is reduced to:

$$\nabla \cdot \mathbf{u} = 0 \quad (3.2)$$

The momentum equation can be derived from Newton's second law, which states that the net change in momentum is equal to the sum of the forces acting on the system. The momentum balance on a viscous, compressible, non-Newtonian fluid yields to the *Cauchy equation*:

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \nabla \cdot (\rho \mathbf{u} \mathbf{u}) = \nabla \cdot \mathbf{T} + \rho \mathbf{F} \quad (3.3)$$

where $\mathbf{T}$ represents the stress tensor and $\rho \mathbf{F}$ includes all the contributions of body forces. For Newtonian fluids, a linear relationship exists between stress and rate of deformation which permits the simplification of the equation and to express the momentum balance through the *Navier-Stokes equations*:

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \nabla \cdot (\mu \nabla \mathbf{u}) + \rho \mathbf{F} \quad (3.4)$$

where p is the static pressure, and μ is the viscosity of the fluid [92].

Blood is a multiphase medium comprising a fluid phase called plasma and a solid phase mainly composed of cellular organisms (Red Blood Cells (RBCs), White Blood Cells (WBCs), and platelets) commonly defined as formed elements. Due to its multiphase nature, blood exhibits a non-Newtonian shear-thinning behaviour, which is more pronounced at low shear rates, where blood is more viscous. The viscosity of blood is strongly dependent on plasma viscosity, hematocrit (percentage of RBCs), temperature, and RBCs deformability [93]. For small vessel diameters ($< 300 \mu\text{m}$), the multiphase nature of blood has a stronger influence on rheological properties, leading to the formation of a cell-free region near the vessel walls and a central core region with highly concentrated cells. In large vessels, when shear rates are sufficiently high and the effects of cells are negligible, blood can be reasonably assumed to behave as a Newtonian fluid [93], allowing a simplification of the biomechanical problem and reducing computational costs. Several models have been proposed to describe the non-Newtonian behaviour of blood. Among these, Casson, Carreau-Yasuda, and Quemada model are the most commonly used. All the simulations presented in this thesis account for the non-Newtonian behaviour of blood through the Quemada viscosity model [94]:

$$\mu = \mu_p \left(1 - \frac{1}{2} \frac{k_0 - k_\infty \sqrt{\dot{\gamma}/\gamma_c}}{1 + \sqrt{\dot{\gamma}/\gamma_c}} H_t \right)^{-2} \quad (3.5)$$

where μ_p is the plasma viscosity, k_0 is the maximum volume fraction for zero shear rate, k_∞ is the maximum volume fraction for infinite shear rate, γ_c is the characteristic rate of rouleaux formation/degradation and H_t is the hematocrit.

The mass conservation of a generic species i transported with the fluid can be modelled through a convection-diffusion-reaction equation derived from a mass balance over the system:

$$\rho \frac{\partial c_i}{\partial t} + \mathbf{u} \cdot \nabla c_i = \mathcal{D} \nabla^2 c_i + R_i \quad (3.6)$$

where c_i represents the concentration of the species i , $\mathcal{D}$ the effective diffusivity and R_i is the reaction rate per unit volume [95].

3.2 Modelling Thrombus Formation and Growth

The evolution of aortic dissection causes significant morphological changes in the aorta. The formation of intimal tears and a false lumen tends to lead to highly disturbed flow, including turbulence,

recirculation zones, and large variation in wall shear stress. All these parameters have a major influence on thrombus formation within the false lumen. The tearing of the aortic wall, the high shear stress levels detected in the proximity of tears, and the existence of shear micro-gradients can potentially promote the initial activation of platelets and the formation of platelet aggregates [57, 61, 60]. At the same time, the formation of recirculation zones within the false lumen characterized by stasis, long residence times, low shear stress and therefore high viscosity together with the potential thrombogenicity of the subendothelial tissue create an ideal environment for platelet aggregation and deposition, leading to thrombus formation on the walls [52, 48, 63]. Based on these considerations, a novel computational model has been developed in this thesis, with the aim to predict thrombus formation in aortic dissection. Blood flow is simulated by means of Computational Fluid Dynamics (CFD) and is integrated with mass transfer equations to model thrombus growth. Areas with high probability for thrombus growth are identified through the evaluation of local shear rates, residence time, and distribution of activated platelets. The number of species modelled is significantly reduced as compared with models of the coagulation cascade, and time scales of thrombus growth have been adapted to facilitate simulation of the system in a short time frame.

The model predictions are based on the following assumptions: (i) cell adhesion can only occur in regions where wall shear rates fall below the physiological threshold of 100 s^{-1} [63]; (ii) the concentration of coagulation factors is high in regions of flow recirculation and stasis, characterized by long residence times, stabilizing the forming thrombi [61]. These assumptions allow us to focus on the transport of a limited number of species and to evaluate the growth of thrombus based on average parameters, significantly reducing the overall computational cost of the model. We assume that the initial activation of platelets is triggered by the inflammatory response caused by the splitting of the aortic wall and by the high shear stress experienced in the tear regions [61, 60], where the local time-averaged shear stress (TAWSS) can reach values above 40 Pa [10]. The initial platelet activation is accounted for through a 5% background activation level (see Section 3.2 - *Platelet Activation*). The main features of the model and key species transported are described below.

Residence Time (RT). This variable is used to identify regions of stagnancy and flow recirculation, which are associated with an increased likelihood for thrombus formation. RT is modelled

as a tracer passively transported with the flow and obeying to the following equation [96]:

$$\frac{\partial RT}{\partial t} + v \cdot \nabla RT = D_{RT} \nabla^2 RT + 1 \quad (3.7)$$

where t is time, v is the velocity of blood, D_{RT} represents the self-diffusivity of blood ($D_{RT} = 1.14 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$, Harrison et al. [97]) and the source term considers a unit increase in RT for each unit increase in time. As the absolute residence time is a function of time, the increase in RT for each cardiac cycle has been normalized with respect to cycle period and its non-dimensional counterpart is called relative residence time (RRT).

Resting and Activated Platelets (RP and AP) are modelled as dilute chemical species passively transported with the flow, which can be described by a convection-diffusion-reaction transport equation [78]:

$$\frac{\partial c_i}{\partial t} + v \cdot \nabla c_i = D_p \nabla^2 c_i + S_i \quad i = AP, RP \quad (3.8)$$

where c_i represents the concentration of platelets (RP or AP). The diffusivity D_p accounts for the shear-enhancing effect of RBCs through the diffusivity model proposed by Wootton et al. [85]:

$$D_p = D_{pt} + \alpha \dot{\gamma} \quad (3.9)$$

where D_{pt} is the thermal diffusivity ($D_{pt} = 1.6 \times 10^{-9} \text{ cm}^2/\text{s}$) and the coefficient α is equal to $7 \times 10^{-9} \text{ cm}^2$ [85]. The reactive source term S_i is the sum of two different contributions that model the effect of APs on the further activation of RPs (r_1) and activation by thrombin exposure (r_2) [88]. As the transport of thrombin is not included in the model, it is assumed that the concentration of thrombin would be higher in areas of high residence time. Therefore, the value of r_2 has been scaled by RRT:

$$r_1 = k_1 [AP][RP] \quad r_2 = k_2 [RP] \text{ RRT} \quad (3.10)$$

k_1 and k_2 are the kinetic constants, whose values presented in Table 3.1 have been taken from Anand et al. [88]. To avoid numerical ill-conditioning, the concentrations [AP] and [RP] have been normalized against their initial values.

The local concentration of AP and RP should be interpreted as a measure for platelet activity

rather than a specific value [98]. High AP levels represent a higher probability to encounter activated platelet in a specific region, which is a key element to allow the formation of thrombus.

Platelet Activation. The longitudinal tearing of the aortic wall layers is likely to cause an inflammatory response, which may stimulate platelet activation. Additionally, as particularly high shear rates are generally observed in proximity to the tears, it is hypothesised that a shear-induced process might also be involved in the activation of platelets leading to false lumen thrombosis. For these reasons, a background activation level equal to 5% of the inlet concentration of resting platelets [78] is assumed as an initial condition, which allows us to neglect the initial activation process and lag times, and focus on the propagation of platelet activation, described by the reaction rates r_1 and r_2 .

Multiple authors have observed a threshold response of platelet activation to shear stress, dependent on both exposure time and shear magnitude [57, 60]. As the tear regions are characterised by low exposure times due to a fast flowing stream of blood, it is reasonable to assume that, for aortic dissection, the peak shear observed in this area will have the strongest impact on shear-induced platelet activation. A shear rate threshold of $10,000 \text{ s}^{-1}$ (equivalent to a shear stress of $\sim 40 \text{ Pa}$ based on the Quemada model) is used in this study to evaluate the likelihood for shear-induced platelet activation at low exposure times [99].

Coagulant (C) and bound platelets (BP). The variable coagulant (C) accounts for the processes involved in the coagulation cascade, and is formed on the walls where the local time-averaged shear rate is lower than a fixed threshold. The formation of coagulant on the walls in the model is associated with tissue factor exposure and interaction of cells with fibrinogen, which is enhanced at low shear rates [100]. Its diffusion in the bulk is related to the propagation of coagulation factors and thrombin generation. As several studies report the occurrence of thrombosis for shear rates below 100 s^{-1} [63, 48], a local time-averaged wall shear rate threshold of 90 s^{-1} has been chosen for this study. Although the minimum shear rate might have a stronger impact on thrombus formation, this value is more sensitive to the rheological model used and is affected by the upstream flow, which is subject to variation during the long time scale of thrombus growth of weeks or months. For this reason, time-averaged values are considered more reliable and robust, which are used to determine coagulant formation on the wall. In the model presented the coagulant promotes the coagulation of activated platelets and the formation of thrombus, defined through

a static variable called bound platelets (BP). The BP concentration field defines indirectly the effective boundary of the evolving thrombus.

The formation of blood clots is defined by a complex chain of biochemical reactions taking place on the surface of a growing thrombus. While the transport of proteins and coagulation factors in the bulk is convection-dominated, in the near-wall areas and in zones of low velocity and high residence time the transport of clotting factors is diffusion-limited. The growth rate is therefore determined by the slow diffusion of coagulation factors to the thrombus surface, which controls the surface reaction rates. The large difference in time-scales between processes taking place on the macro-scale and micro-scale makes it extremely challenging to simulate the growth process over time. To circumvent this problem, the different time-scales of convection-dominated flow and diffusion-limited surface reactions are considered separately. This is achieved by modelling the transport of coagulant via a shear-dependent diffusive mechanism. This represents a moving boundary condition emulating surface reactions taking place on the advancing front of a growing thrombus. The effects of convection on surface reactions are considered through a coefficient $\phi_{\dot{\gamma}}$ (defined later). The transport equations for C and BP are the following:

$$\frac{\partial C}{\partial t} = D_{eff} \nabla^2 C + k_c \phi_C \phi_{\dot{\gamma}} \quad (3.11)$$

$$D_{eff} = \phi_{\dot{\gamma}} D_c \quad (3.12)$$

$$\phi_C = \phi_C(BP) \quad (3.13)$$

$$\frac{\partial BP}{\partial t} = k_{BP} \phi_{BP} \phi_{\dot{\gamma}} [AP] \quad (3.14)$$

$$\phi_{BP} = \phi_{BP}(C, RRT) \quad (3.15)$$

The coagulant is initially formed on the walls in low shear regions. When the local values of C, AP, and RRT are sufficiently high, BP will be formed and will activate a feedback mechanism promoting further formation of coagulation factors, as outlined in Fig 3.1. $\phi_C(BP)$ and $\phi_{BP}(C, RRT)$ are coefficients which can assume values between 0 and 1, defined by simple saturation (or switching) functions (Equation 3.16). These functions can gradually turn on and off the thrombus formation process depending on the local environment.

$$\phi = \prod \frac{X_i^2}{X_i^2 + X_{it}^2} \quad (3.16)$$

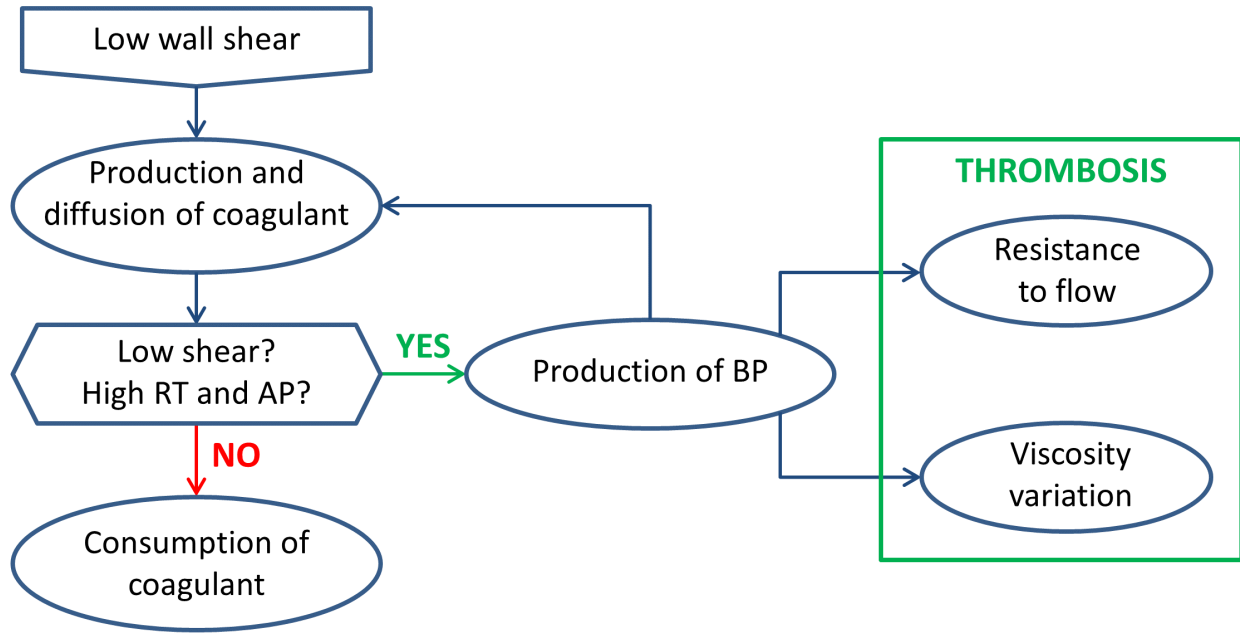


Figure 3.1: Feedback loop regulating thrombus formation and its effects on blood flow.

If the local concentration of any of the variables involved in the process X_i is at least 2-3 times smaller than a defined threshold X_{it} ($RRT_t = 0.9$, $C_t = 10 \text{ nmol}$ and $BP_t = 20 \text{ nmol}$), the reaction will stop. The saturation functions prevent the occurrence of sharp changes in concentration and avoid numerical instabilities related to the use of discontinuous step functions. The coefficient $\phi_{\dot{\gamma}}$ was introduced in the model to control transport and formation of coagulant and prevent the formation of thrombus in high shear regions, which would be physically unrealistic. $\phi_{\dot{\gamma}}$ is a function of the local time-averaged shear rate $\bar{\dot{\gamma}}$ and is defined as:

$$\phi_{\dot{\gamma}} = \frac{\bar{\dot{\gamma}}_t^2}{\bar{\dot{\gamma}}^2 + \bar{\dot{\gamma}}_t^2} \quad (3.17)$$

where the bulk shear rate threshold $\bar{\dot{\gamma}}_t$ in Equation 3.17 is fixed at 100 s^{-1} in this study. The coefficient $\phi_{\dot{\gamma}}$ assumes a maximum value of 1 corresponding to no flow conditions and tends to a minimum of 0 for very large shear rates. For low values of $\phi_{\dot{\gamma}}$, the convective flow will oppose the deposition of blood cells on the thrombus surface and cause washout of coagulation factors. Conversely, for low bulk shear rates the adhesion strength between platelets will be stronger than the tangential force exerted by the flow. This measure was introduced in the model in order to account for the effects of blood flow on growth while overcoming the issues related to the difference

Table 3.1: Rate constants used in the computational model

	Value	Units	Reference
k_1	0.5	s^{-1}	Anand et al. [88]
k_2	1.2×10^{-8}	$mL/platelets \cdot s$	Anand et al. [88]
k_c	200	$nmol/L \cdot s$	
k_{BP}	10^a	$nmol/L \cdot s$	
k_M	10^7	kg/m^3s	

^a k_{BP} refers to a concentration [AP] normalized against its initial value $1.25 \times 10^7 \text{ platelets/mL}$

in time scales between diffusion-limited biochemical reactions and convection-dominated blood flow, allowing reasonable simulation times.

Momentum source. The momentum balance is described by the Navier-Stokes equations. Following the approach proposed by Leiderman and Fogelson [50], the effects of a growing thrombus on blood flow are modelled by introducing in the momentum equations a negative source term proportional to the concentration of BP. This source term represents a fictitious force opposing fluid motion in regions where thrombus is growing. The adapted equation is reported below:

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \nabla \cdot (\mu \nabla \mathbf{u}) - S_M \quad (3.18)$$

$$S_M = k_M \frac{BP^2}{BP^2 + BP_t^2} \mathbf{u} \quad (3.19)$$

Once again, a saturation function has been introduced in the source term rather than a step function to avoid numerical instabilities. The value chosen for k_M is large enough to stop the flow where thrombus is formed (see Table 3.1).

Viscosity Variation. Within in a growing thrombus, blood viscosity is allowed to change to simulate increased resistance. A viscosity function was introduced for this purpose accounting for an increase up to 100 fold normal viscosity values [71], proportionally to the concentration of BP (Equation 3.20). The viscosity of blood μ only deviates from its reference value μ_0 in regions with a BP concentration greater than 0.

$$\mu = \mu_0 \left(1 + 100 \frac{BP^2}{BP^2 + BP_t^2} \right) \quad (3.20)$$

3.3 Geometry Reconstruction and Mesh Generation

The patient-specific geometries used in this thesis have been reconstructed from CT scans by using the commercial medical image processing software Mimics (Materialize HQ, Leuven, Belgium). The Mimics package offers a set of powerful functions for image segmentation, smoothing and taking measurements.

Fig. 3.2 shows the workflow for the reconstruction of patient-specific models. The first step in the workflow followed for image segmentation consists in segmenting the CT scans stored in DICOM format based on their greyscale intensities. In this way, a mask is created including the aorta and other regions which are within the same thresholding range. The regions of interest are then separated from the others by a combination of mask cropping and splitting, region growing operations and manual adjustments. The final mask is then smoothed and converted into a 3D object by interpolation of the 2D contours. Smoothing algorithms are then applied on the 3D object obtained to ensure a smooth wall surface.

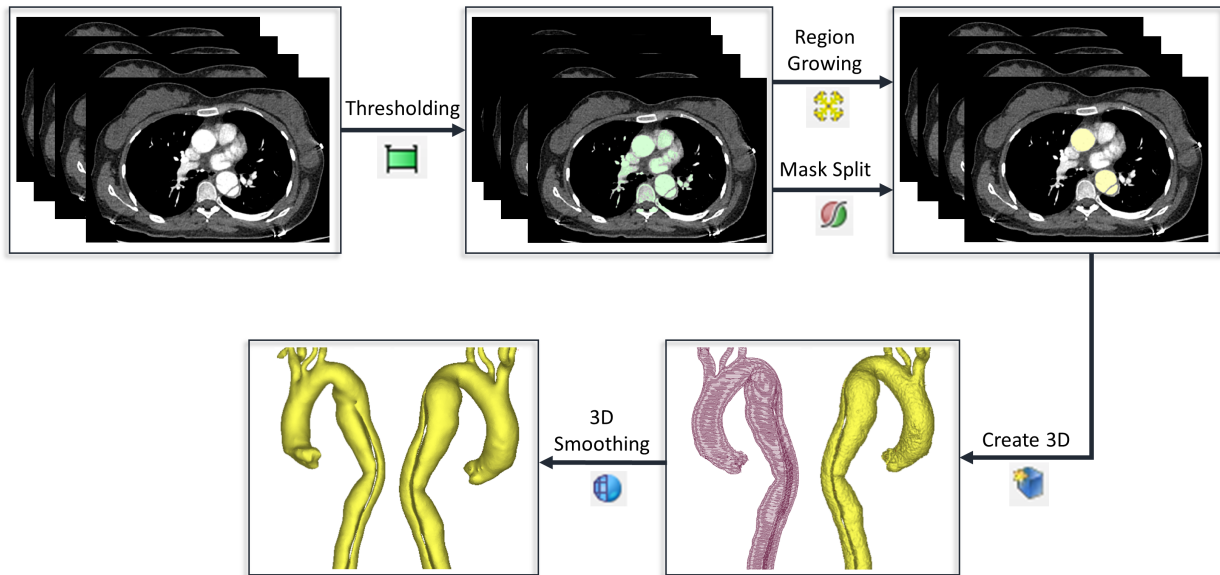


Figure 3.2: Summary of the workflow followed for image segmentation in Mimics.

The numerical solution of a differential equation requires the generation of a numerical grid. Different techniques can be used to discretize the spatial flow domain, which can involve the use of structured or unstructured grids. Structured meshes are based on mapping the domain with simple structures like hexahedrons, and often make use of blocks to divide the domain into sub-domains (Fig. 3.3b). Conversely, unstructured meshes do not present uniform patterns and have

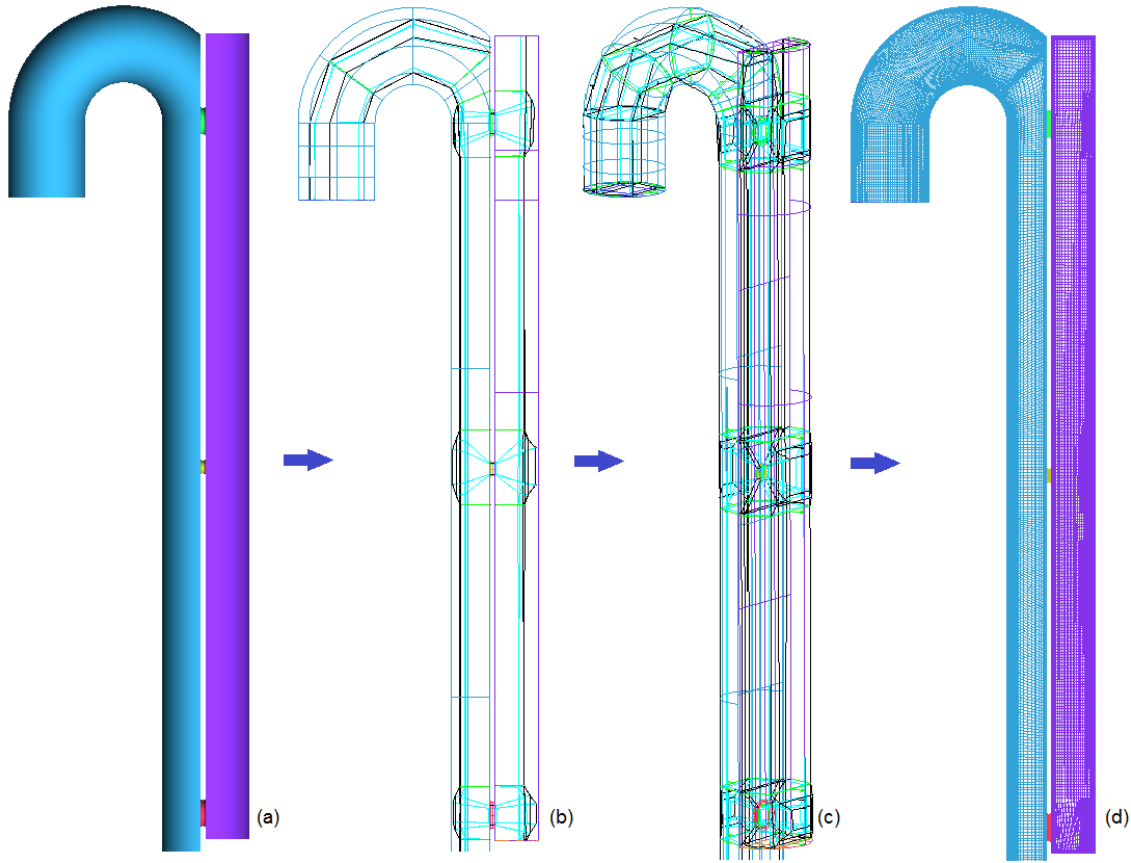


Figure 3.3: Meshing protocol for the structured grids: CAD geometry (a), blocking (b), associations of edges and faces with surfaces and curves (c), and mesh generation (d).

no restriction in element shape and number of neighbouring elements. Structured grids generally present better quality and control, but they are less easily adaptable to complex geometries than unstructured meshes [101].

Part of this PhD project has been focused on computational studies on 2 and 3D idealized phantom geometries for aortic dissection designed by Dr. Zhuo Cheng (Fig.3.3a), discretized into a block-structured grid made of hexahedral elements using ICEM (Ansys Inc.). A structured hexahedral mesh has been chosen rather than unstructured tetrahedral elements to exploit the greater flexibility and better quality offered by structured meshing tools. Firstly, different blocks have been created around the geometry in order to capture the different regions of the phantom: true and false lumen, tears, and aortic arch. The different edges and faces of the blocks have been associated with surfaces and lines of the phantom (Fig. 3.3c), in order to create a correspondence between the blocking elements and the geometry. Lastly, the blocks have been discretized into small elements that approximate the full geometry (Fig. 3.3d).

Due to the geometric complexity of real dissection models, all the patient-specific geometries analysed in this thesis have been discretized into unstructured meshes in ICEM, comprising a tetrahedral core and prism layers near the walls to ensure high resolution of the boundary layer. Mesh information will be provided on a case-to-case basis in the relative chapters.

3.4 Numerical Methods

As seen before, fluid flow and more generally transport phenomena can be modelled through partial differential equations. Unless simplifying assumptions can be made such as steady state or unidirectional flow, the governing equations cannot be solved analytically, and numerical methods must be used to generate approximate solutions. Numerical approaches are based on discretization methods that permit the replacement of the equations with a system of algebraic equations that can be solved analytically or computationally. This consists of discretizing spatial and time domains into small volumes and time units where the equations are approximated, so that the accuracy of the numerical solution will depend on the quality of the spatial and temporal discretization. The spatial discretization is done by generating a numerical grid, or mesh, that subdivides the whole domain into a finite number of subdomains. More details about different meshing techniques is given in Section 3.3. Time discretization is performed by partitioning the time intervals into small sub-domains defined as time-steps.

Several approaches have been proposed for the discretization of differential equations. The most commonly used methods are finite difference, finite volume, and finite element. In the finite difference method differential equations are approximated at each node by expressing variables as a function of nodal values. This method results to be easily applicable for simple geometries, and it is generally applied for structured meshes (see Section 3.3). Finite volume methods use the integrated form of the differential equation over a control volume (CV) to obtain a discretized equation which represents a material balance over the control volume taken into consideration. The integrals are then solved by applying numerical integration methods based on quadrature formulae. For CV-centered methods, nodal values are interpolated to evaluate the variables at the centroid of each element. Likewise, in the finite element method the domain is discretized into small bi-dimensional or tri-dimensional elements and the equations are multiplied by a weight factor before being integrated over the control volume [101].

In this work, the computational meshes generated in ICEM have been imported in the CFD software Ansys CFX (Ansys Inc.), which has been selected for the numerical solution of transport phenomena. For the discretization of the governing equations the software adopts a unique hybrid finite-element/finite-volume method developed by Ansys CFX and defined as element-based finite volume method. The thrombus model is incorporated into Ansys CFX through user-developed CEL functions and Fortran sub-routines.

3.5 Boundary Conditions

The choice of appropriate boundary conditions is of paramount importance to ensure physiological relevance of the computational model and validity of the predictions. Given below is a brief overview of the boundary conditions chosen for the inlet, outlets, and walls of the computational models built in this thesis (Fig. 3.4).

Inlet and Walls

In all the case studies presented in this thesis pulsatile velocity profiles have been applied at the inlet, generally derived from PC-MRI data. At the model inlet in the ascending aorta, a flat velocity profile, equal to the average flow measured, is usually assumed. This assumption had been previously validated by Cheng et al. [40], who showed good overall agreement between CFD flow predictions and PC-MRI data in the descending aorta which is the main region of interest for Type B aortic dissection. Morbiducci et al. [102] also demonstrated that while the velocity profile imposed at the inlet has significant repercussions on wall shear and other hemodynamic variables in the ascending aorta, minimal differences were observed in the descending aorta. In Chapter 8, the flat profile will be replaced with a 3D velocity map reconstructed from 4D MRI images. More information on the velocity mapping will be provided in the relative section.

Vessel walls have been assumed to be rigid and a no-slip condition has been applied. The rigid wall assumption, widely used in computational studies of aortic dissection, is partially justified by the lack of availability of data regarding the heterogeneous wall thickness and mechanical properties of the dissected wall, and by the high computing power required for fluid-structure interaction (FSI) simulations. Even though the rigid wall assumption neglects the compliant nature of aortic walls, this is not expected to have a major impact on thrombus predictions as significantly reduced wall

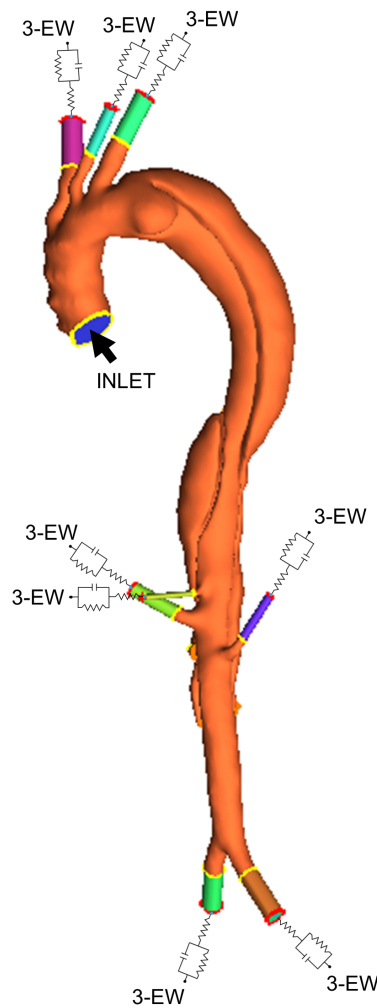


Figure 3.4: Example of a patient-specific model, showing the location of inlet and outlets. 3-EW = 3-Element Windkessel model.

distensibility has been observed for Type B dissections as compared to healthy subjects, with a 4.4% average true lumen narrowing caused by flap motion [103]. Also, reduced flap mobility has been reported for chronic cases as compared to acute dissections [104].

Outlet

The choice of outlet boundary conditions has been made on a case-by-case basis. In models with only one outlet, a choice of either an opening with relative static pressure of 0 Pa or pressure waveform has been made, as these are considered appropriate for the simulated conditions. To account for pressure variations in patient-specific models comprising multiple outlets, 3-element Windkessel (3-EW) boundary conditions have been applied. The Windkessel model is based on

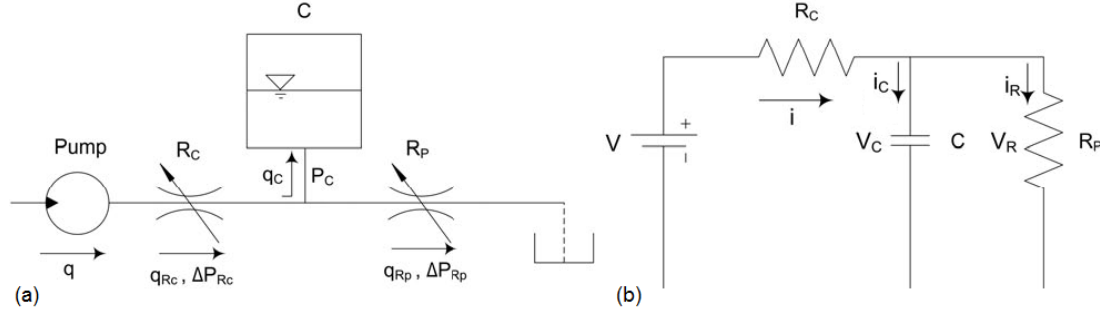


Figure 3.5: (a) Compartmental model for the aorta. (b) Electrical analog of the 3-element Windkessel model. Adapted from Ruel and Lachance [105], Copyright © Ruel and Lachance [105] licensed under a Creative Commons Attribution 3.0 License (by-nc 3.0).

the analogy between electrical circuits and the cardiovascular system. For the 3-EW model, the system can be represented by the compartmental model presented in Fig. 3.5, where the potential V represents the arterial pressure, the current i the flowrate, and characteristic impedance of the aorta, wall compliance, and peripheral resistance of the vessel are respectively represented by R_c , C , and R_p [105]. By solving the circuit and considering the analogy between pressure, flowrate, potential, and current, the following equation can be obtained:

$$P = Q (R_p + R_c) + CR_p R_c \frac{dQ}{dt} - CR_p \frac{dP}{dt} \quad (3.21)$$

where C , R_p , and R_c are fitting parameters. The methodology used to calculate proximal and distal resistances and vessel compliance will be described in the relative chapters.

For additional variables such as residence time and platelet concentrations a zero gradient boundary condition has been specified at the outlets.

Model Evaluation: Simulation of Thrombus Formation in Idealised Models of Aortic Dissection[†]

The formation of a false lumen causes highly disturbed flow patterns and creates local hemodynamic conditions likely to promote thrombosis therein. As explained in the previous chapters, several studies have demonstrated that patient prognosis is influenced by the level of thrombosis in the false lumen, with false lumen patency and partial thrombosis being associated with late complications and complete thrombosis of the false lumen having beneficial effects on patient outcomes.

The first part of this PhD project has been focused on the development and application of a computational model that is able to identify areas of high probability of blood clotting based on the analysis of hemodynamic parameters and to incorporate the effects of thrombus growth on fluid flow, as well as the effects of fluid flow on thrombus growth. The model, which is described in detail in Chapter 3, employs shear rates, fluid residence time, and platelet distribution to evaluate the likelihood for thrombosis and to simulate the growth of thrombus and its effects on blood flow over time.

In this chapter, the hemodynamics-based thrombus model is first applied to a backward facing step in order to validate predictions against experimental data, and then compared to a biochemical model in order to assess its performance as compared to established modelling approaches, both in terms of predictive power and computational costs. Lastly, the model is applied to six phantom geometries of aortic dissection with different tear configuration and sizes to investigate the effect of geometric features on hemodynamics and thrombus formation in Type B aortic dissection.

[†]The content of this chapter is partially adapted from: *Menichini, C and Xu, XY (2016). Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications. Journal of mathematical biology, 73(5), 1205-1226.*

4.1 Benchmark Test: Thrombus Formation in Backward Facing Step

To test the performance of the hemodynamics-based model described in Chapter 3 before applying it to dissection geometries, thrombus formation in a backward facing step was simulated, so as to reproduce the conditions adopted by Taylor et al. [106] and compare with their experimental results. The geometry consists of a 3D backward facing step of circular cross section, with a diameter of 10 mm and a step height of 2.5 mm. A fine structured mesh was generated, consisting of approximately 1.2 million hexahedral elements. A fixed flowrate of 0.76 L/min was applied at the inlet, and a zero pressure was assumed at the outlet. The Quemada viscosity model was adapted to incorporate the reported hematocrit of 30% [107]. As the flow is non-pulsatile, a lower wall shear rate threshold for thrombus formation of 1 s^{-1} was adopted, which is consistent with values reported by Polanczyk et al. [108] for blood hematocrit near 30%. The bulk shear rate threshold $\bar{\gamma}_t$ was set to 10 s^{-1} , while all the other parameters were the same as given in Table 3.1. The simulation was run for 50 s with a time step of 0.01 s.

Fig 4.1 shows the predicted thrombus formation as a function of time. Initial growth takes place downstream of the step in both axial and radial directions. Radial growth is stopped when the thrombus height reaches the step height (2.5 mm) and a maximum width equal to that of the step. After the thrombus reaches a total length of approximately 8 times the step height, growth is significantly slowed down, reaching a maximum length of about 23 mm. These observations are in good agreement with the experimental results of Taylor et al. [106].

4.2 Comparison With a Biochemical Approach

The main advantage of the model developed in this thesis is its hemodynamics-based character. As biochemical reactions are not modelled directly, the computational cost of the simulation is significantly lower than that of kinetics-based models. This allows us to simulate pulsatile flow, which is of paramount importance for analysis of blood flow in the aorta, while obtaining solutions within a reasonable computational time. On the other hand, the kinetic processes included in the model are based on empirical correlations, developed on the basis of an in-depth flow analysis on aortic dissection cases [9, 40]. In order to evaluate how the model performed in terms of computational

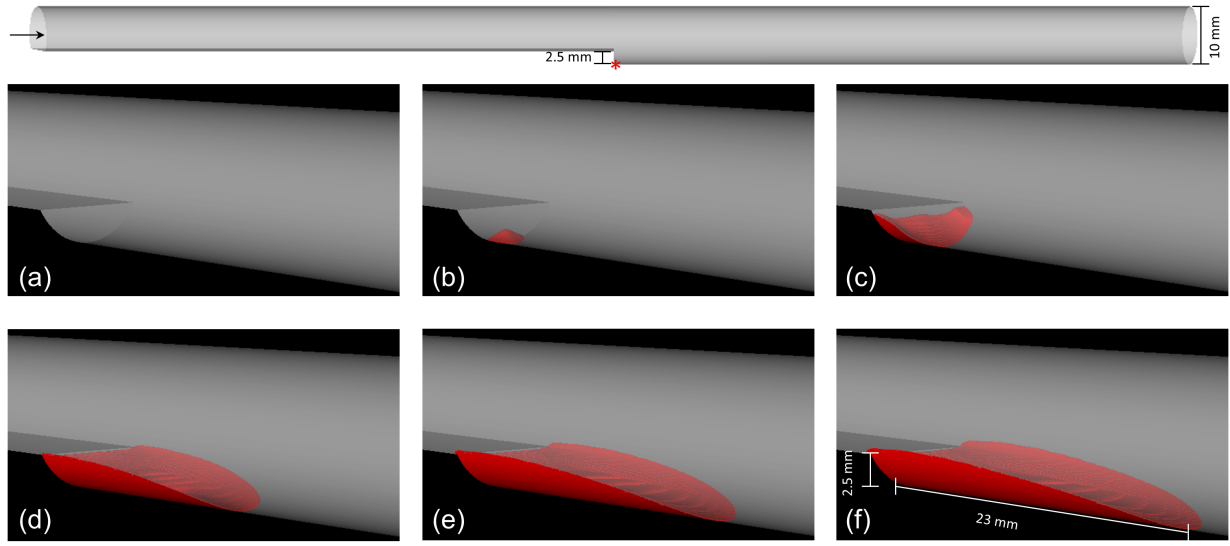
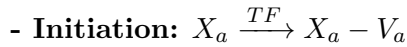


Figure 4.1: Predicted thrombus formation (red) in the BFS geometry at (a) $t = 1$ s, (b) $t = 7$ s, (c) $t = 14$ s, (d) $t = 28$ s, (e) $t = 39$ s, (f) $t = 50$ s. The asterisk shows the location where thrombus growth is started.

costs and predictive power as compared to established modelling approaches relying on biochemical reactions, a biochemical model presented in the literature was adopted for comparison. This was achieved during a brief visiting period at the University of Cape Town. The kinetics-based thrombosis model developed by Ngoepe and Ventikos [109] was used for this purpose, which was designed to describe a thrombin generation profile (Thrombogram) proposed by Hemker et al. [110] and Wagenvoort et al. [111] in dynamic flow conditions. The Thrombogram describes a typical course of thrombin formation over time, and is characterized by three phases: (i) a lag phase, when thrombin formation is initiated; (ii) a steep increase in thrombin concentration; (iii) after reaching a peak value, the concentration of thrombin goes back to zero. The following components are included in the model: Tissue Factor (TF), which is formed on the walls ($[TF] = 10^{-8}$ nmol/L) where the local time-averaged shear stress is below 0.36 Pa, Prothrombin (PT), Thrombin (TB), factors Xa and Va, complex Xa-Va, Anti-Thrombin (AT), Inactivated product (INACT). The model is based on four main reactions:



$$R_1 = k_1[TF] \frac{[X_a]}{[X_a] + K_1} \quad (4.1)$$

This reaction was introduced in the model as a surface flux boundary condition.

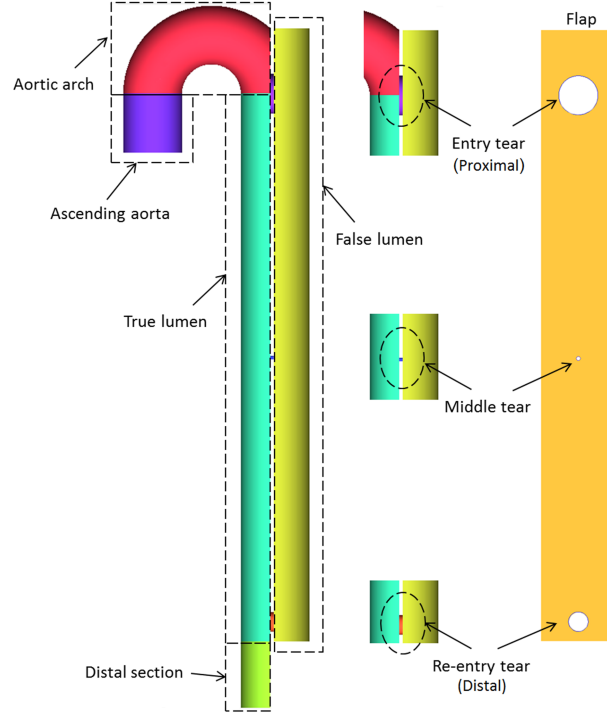


Figure 4.2: Hypothetical phantom for aortic dissection used in this study. Tear size and configurations are varied in the different models analysed.

Thrombin formation: $PT \xrightarrow{X_a - V_a} TB$

$$R_2 = k_2[X_a - V_a] \frac{[PT]}{[PT] + K_2} \quad (4.2)$$

Propagation: $V_a \xrightarrow{TB} X_a - V_a$

$$R_3 = k_3[TB] \frac{[V_a]}{[V_a] + K_3} \quad (4.3)$$

Termination: $TB \xrightarrow{AT} INACT$

$$R_4 = k_4[TB][AT] \quad (4.4)$$

The hemodynamics-based model and the biochemical model were applied to a 2D phantom geometry extracted from the 3D phantom model designed by Dr. Zhuo Cheng [112] and shown in Fig. 4.2. Results are compared in Fig. 4.3 and 4.4, which show very similar flow patterns of

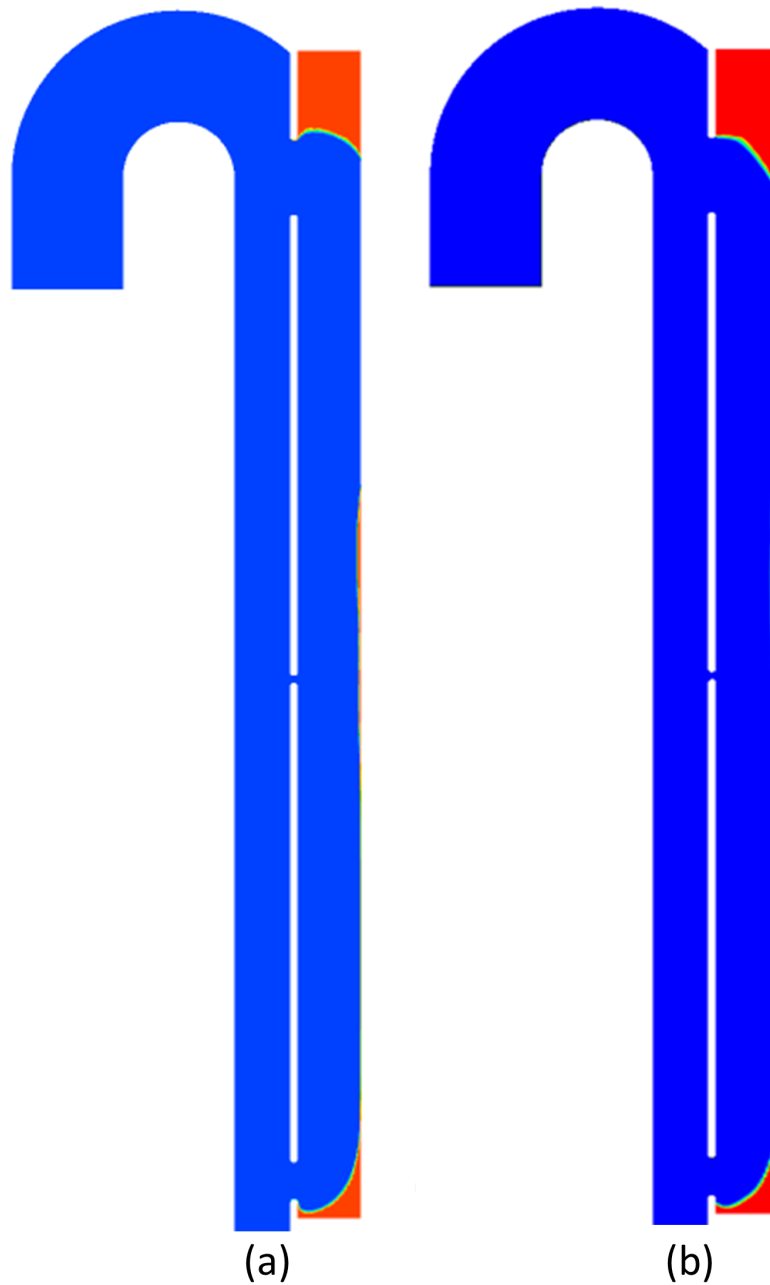


Figure 4.3: (a) In red, thrombus predicted by the biochemical model after a simulation time of 9000 s. (b) In red, thrombus predicted by the hemodynamics-based model after a simulation time of 40 s.

thrombus formation. However, for a steady flow case presented in Fig 4.3, the computational time with the hemodynamics-based model was 7x less than that with the kinetics-based model. When simulating pulsatile flow with a patient-specific flow waveform [9], this difference was more than doubled ($\sim 15x$), even though accelerated kinetics were used for the biochemical model (Fig 4.4).

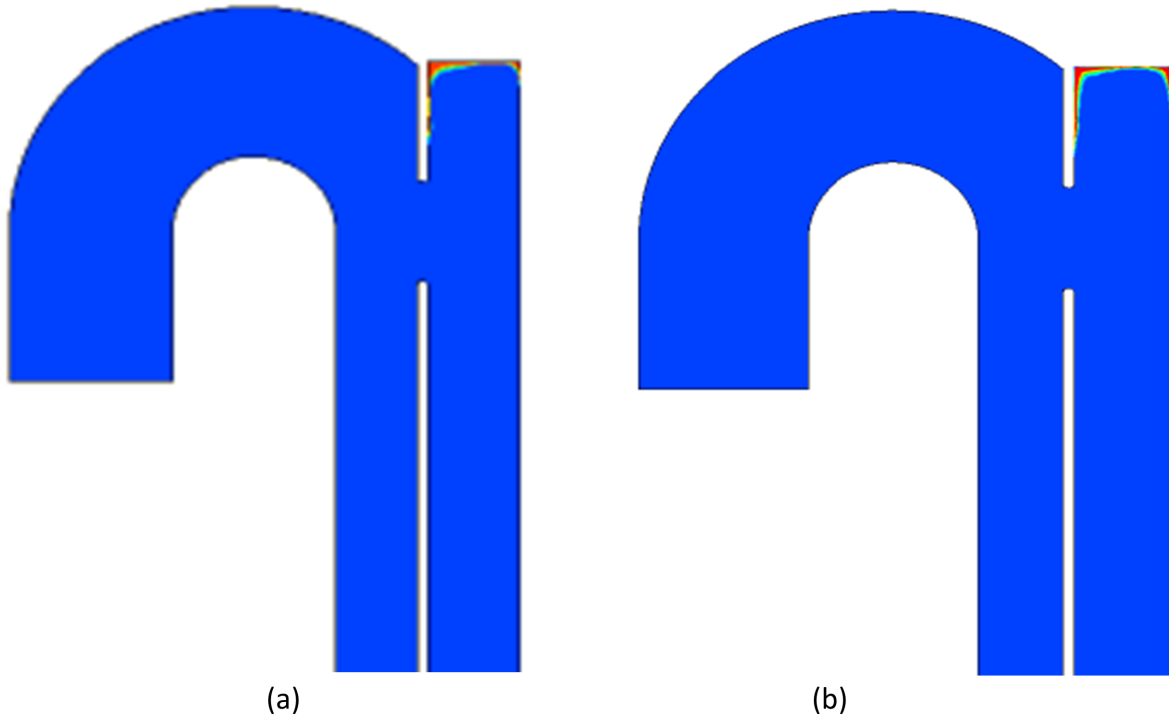


Figure 4.4: (a) In red, thrombus predicted by the biochemical model after a simulation time of 150 s. (b) In red, thrombus predicted by the hemodynamics-based model after a simulation time of 2 s.

This brief comparative study demonstrated that thrombus growth predictions obtained with a kinetics-based approach could be reproduced with the hemodynamics-based approach developed in this thesis, but at significantly lower computational costs. As the goal of this thesis is to predict the formation of thrombus in clinically relevant cases, including patient-specific dissections and pulsatile flow conditions, reducing computational costs is of paramount importance. The remainder work presented in this thesis will be therefore focused on the application of the hemodynamics-based model.

4.3 Simulation of Thrombus Formation in Idealised Models of Aortic Dissection

Having been validated against experimental data and a kinetics-based approach, the hemodynamics-based model was applied to six phantom geometries of aortic dissection with different tear configurations and sizes to investigate the effect of geometric features on hemodynamics and thrombus

formation in Type B aortic dissection. The methodology employed in this study and results are presented below, with a discussion of the major findings.

4.3.1 Methodology

Geometry

Six different 2D phantom models of aortic dissection were generated in SolidWorks based on the design shown in Fig 4.2. The geometric features of the models are summarised in Table 4.1. Tear size and location were varied in order to analyse different scenarios and to investigate the influence of morphological features on the formation of thrombus in aortic dissection. The six phantom models were discretized into a block-structured grid made of hexahedral elements using ICEM (Ansys Inc.). For each of the 2D geometries created, a mesh sensitivity test was carried out, and a mesh consisting of 53,000-56,000 elements depending on the number and size of the tears was found to be adequate for mesh independent solutions.

Flow Model, Initialisation, and Boundary Conditions

The thrombus model presented in Chapter 3 was implemented in Ansys CFX 15 (Ansys Inc.) via user defined subroutines and initialized with a physiological concentration of resting platelets ($2.5 \cdot 10^8$ platelets/mL [85]), zero for RT, BP, and C, and a background activation level equal to 5% of the inlet concentration of RP was prescribed [78]. The flow was initialized by simulating the system for two cardiac cycles in order to achieve a periodic solution, and the thrombus model

Table 4.1: Geometric features of the phantom models analysed in this study, with maximum peak shear stress and time-averaged wall shear stress (TAWSS), and percentage of flow diverted into the false lumen. The flow into the false lumen is calculated at peak systole. PT = proximal tear, DT = distal tea, FL = false lumen.

	No. of Tears	Diameter (mm)		Max WSS (Pa)	Max TAWSS (Pa)		Flow % into FL
		PT	DT		PT	DT	
C1	1	10	n/a	55	9	n/a	~ 0%
C2	1	n/a	10	37	n/a	5.8	~ 0%
C3	2	10	5 ^a	120	18	24	26%
C4	2	10	5	138	20	24	35%
C5	2	10	10	128	12.5	18	37%
C6	2	20	10	120	15	19	41%

^aRe-entry tear placed in the middle section

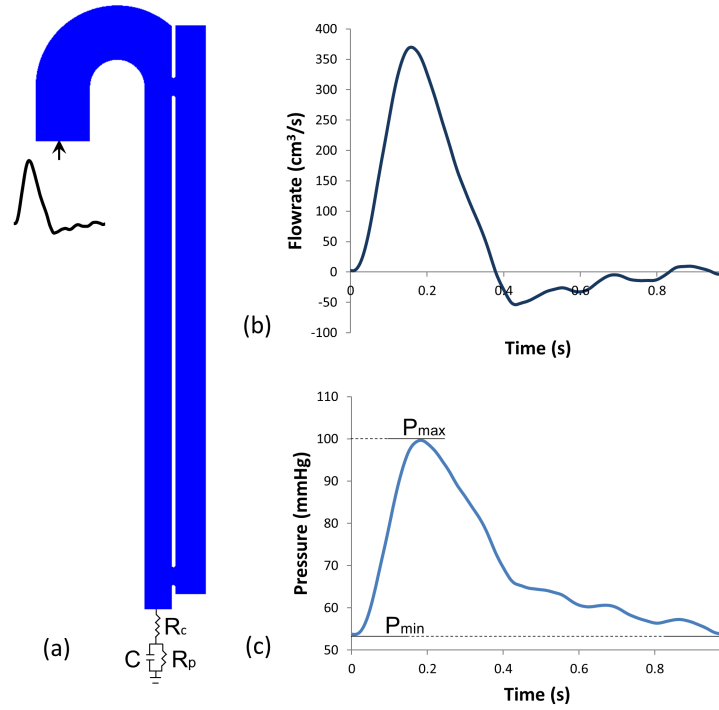


Figure 4.5: (a) Geometric model with inlet and outlet boundary conditions. R_c = impedance of the aorta, C = compliance of aortic walls, R_p = resistance of peripheral vessels. (b) Flow waveform applied at the inlet through a flat inlet velocity profile. (c) Pressure waveform calculated from the 3-element Windkessel model, implemented as outlet boundary condition. A lag time of 0.024 s exists between pressure and flow waveform.

was introduced only from the third cardiac cycle. Blood was modelled as a non-Newtonian fluid described by the viscosity model proposed by Quemada [94]. As Reynolds numbers in large vessels are generally below the threshold for turbulent flow, blood flow was assumed to be laminar [93].

A realistic aortic flow waveform was applied at the model inlet, together with a flat velocity profile ([113], Fig.4.5). The waveform presents a frequency of 1.02 Hz, maximum velocity 0.51 m/s and a Womersley number of 18.8. A no-slip condition was imposed at the rigid walls, with (i) specified concentration of C at 100 or 0 nmol/L depending on the local shear rate; (ii) flux boundary condition described through a first order adhesion function for RP and AP [85] in areas of low shear ($\dot{\gamma} < 90 \text{ s}^{-1}$); and (iii) zero flux for other species. Only on the aortic arch a zero flux boundary condition was adopted for all variables to avoid thrombus formation in artificial recirculation zones created by the exclusion of the aortic branches.

A pressure waveform calculated through a three-element Windkessel model was applied at the outlet (Fig. 4.5c). The fitting parameters C , R_p , and R_c were calculated by matching the velocity waveform with the pressure measurements reported in the literature for the distal region

in aortic dissection [8], and minimizing the difference between experimental measurements and computational solution through a user-developed Matlab code.

A sensitivity analysis was carried out in order to calibrate the kinetic constants of the model. The sensitivity test showed that as thrombus formation is originated in areas of high residence time, the extent of thrombus is independent of the kinetic constants k_c and k_{BP} , which regulate how fast the threshold concentrations C_t and BP_t are reached. In fact, as thrombus growth occurs in regions of slow flow, clot formation only causes gradual changes to the flow field. This has allowed us to artificially accelerate the process so that evidence of thrombosis could be observed in a reasonably short time frame (20 cardiac cycles). A time-step sensitivity test was also performed, and a value of 0.005 s was found to be sufficient for an acceptable numerical accuracy. Each simulation required approximately 24 hours on a 16.0 GB RAM desktop PC with Intel Core i7-2600 3.40 GHz. The results were analysed through the post-processing software CEI Enight 10 (CEI Inc., Apex, NC, USA).

4.3.2 Results

Wall Shear Distribution and Platelet Activation

The complex geometry of aortic dissection allows a wide spectrum of shear rates on the walls. Particularly high shear stress is observed in the tear region, where a high-velocity jet of blood enters the false lumen. The time-averaged and maximum shear stress values are reported in Table 4.1. As it can be observed, these values are affected by the respective sizes and location of tears. Smaller tears and larger distances between proximal (near the aortic arch) and distal (placed in the distal section) tears are related to higher peak and time-averaged shear values. This result implies a higher likelihood for platelet activation in the initial stages of dissection, where the size of the tears is generally small, and in dissections presenting a large distance between tears. In most of the cases studied the peak shear stress for both tears is above the defined activation threshold of 40 Pa. The only exception is model C2 which has no primary tear and was designed to simulate a stented aortic dissection.

The size and location of tears also affect the distribution of low shear areas, and regions of stagnancy and flow recirculation are characterized by particularly low shear rates on the walls and high RT, as shown in Fig. 4.6 and 4.8. The local shear stress in these areas can possibly

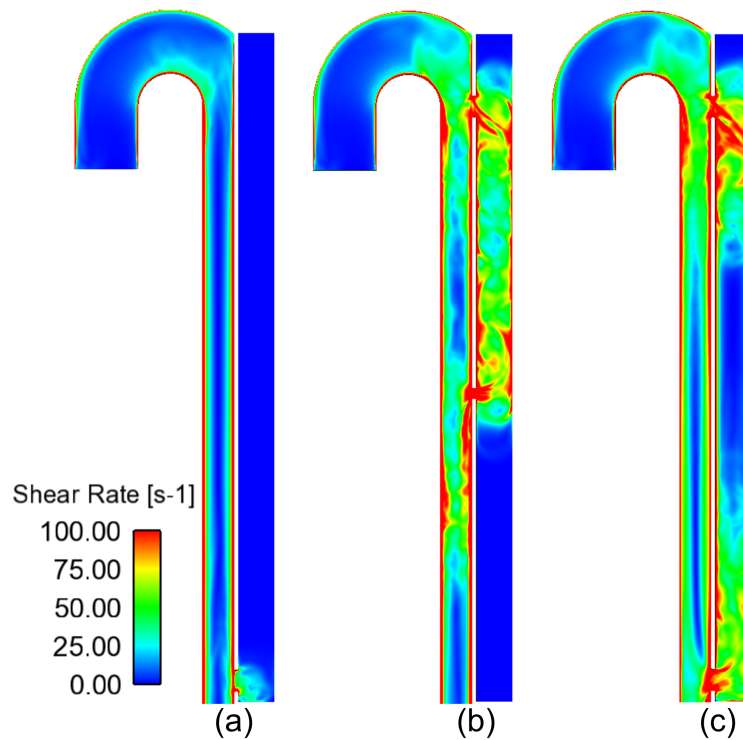


Figure 4.6: Cycle-averaged shear rates in models (a) C2, (b) C3, (c) C5.

fall below the yield stress of blood, which represents the minimum shear necessary to prevent cell aggregation and cell-fibrinogen interaction, allowing blood to start flowing [114]. For larger openings and multiple connecting tears, the extent of these regions is reduced, with a lower probability for flow recirculation, stasis, and a long residence time, which would promote a build-up of coagulation factors and possibly lead to thrombosis.

Distribution of Residence Time and Activated Platelets

The size, number, and location of the entry and re-entry tears affect the amount of blood entering the false lumen, local velocities, and flow patterns. For smaller proximal and distal connections, a reduced amount of blood is diverted into the false lumen (Table 4.1) resulting in lower local velocities and higher residence times. This pattern can be clearly observed by comparing the particle pathlines and time-averaged residence time distributions in the different geometries presented in Fig. 4.7 and Fig. 4.8. The models containing both a proximal and a distal tear exhibit flow recirculation and high residence time in the top and bottom regions of the false lumen and between the two tears (Fig. 4.7b-4.7c and Fig. 4.8c-4.8d-4.8e). During a cardiac cycle, the two tears alternate their

roles as entry and re-entry tears causing an inversion of the flow in the middle of the false lumen, reflected in a high residence time in the models with a large distance between tears (Fig 4.8d-4.8e). However, flow in the mid-section of the false lumen is organised, as shown by the linear trajectories in Fig. 4.7c, allowing normal physiological wall shear rates (Fig 4.6) which prevent the occurrence of thrombosis in the idealized models. For smaller connections and reduced tear distance, larger recirculation zones with a high RRT are observed in the top and bottom regions of the false lumen (Fig. 4.8c-4.8d). The models containing only one proximal or distal tear present a long residence time in the entire false lumen, with slow flow recirculation and stagnant flow (Fig. 4.7a and Fig. 4.8a-4.8b).

Similar observations can be made regarding the distribution of activated platelets. For all models, the highest concentration of AP is also located in the false lumen, implying higher platelet activity in this region. Local peaks are observed in areas of higher residence time and flow recirculation (Fig. 4.9). This higher concentration can be attributed to the partially stagnant flow and high residence time in the FL, which allows longer reaction time. The discharge of blood flow from the FL into the true lumen (TL) also causes higher AP concentrations around the tear regions in the TL (Fig. 4.9a).

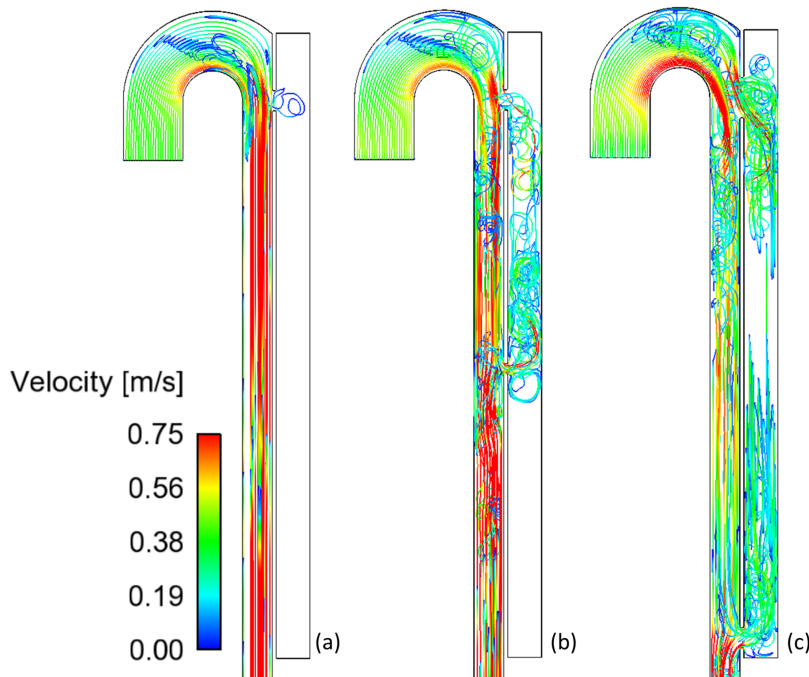


Figure 4.7: Pathlines of particle emitted in mid-systolic acceleration phase from the inlet section and tracked for 15 cardiac cycles in (a) C1, (b) C3, (c) C6.

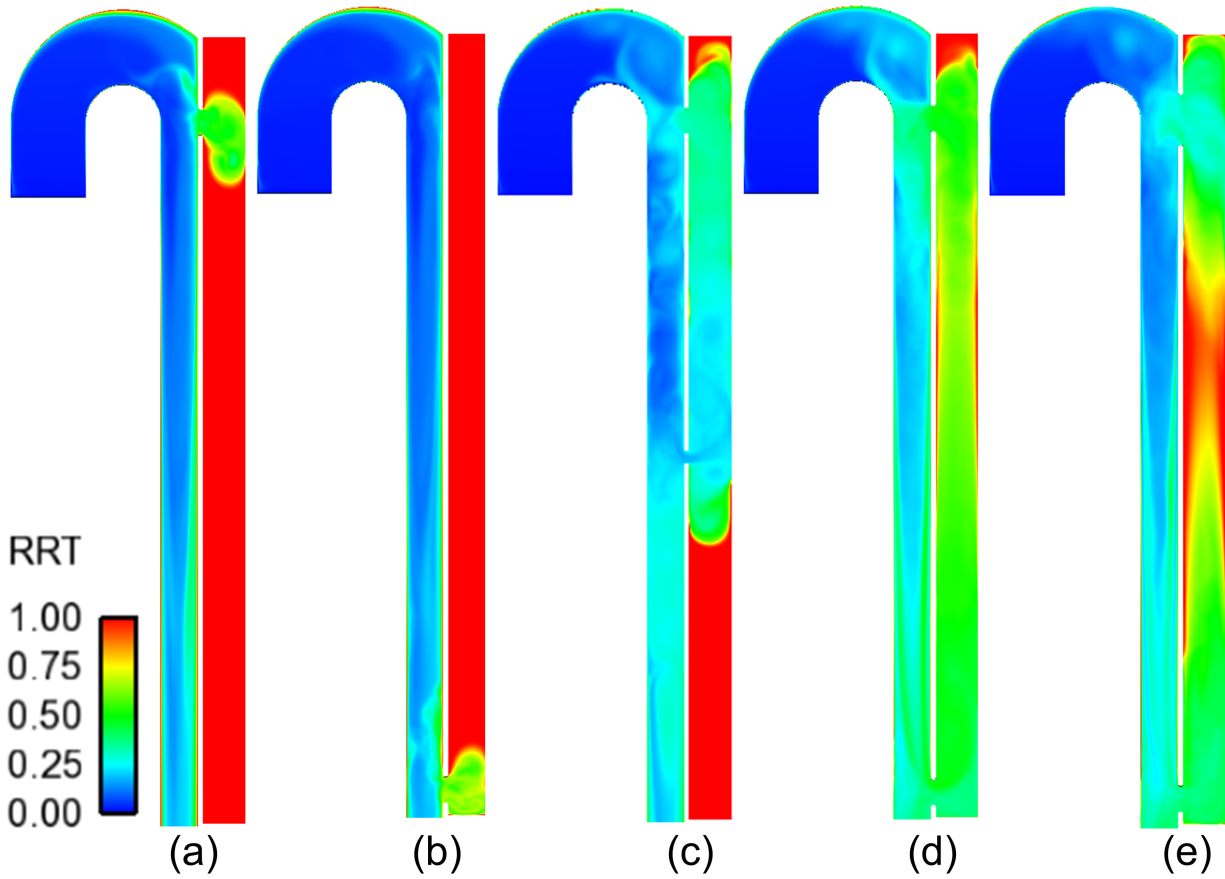


Figure 4.8: Cycle-averaged residence time distribution in different geometric models, normalized over time. (a) C1; (b) C2; (c) C3; (d) C5; (e) C6.

Thrombus Growth Over Time

The threshold for platelets adhesion is set at 90 s^{-1} . As expected, for all the geometric models thrombus growth is observed in areas of recirculating flow and stagnancy, where flow patterns follow chaotic trajectories and wall shear stress is low. The thrombosed region rapidly expands over time and is shaped by the flow features. For the models presenting both a proximal and distal tear, the thrombus is confined to top and bottom areas of the FL, while in the one-tear models the entire FL is exposed to clotting. When the thrombus reaches the tears, growth slows down significantly and eventually stops due to the high shear rates in the bulk caused by the high-velocity jet of blood which crosses the tears (Fig.4.10a-4.10b-4.10d). All these observations are in qualitative agreement with *in vivo* studies performed on patient-specific follow-ups [40].

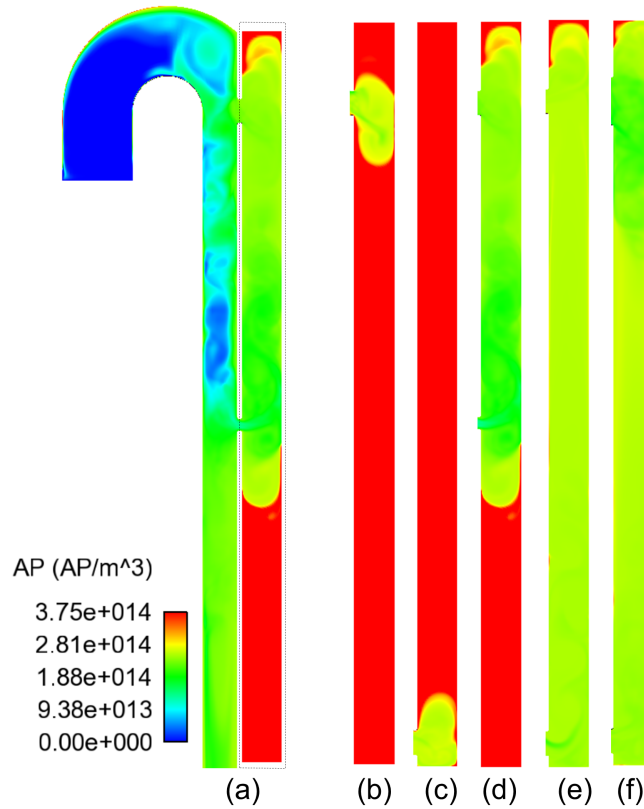


Figure 4.9: Distribution of AP in C3 (a), averaged over a full cardiac cycle, and false lumen details of: (b) C1; (c) C2; (d) C3; (e) C5; (f) C6.

4.3.3 Discussion

The progression of false lumen (FL) thrombosis has been recognised to have a major influence on patients' survival and therapeutic outcomes. Bernard et al. [13] and Tsai et al. [46] identified FL patency as a key parameter to predict the progression of aortic dissection and underlined a link between evolution of the aortic diameter and FL patency and thrombosis. A positive connection was found by the authors between partial thrombosis and aortic expansion, justified by the possible increase in FL pressure caused by the formation of thrombi, which could lead to occlusion of the distal tear and further increase the risk for enlargement and rupture. On the other hand, complete FL thrombosis is generally considered as a positive sign for improved outcomes [46, 5], and the effectiveness of endovascular and medical treatments is associated with spontaneous FL thrombosis.

Several models have been proposed in the literature for prediction of thrombus formation, which incorporate one or more stages of the coagulation cascade [78, 50, 88, 71]. The application of such models has been limited to simplified geometries and has required a number of assumptions to

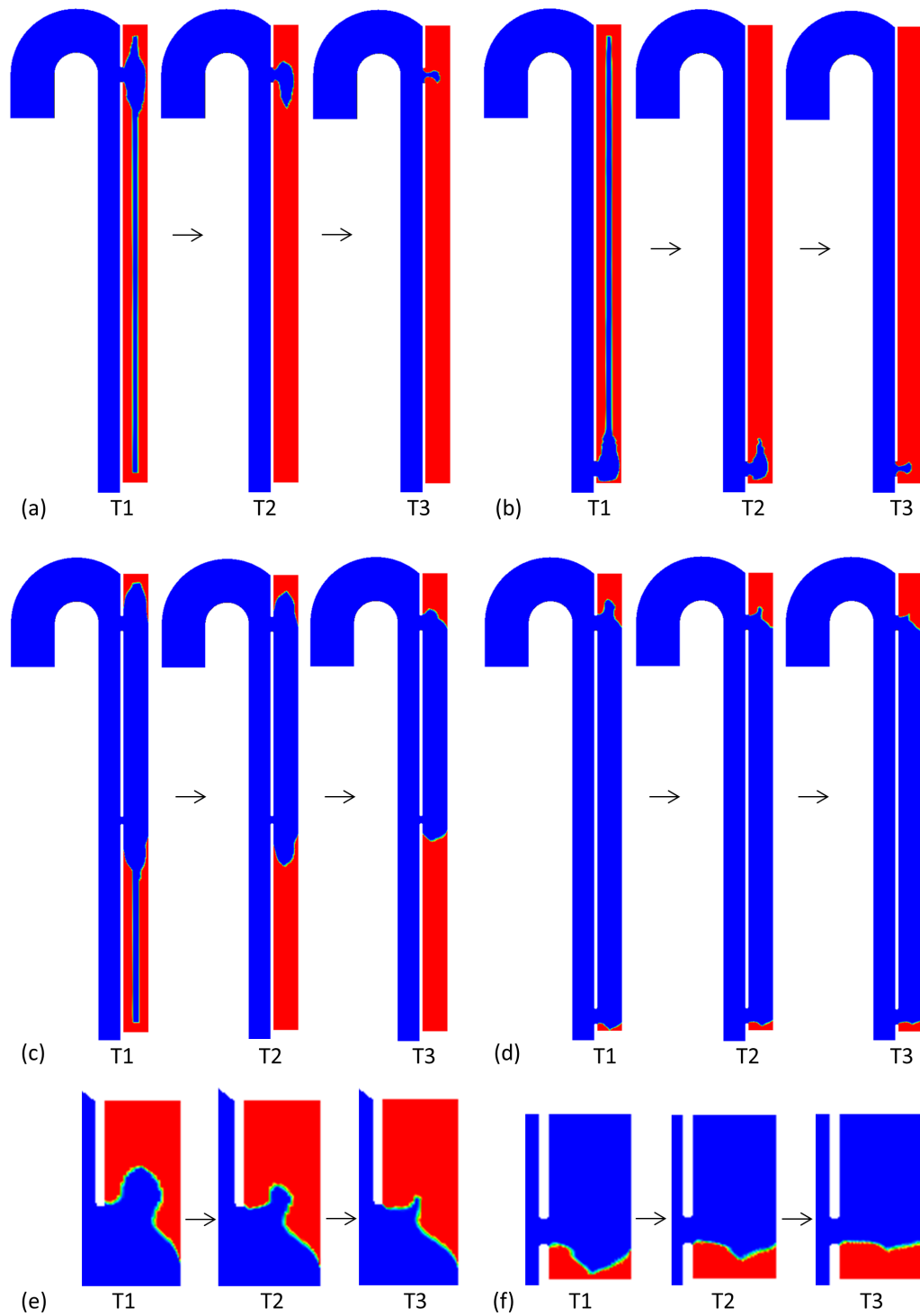


Figure 4.10: Thrombus growth over time in the six different geometric models. In red, areas where the concentration of BP is above the threshold fixed to activate the momentum sink. In blue, areas where the concentration of BP is zero. T1 = 10 s; T2 = 15 s; T3 = 20 s. (a) C1; (b) C2; (c) C3; (d) C4; (e) detail in top FL region in C5; (f) detail in bottom FL region in C6.

reduce computational costs, such as constant velocity and Newtonian behaviour of blood. Moreover, the effects of thrombus growth on fluid flow have often been neglected. These assumptions limit the applicability of existing models to clinically relevant studies where the pulsatility of blood flow, the complexity of the geometry, and the effects of thrombus growth on the fluid domain need to be considered to obtain physiologically relevant predictions. This is further complicated by the difference in time scales between biochemical reactions, thrombus growth, and cardiac cycles which requires small time steps and large computational meshes to obtain robust solutions, increasing the overall computational cost.

The main aim of this study was to evaluate if the hemodynamics-based model developed and described in Chapter 3 could be used to investigate the relationship between thrombus formation and hemodynamics in complex geometries and to predict the possible evolution of false lumen thrombosis in patients affected by Type B aortic dissection. As simulating the process of thrombosis in aortic dissection over realistic time scales of days/months would be computationally prohibitive, the process has been artificially accelerated to allow simulation over a short time frame of 20 cardiac cycles. This acceleration is possible as FL thrombosis usually occurs in regions of low velocities, so that the formation and growth of thrombus only cause gradual changes in the flow field. Areas of high probability of thrombus formation are identified through cycle-averaged parameters, allowing us to simulate the overall growth process in a short time frame, thereby overcoming the limitations related to the large difference in time scales between biochemical reactions and transport processes. This approach is considered preferable to kinetics-based models which usually assume steady flow, as the pulsatile nature of blood flow and the large difference between systolic and diastolic velocities in the aorta affect the distribution of hemodynamic parameters. The use of cycle-averaged rather than steady parameters provides therefore a more accurate representation of the flow field and allows us to identify regions of low shear with more confidence. A preliminary sensitivity study has indicated that the low shear rate threshold is the most sensitive parameter to define the regions of growth. A local wall shear rate threshold value of 90 s^{-1} was chosen to initiate platelet adhesion in the phantom models under pulsatile flow, while a threshold of 1 s^{-1} had been used in the BFS geometry for a fixed inlet velocity. Further validations will be needed to determine the most appropriate value for this threshold in physiologically realistic pulsatile and static flow conditions. A comprehensive sensitivity analysis will also be required to determine the importance of the other model parameters.

Size and number of tears and distance between the tears affect local flow patterns and the development of areas of recirculation and stasis. The effects of geometric features on the distribution of activated platelets, residence time, and thrombus formation was investigated and results show that smaller tears increase the likelihood for thrombosis, as the percentage of flow diverted into the FL is lower resulting in more extended recirculation zones. Smaller tears are also associated with higher local shear stress, which is more likely to promote platelet activation. In the models containing only one proximal or distal tear the entire FL is exposed to very high residence time. However, in these models the local shear stress on the tears could be lower than the platelet activation threshold, such as model C2, presenting only one distal tear to simulate post-stenting geometry. In this case, the initial tearing of the aortic wall and the high shear rates experienced by cells pre-stenting are still considered likely to stimulate platelet activity, justifying the background activation level applied and the subsequent thrombus growth.

The computational model proposed in this thesis allows the simulation of thrombus growth over time. The extent of the thrombosed area is determined by the flow features and varies in different geometric models depending on the size and configuration of the tears. Previous studies have shown a possible correlation between low shear, high relative residence time, flow patterns, and thrombosis [40], which is well captured in the present model. Preliminary results show good qualitative agreement with previous *in vivo* studies and are consistent with the patient-specific case study analysed by Cheng et al. [40] where an aortic dissection patient was monitored over a period of three years. In all the models, thrombus begins to form in the top of the FL where wall shear stress is particularly low due to flow recirculation, and gradually expands to the entire region above the entry tear. The possibility of thrombosis in other regions is determined by the tear configuration, which affects the flow patterns in FL.

The likelihood for shear-related platelet activation is currently estimated based on instantaneous wall shear near the tears. In the tear regions, cells are generally exposed for short periods of time to high shear rates, often above the defined threshold of $10,000 \text{ s}^{-1}$, whereas shear rates in the other regions are usually at least one order of magnitude below the threshold. This has led to the assumption that in aortic dissection the peak shear stress on the tears will have a major impact on the activation process. A more comprehensive and more robust model which includes the effects of exposure time as well as shear loading history [55, 115] would be desirable to evaluate the likelihood for shear-related platelet activation. Also, experimental evidence shows that high shear rates could

potentially lead to local platelet aggregation through the action of von Willebrand factor (vWF) [72, 116, 117]. The high-shear thrombotic pathway is neglected in the current model, but it will be interesting to incorporate this pathway as future work.

The model presented here aims to reproduce major changes in the flow domain by using simplified 2D models and neglects morphological changes that can take place *in vivo*. The simulated time frame of 20 s is not representative of the real time scale in patient-specific dissections, where long periods of weeks/months are required to observe FL thrombosis, depending on morphological features and treatment strategies adopted. This approach allows us to observe major qualitative changes caused by thrombus growth to the flow field, although neglecting actual growth rates and realistic time-scales of the process. Careful validations with patient-specific follow-ups will be needed to evaluate the impact of the assumptions made, in particular neglecting the time-scales of biochemical reactions and speeding up the growth process by neglecting the effects of convection on the coagulation cascade. These will allow us to test the predictive power of the model and understand to what extent thrombus formation can be reliably represented.

Several assumptions have been made in the development of the phantom models. The use of 2D rigid geometries does not allow full representation of the complexity of flow in aortic dissection, which usually involves highly disturbed flow patterns, characterised by asymmetric helices, secondary motion, and regions of strong recirculation. Additionally, the presence of aortic branches and the compliant nature of aortic walls have an important role in modulating velocities and flow distribution between true and false lumen. The application of the model to patient geometries and further fluid-structure interaction (FSI) studies will allow us to study the impact of more realistic features on thrombosis in the false lumen.

4.4 Summary

In this chapter, the hemodynamics-based model presented in Chapter 3 was validated against the experimental data reported by Taylor et al. [106], showing good agreement between predicted thrombus growth patterns and experimental results. In order to evaluate the predictive power of the model as compared to established modelling approaches relying on biochemical reactions, thrombus predictions were compared with those obtained with a kinetics-based thrombus model. This comparative study showed that the hemodynamics-based model was able to produce similar thrombus predictions, but at significantly lower computational costs.

Lastly, this chapter presented the application of the hemodynamics-based model to the study of thrombosis in idealized Type B aortic dissection models under realistic flow conditions. Key geometric parameters were varied in order to study their effects on thrombosis, and the results showed a potential association between size and location of tears and the formation of thrombus in the false lumen. A higher probability for complete thrombosis of the false lumen was predicted for dissections presenting only one proximal or distal tear, while in cases with multiple tears thrombus formation was confined to specific regions of the FL. This study showed that smaller tears could increase the likelihood for thrombosis as they produce higher shear stress on the tears, promoting platelet activation, and favour the formation of extended recirculations zones. The effect of varying the distance between proximal and distal tears was also studied. Although a larger distance between tears was associated with higher local shear stress and flow recirculation in the middle region of the FL, a shorter distance between tears resulted in more disorganized flow patterns between the tears, increasing the probability for thrombosis in this region.

Results presented in this chapter show good qualitative agreement with previous *in vivo* observations, highlighting the potential applicability of such a modelling approach to thrombosis prediction in realistic geometries. In the following chapters, the hemodynamics-based model developed in this study will be applied to patient-specific case studies, in order to validate the model and to investigate the impact of the assumptions made.

Model Validation (1) - Patient-Specific Prediction of False Lumen Thrombosis in Medically Treated Aortic Dissection[†]

The results obtained in the previous chapter demonstrate the potential applicability of the proposed computational approach to the study of false lumen thrombosis in patient-specific dissection. The application of the model to patient-specific geometries is an essential step in the validation and evaluation of the model's suitability for clinically relevant studies. In this chapter, the model is further refined and applied to a patient-specific Type B aortic dissection reconstructed from medical images. Predicted patterns of thrombus formation and growth are compared with multiple follow-up CT scans of the same patient in order to demonstrate the applicability of this approach to clinical studies.

5.1 Methodology

5.1.1 Thrombosis Model

Thrombus formation was simulated by using the hemodynamics-based model presented in Chapter 3. The computational model is based on transport equations for fluid residence time (RT), resting and activated platelets (RP and AP), and a coagulant (C), while a growing thrombus is identified

[†]This chapter is adapted from: *Menichini, C, Cheng, Z, Gibbs, RG and Xu, XY (2016). Predicting false lumen thrombosis in patient-specific models of aortic dissection. Journal of The Royal Society Interface, 13(124), 20160759. [118]*

through the local concentration of bound platelets (BP). The transport equations have been simplified in specific regions for more efficient computation, and thrombus growth is controlled through a feedback loop involving C and BP. Details of the mathematical equations can be found in Chapter 3, but a number of important changes have been made which are described below.

For the transport of coagulant, a fixed coagulant concentration was applied at the walls in the previous chapters. This has been replaced with a flux boundary condition, with the flux depending on the local time-averaged wall shear stress (TAWSS) of the previous cardiac cycle and the local concentration of BP:

$$D_{eff} \frac{\partial C}{\partial n} \Big|_{wall} = \begin{cases} k_{c_{wall}} & \text{if } TAWSS \leq 0.2 \text{ Pa} \ \& \ BP \leq 200 \text{ nM} \\ 0 & \text{otherwise} \end{cases} \quad (5.1)$$

$$D_{eff} = \phi_{\dot{\gamma}} D_c \quad (5.2)$$

$$TAWSS = \frac{1}{T} \int_0^T |\tau_w| dt \quad (5.3)$$

where D_{eff} is the effective coagulant diffusivity, T is the cycle period and $|\tau_w|$ is the magnitude of instantaneous local wall shear stress. The $k_{c_{wall}}$ value is fixed at $20 \text{ nmol} \cdot \text{m}/\text{L} \cdot \text{s}$. The flux becomes zero when complete thrombosis is achieved ($BP > 200 \text{ nM}$). Thrombus growth on the walls can only occur if local TAWSS is lower than 0.2 Pa, and a bulk shear rate threshold of 50 s^{-1} is adopted for thrombus growth away from the wall. Also, a consumption term is introduced in the coagulant transport equation, in order to prevent accumulation of C in regions of high shear:

$$\frac{\partial C}{\partial t} = D_{eff} \nabla^2 C + k_c \phi_C - k_c (1 - \phi_{\dot{\gamma}}) \quad (5.4)$$

Definitions of symbols and parameter values are given in Table 5.1.

Also included in the model is transport within formed clots which are treated as porous media, with their porosities varying between 0.75 for completely formed clots and 1 for no-thrombus [119], depending on the BP concentration:

$$\epsilon = \max\left(1 - \frac{BP^2}{BP^2 + BP_t^2}, 0.75\right) \quad (5.5)$$

where BP_t is a threshold value fixed at $20 \text{ nmol}/\text{L}$. In addition, the momentum equation has been modified to account for the effects of time-varying porosity and includes a momentum source

Table 5.1: Definition of symbols and parameter values.

Symbol	Parameter	Value	Units
ϵ	Clot porosity		-
k_c	Coagulant kinetic constant	200	$nmol/L \cdot s$
$k_{c_{wall}}$	Coagulant wall-kinetic constant	200	$nmol/L \cdot s$
k_M	Momentum source constant	10^7	kg/m^3s
D_c	Coagulant diffusivity	10^{-8}	m^2/s
$D_{c_{eff}}$	Effective coagulant diffusivity		m^2/s
BP_t	BP threshold	20	$nmol/L$
$\dot{\gamma}$	Shear rate threshold	50	s^{-1}
ϕ_{BP}	Switching coefficient for BP		-
ϕ_C	Switching coefficient for coagulant		-
$\phi_{\dot{\gamma}}$	Switching coefficient for shear rate		-
S_M	Momentum source		kg/m^2s^2

proportional to the concentration of BP to account for the effects of thrombus growth on the flow field:

$$\rho \frac{\partial \epsilon \mathbf{u}}{\partial t} + \nabla \cdot (\rho \epsilon \mathbf{u} \times \mathbf{u}) = -\epsilon \nabla p + \nabla \cdot (\mu \epsilon (\nabla \mathbf{u} + \nabla \mathbf{u}^T)) - \epsilon S_M \quad (5.6)$$

$$S_M = k_M \frac{BP^2}{BP^2 + BP_t^2} \mathbf{u} \quad (5.7)$$

where the vector $\mathbf{u}$ is velocity, t is time, ρ is blood density, p is pressure, and μ is blood viscosity. The momentum source S_M accounts for the resistance imposed by clots on blood flow. This modification replaces the hyperviscous model adopted in the previous chapter to simulate the solid nature of clots.

5.1.2 Model Geometry

A 44-year old male patient presenting acute uncomplicated aortic dissection extended beyond the iliac bifurcation was analysed in this study. The patient was given medical treatments and kept under surveillance after being released from the hospital. Follow-up CT scans at 8 different stages during an overall period of three years showed spontaneous formation of thrombus in several regions of the FL (Fig. 5.1). Two different phases could be clearly distinguished: in early stages thrombus formation was initiated at the top of the FL and expanded in the proximal region (Fig. 5.1 S1-S4); in a second phase, lateral thrombosis of the FL was observed, which appeared to be associated with the formation of a second tear in the middle region (Fig. 5.1 S5-S8).

Two computational models of the dissected aortas were reconstructed from CT scans by using the image processing software Mimics (Materialise HQ, Leuven, Belgium): one corresponding to

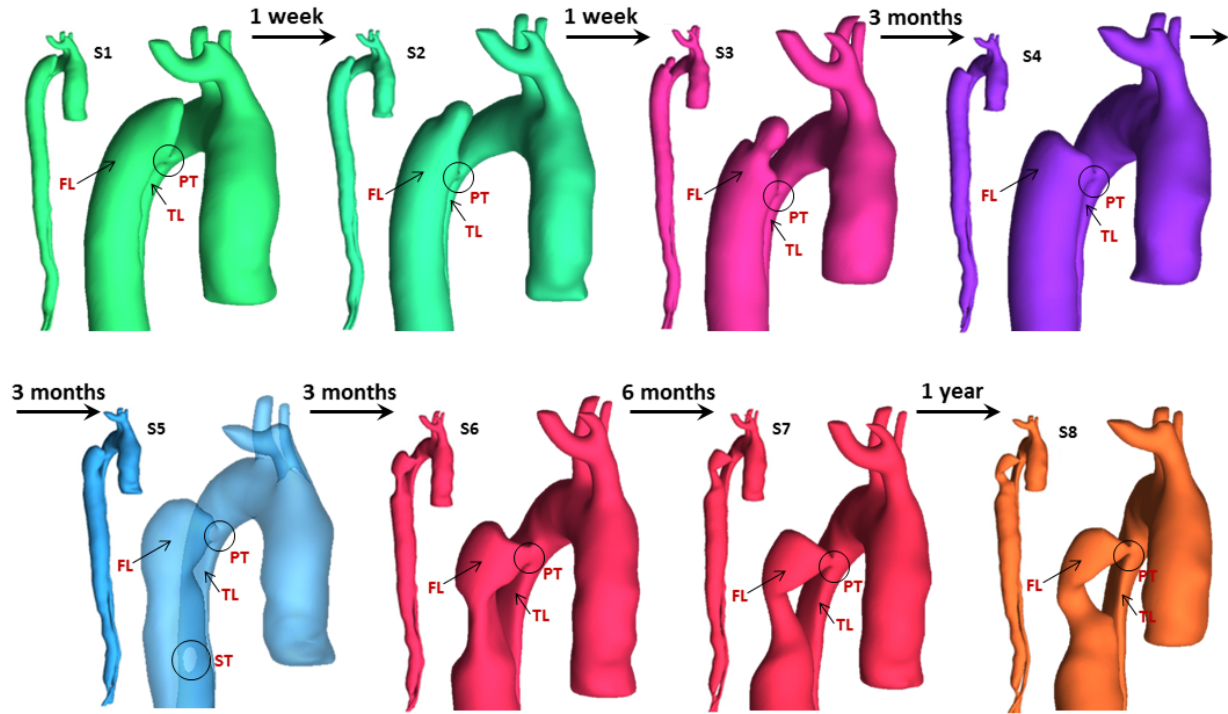


Figure 5.1: Geometrical descriptions of the aortic dissection at eight follow-up stages. The primary entry tear (PT), true lumen (TL), false lumen (FL) and second tear (ST) are indicated.

the first set of CT scans collected on admission (S1), and one corresponding to the end of the first phase (S4) in order to test the models capability to predict the lateral thrombus observed in the second phase (S5-S8). Although images acquired at S4 did not show the presence of a middle tear, it was clearly visible at S5, suggesting that the middle tear was formed during the period between S4 and S5, but no scan was performed to capture the exact moment. To overcome this problem, a middle tear was artificially introduced in the second geometry (Fig. 5.2) based on information extracted from S5. As the primary aim of this study was to predict thrombus formation within the false lumen, all the aortic branches were excluded, and those regions were assumed to be non-thrombotic.

The two geometries were meshed using ICEM 15 (Ansys Inc.) and discretized into unstructured grids of approximately 3 million elements each comprising a tetrahedral core with a maximum element size of 1.5 mm and 10 prismatic layers near the walls. The prismatic layers were necessary to control mesh resolution in the boundary layer and ensure convergence of the near wall transport equations. Mesh sensitivity tests were performed together with local mesh refinement around the tears to obtain a final mesh which was deemed sufficient for mesh independent solutions.

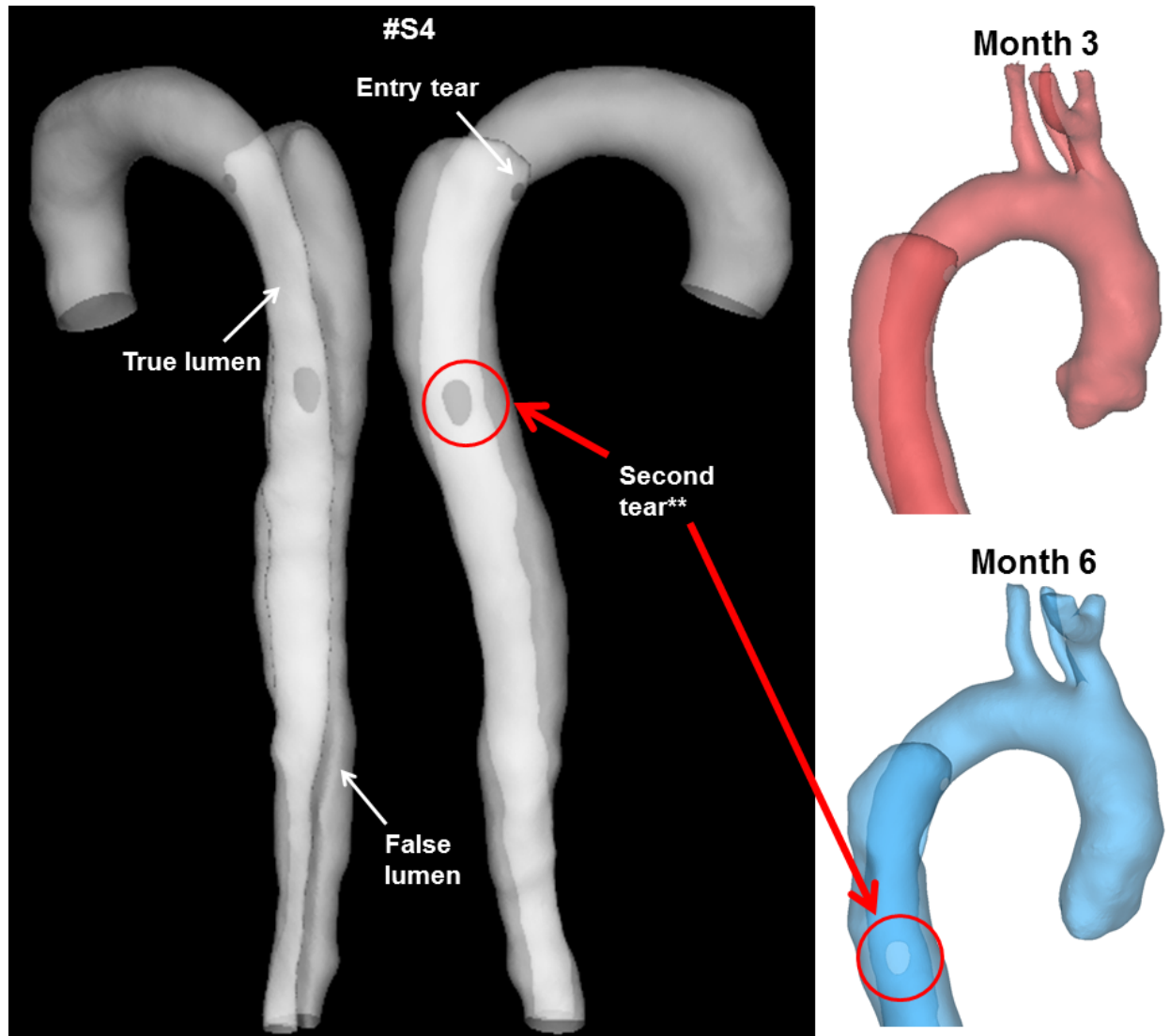


Figure 5.2: Transparent view of the model S4, showing true lumen, false lumen, and tears. The original model S4 (top-right, “Month 3”) was modified by artificially introducing a second tear based on the follow-up model S5 (bottom-right, “Month 6”).

5.1.3 Computational Details

The patient-specific models were implemented in Ansys CFX 15 and simulated for a total of 20 cardiac cycles. Blood was treated as a non-Newtonian fluid described by the Quemada viscosity model [94] and the flow was assumed to be laminar. The model variables were initialized at steady state with a physiological concentration of $2.5 \cdot 10^8$ platelets/mL, a background activation level equivalent to 5% of the inlet platelet concentration [78] (further details and justification are given in the next subsection) and zero concentration for all other species.

A realistic flow waveform was applied at the inlet with a flat profile and a period of 1.054 s and a Womersley number of 20.8 [40]. Zero relative pressure was imposed at the outlet [40], which was located slightly above the iliac bifurcation. The walls were assumed to be rigid with no slip conditions. A physiological concentration of $2.5 \cdot 10^8$ platelets/mL was specified at the inlet, with zero concentration for all other species. The system was simulated for 2 cardiac cycles to obtain a periodic flow solution and to initialize the model variables, and the thrombus model was introduced from the third cardiac cycle. The results were analyzed with the post-processing software CEI Ensight 10.

For model S4, an initial wall coagulant concentration equivalent to 1% of the maximum value observed in the patient model S1 was specified to account for the convective effects which are neglected in the thrombus model. Coagulant consumption and production were allowed from the second cardiac cycle, before introducing the actual thrombosis model. This allowed the coagulant concentration to build up in regions of high viscosity and high residence time, or to drop back to zero. As the top region of the FL in S4 was already thrombosed, the top FL surface was specified as thrombus, with a fixed coagulant flux.

5.1.4 Mechanical Activation of Platelets

A background activation level equivalent to 5% of the inlet platelet concentration was assumed [78, 120] on the basis of a potentially thrombogenic surface caused by the tearing of the aortic wall and mechanical activation of platelets by the high shear stress experienced in proximity of the tears. This assumption was evaluated by using the Lagrangian-based model of shear-induced platelet activation introduced by Grigioni et al. [121] and calibrated through *in vivo* experiments by Nobili et al. [115]. The model quantifies the cumulative load history acting on platelets exposed to time-varying shear stress levels. This is represented by the Platelet Activation State (PAS) index, which (for the $k - th$ trajectory) can be calculated as:

$$PAS_k = \int_{t_k^0}^{t_k} Ca \left[\int_{t_k^{start}}^{\zeta} \tau_k(\xi)^{b/a} d\xi + \frac{PAS_k(t_k^0)^{1/a}}{C} \right]^{a-1} \times \tau_k(\zeta)^{b/a} d\zeta \quad (5.8)$$

where t_k represents the exposure time, τ_k is the time-varying shear stress load, $PAS_k(t_k^0)$ the initial platelet activation value, which was assumed to be zero. The constants a , b and C were taken from Nobili et al. [115] with $a = 1.3198$, $b = 0.6256$, and $C = 10^5$. This function was integrated over

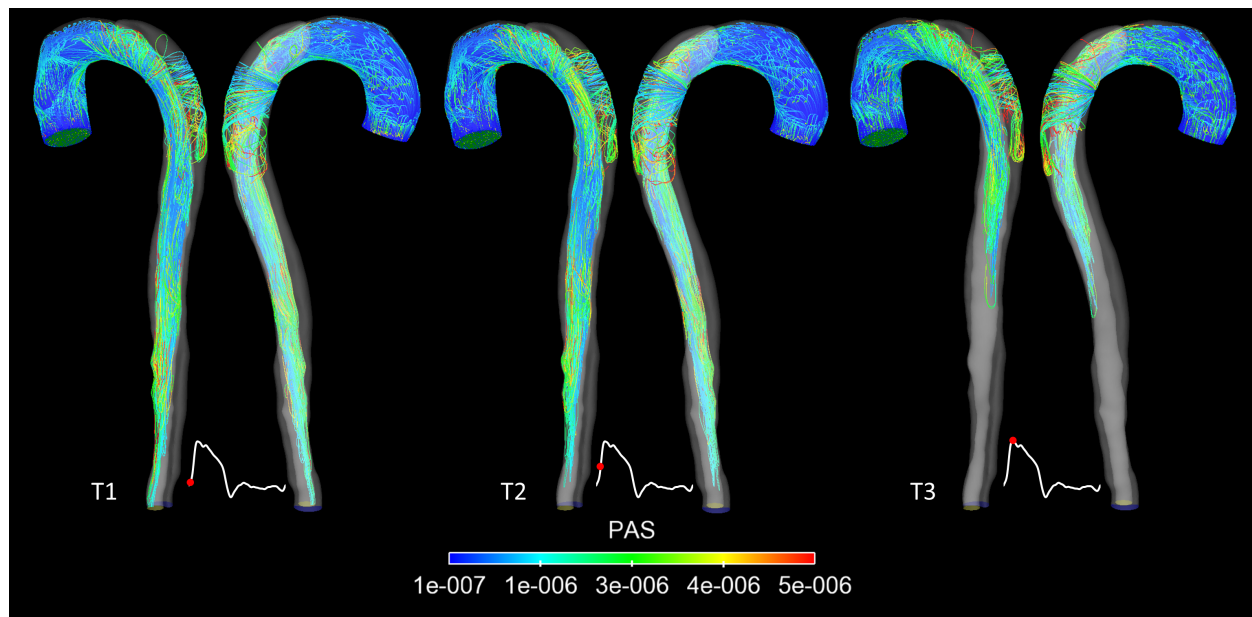


Figure 5.3: Pathlines of particles ejected at three different time points over the cardiac cycles in the model S1. The trajectories are color-coded with local PAS values and show the effects of mechanical shear load history on platelet activation.

the trajectories of particles emitted from the inlet at four different time points in a cardiac cycle: beginning of systole, mid-systolic acceleration, peak systole, and mid-systolic deceleration. The particle trajectories were created in Ensight and imported into a user-developed Python code in order to integrate the PAS function over the particle pathlines. The results were then visualized in CEI Ensight 10.

5.2 Results

5.2.1 Platelet Activation

Fig. 5.3 shows color-coded platelet-like particles emitted from the inlet at three different time points over a cardiac cycle and tracked for 10 cycles. Activation levels compare well with values previously reported in the literature [122]. As expected, the highest activation levels are observed for those platelets crossing the entry tear and transported into the false lumen (FL). Platelets emitted during early to peak systole are more likely to be mechanically activated, as there is more flow diverted through the tear in systole than in diastole. The high residence time experienced in the FL and the presence of flow recirculation and stasis will then provide an ideal environment for

deposition of activated platelets. All these observations support the assumption that the action of high shear stress in the tear region may have stimulated the initial platelet activity, justifying an initial non-zero concentration of activated platelets.

5.2.2 Wall Shear and Residence Time Distribution

Large spatial variations in time-averaged wall shear stress (TAWSS) can be observed in both geometries (Fig. 5.4). High TAWSS occurs in proximity of the tears, where flow is diverted into the FL at high velocity. As discussed in the previous section, these high shear values could possibly stimulate cell activity and promote platelet activation. Much lower shear stress values are found in the top FL region in the model S1, corresponding to a high residence time and viscosity. In the model S4, shear stress below 0.4 Pa is observed in the top FL and between the two tears. The formation of a second entry tear clearly affects the flow pattern in the region between the tears, resulting in reduced wall shear stress. As thrombus grows in the top FL, the shear stress in the middle region is reduced even further, leading to the formation of a new thrombus.

Distributions of normalised RT, expressed in number of cycles, at peak systole and mid-diastole in S1 and S4 are presented in Fig. 5.5. In both models, fluid residence time above 5 cardiac

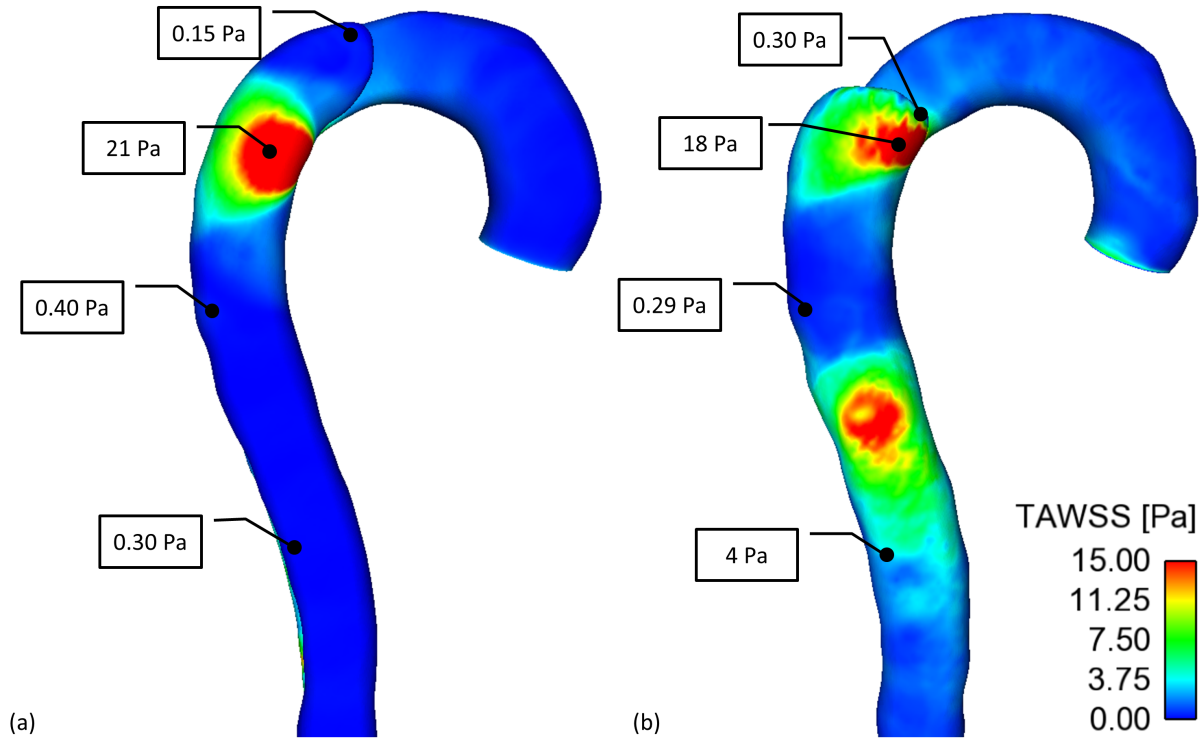


Figure 5.4: TAWSS distribution in (a) S1, and (b) S4, before thrombus growth is initiated.

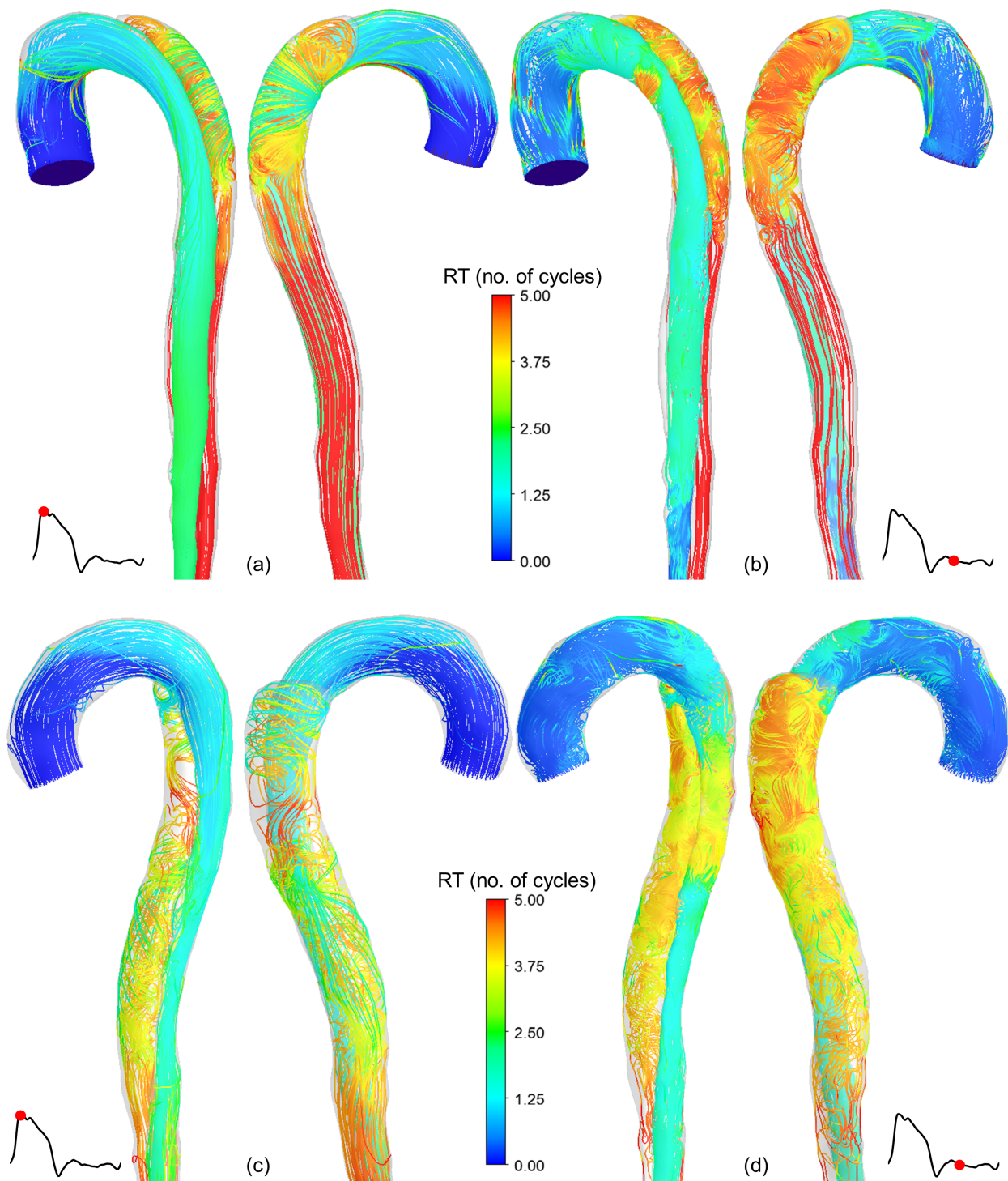


Figure 5.5: Instantaneous streamlines at peak systole in S1 (a) and S4 (c), and in mid-diastole in S1 (b) and S4 (d), showing the local RT distribution, expressed in number of cardiac cycles.

cycles is observed in parts of the FL, suggesting partial flow stagnation there. The formation of a

second tear alters flow features in the FL resulting in more chaotic flow patterns and a reduction in local fluid residence time as compared to model S1. RTs in the true lumen (TL) are within the normal range as compared to a baseline value defined as L/v_{mean} , representing the characteristic time scale of blood convection through the system, where L is the distance travelled along the centerline, and v_{mean} is the mean cycle-velocity. During the diastolic phase, fluid particles with high RTs are transported from the FL into the TL. In the model S4, a recirculation zone between TL and FL is also created between the two tears (Fig. 5.5d). These recirculating fluid particles characterized by a high RT are then transported away from the domain in systole (Fig. 5.5c).

5.2.3 Thrombus Growth Over Time

Thrombus formation is initiated in regions of low shear stress, high residence time, and high concentration of AP. As expected, the top FL region in the model S1 is gradually thrombosed over time (Fig. 5.6). Thrombosis is initiated at different locations, and expands towards the proximal tear, showing good qualitative agreement with *in vivo* observations (Fig. 5.6 #S2 and Fig. 5.7).

In the model S4, the presence of a second tear affects flow patterns in the region between the two tears, and causes a local fall in wall shear stress on the lateral walls, resulting in gradual formation of thrombi in multiple locations. As shown in Fig. 9a and 9b, there is a good qualitative agreement between model predictions and follow-up CT scans of the patient. In particular, the predicted location and shape of thrombus on the lateral FL side agree very well with the geometry reconstructed from images acquired at S6 (Fig. 5.8a), although comparisons at a transverse plane (Fig. 5.8b) reveal some differences near the flap (the thin wall separating the true and false lumen).

5.3 Discussion

The role of hemodynamics in thrombus formation has been investigated by many researchers. Studies by Sheriff et al. [60] and Nesbitt et al. [61] emphasized the importance of shear gradients in the development of thrombosis, showing that thrombus formation is generally associated with rapid changes in blood flow and preferentially takes place in regions of low shear [123]. Nesbitt et al. [61] also revealed that platelet aggregation is primarily driven by changes in rheological properties of blood and local hemodynamics, with soluble agonists having a negligible role. Based on these findings, a hemodynamics-based predictive model for thrombosis in patient-specific dissections

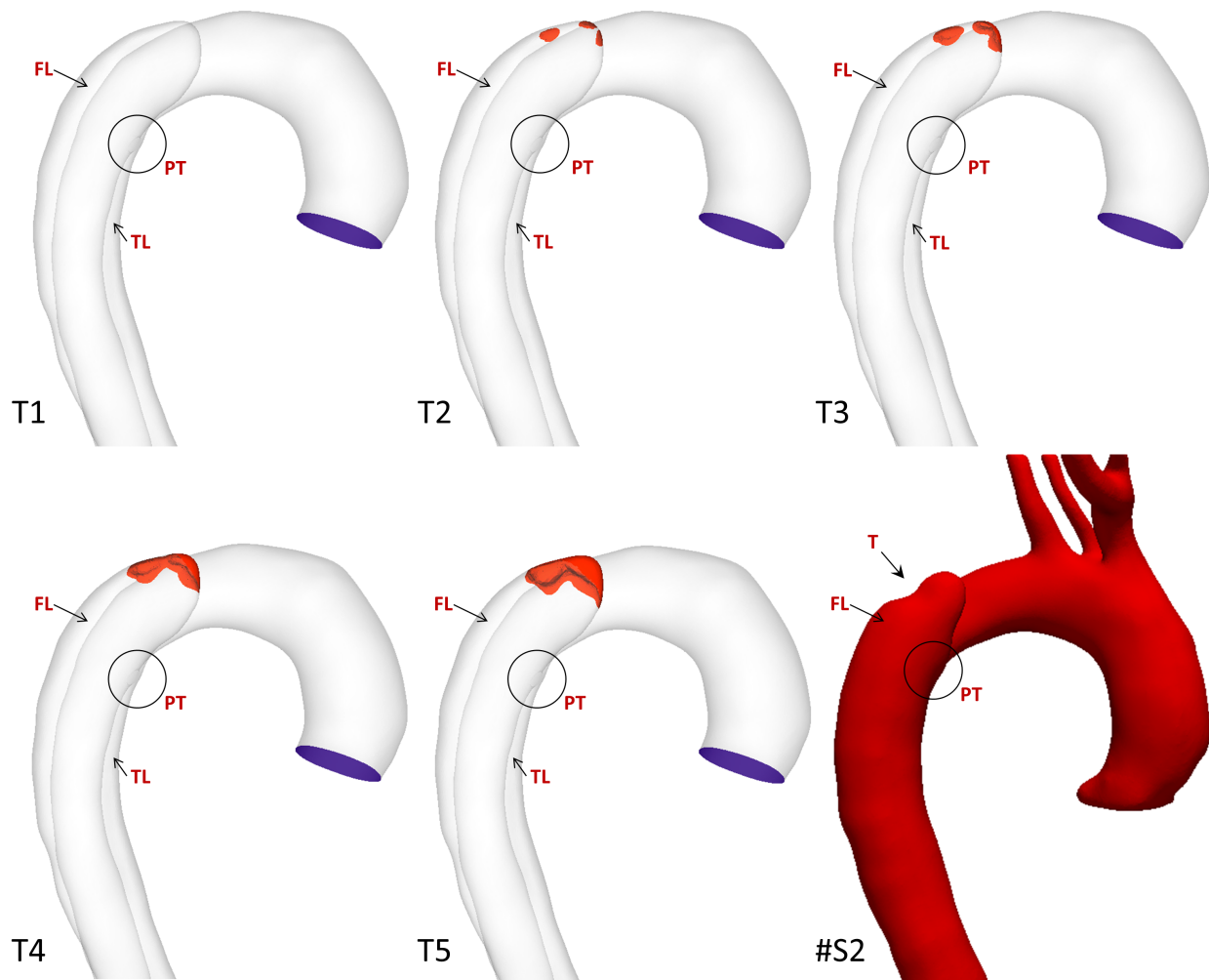


Figure 5.6: In red, thrombus forming over time at $T1 = 2$ s, $T2 = 6$ s, $T3 = 10$ s, $T4 = 15$ s, $T5 = 20$ s, compared to subsequent thrombus formation observed in follow-up geometry S2 extracted from CT scans acquired after one week. FL = false lumen, TL = true lumen, PT = proximal tear, T = thrombosed region.

under pulsatile flow has been developed, which is presented in Chapter 3. This is achieved by using hemodynamics-related parameters as surrogates so as to bypass the need for simulating the complex chain of biochemical processes. The model simulates the coagulation process by using a coagulant which forms on the walls exposed to high residence time and low shear. The transport of coagulant simulates the expansion of the reaction zone, which is characterized by low Peclet numbers and diffusion-limited reactions. To incorporate the effects of convection on thrombus growth, saturation functions controlled by time-averaged shear rates are introduced to turn the process on and off depending on the local hemodynamic environment. The model has been previously tested on idealized 2D aortic dissection models and a 3D backward-facing step (Chapter 4), demonstrating

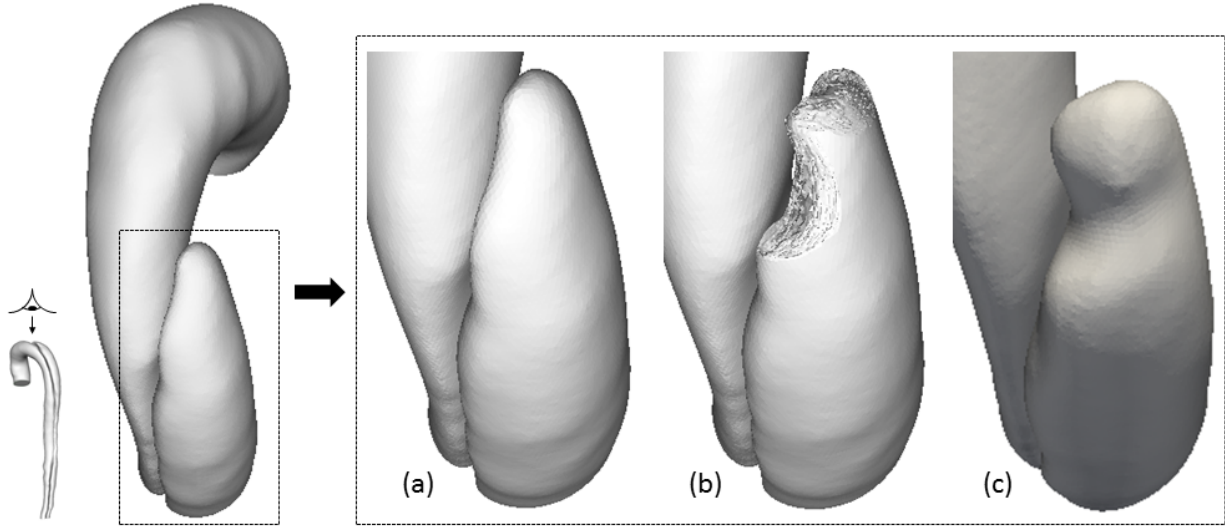


Figure 5.7: Comparison between predicted lumen surface in S1 and follow-up geometry S2. (a) Original lumen surface in S1, (b) predicted lumen surface after thrombus growth, (c) lumen surface in follow-up geometry S2, extracted from images acquired one week after S1.

good agreement with expected trends and experimental observations from Taylor et al. [106]. Here, its applicability to realistic geometries and pulsatile flow has been further tested.

Platelet activation. In order to evaluate the likelihood for shear-induced activation, the PAS function accounting for the mechanical loading history acting on blood cells is integrated over particle trajectories in S1. Results show that particles passing through the tear are subject to a high shear load, which can potentially stimulate cell activity and promote subsequent adhesion on the walls. As flow in the FL is partially stagnant, it is likely that those particles previously exposed to high levels of shear will be trapped in flow recirculation regions, leading to thrombosis in regions of high viscosity and low shear stress. The initial inlet concentration of AP was fixed at 5% of the inlet concentration of RP. This value, previously proposed by Sorensen et al. [78] and also adopted by Anand et al. [88], Bedekar et al. [89] and Taylor et al. [120], allows us to reach local AP concentrations needed for the formation of BP within a short time frame, while still preventing high AP concentrations in non-thrombotic regions. As BP is the only variable directly dependent on local AP values, results are not particularly sensitive to the initial AP concentration. Changes in local BP concentrations are linearly proportional to variations in AP levels [91], thus only large changes in the initial AP concentration by several orders of magnitude would significantly affect BP values and hence thrombus formation and growth.

Identifying regions of thrombus formation. Analysis of flow at different follow-up stages has

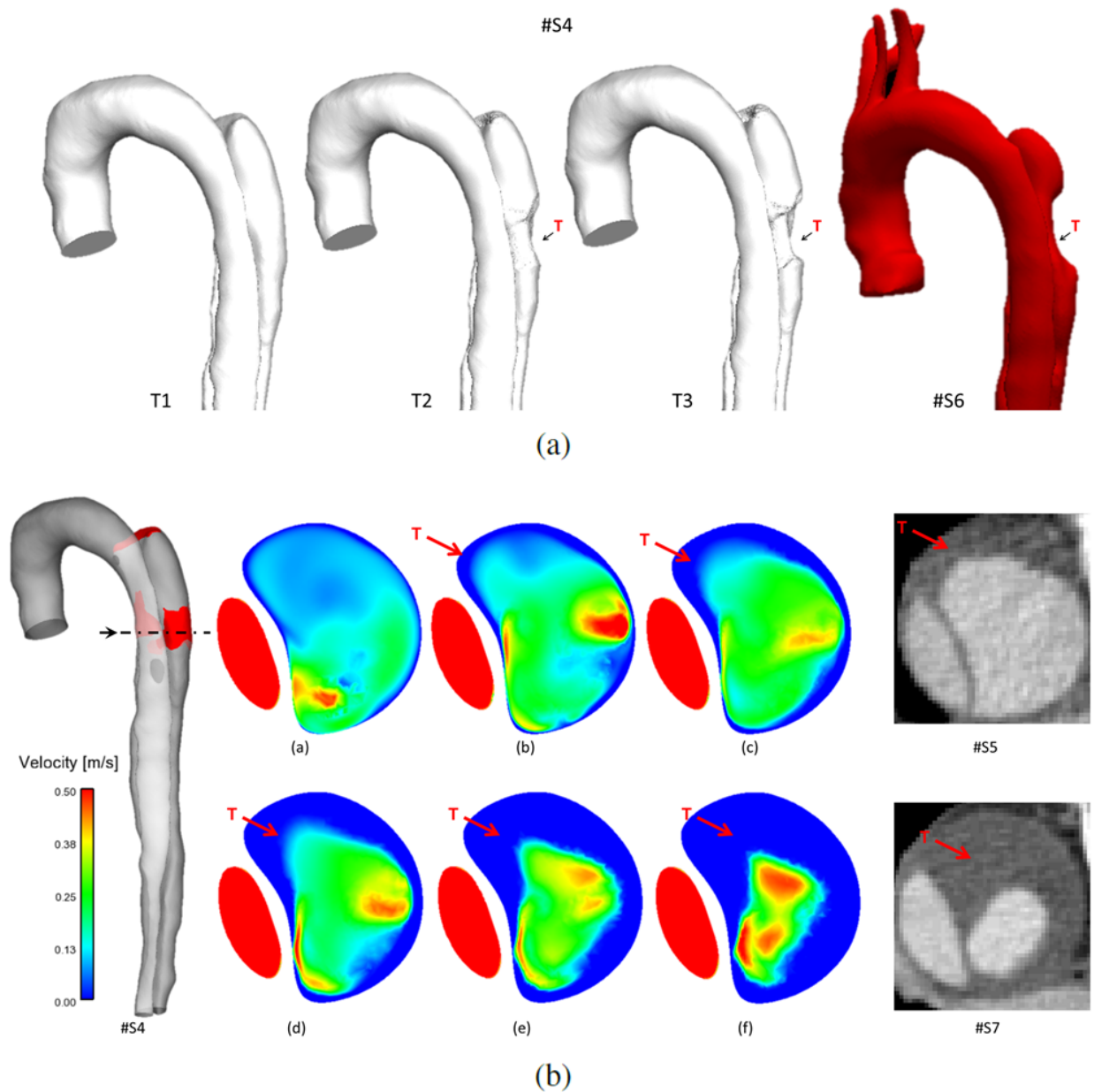


Figure 5.8: (a) Time evolution of the fluid domain at $T1 = 3$ s, $T2 = 14$ s, and $T3 = 21$ s, compared to subsequent thrombus formation (T) observed in follow-up geometry S6, extracted from CT scans acquired six months after S4. (b) Velocity magnitude contours at peak systole just above second tear showing the effects of thrombus growth (T) on the flow field at different time points (a) $t = 3.25$ s, (b) $t = 7.47$ s, (c) $t = 9.58$ s, (d) $t = 13.8$ s, (e) $t = 15.9$ s, and (f) $t = 21.2$ s, compared with follow-up CT scans from models S5 and S7, taken respectively after 3 and 9 months from S4. The velocity in the thrombosed region is gradually reduced as thrombus is formed. In the model S4 (left), in red, thrombus.

shown an association between thrombus formation and low TAWSS, which is used as a key parameter to initiate thrombosis on the wall. Other low-shear based models have been reported by

Harrison et al. [97], Zimny et al. [124] and Malaspinas et al. [125]. Regions of particularly low shear stress are associated with high residence time and increased blood viscosity, which favour cell-cell interactions and increase the likelihood for cell adhesion on vessel walls [52]. Since the predicted thrombus formation is sensitive to the chosen wall shear threshold, it is important to identify a suitable value for clinical applications. From the patient-specific analysis of hemodynamic parameters at different follow-up stages and subsequent CT scans, a single TAWSS threshold of 0.2 Pa was found to be capable of predicting the exact locations of thrombus formation. A lower threshold would cause slower growth while higher thresholds were found to over-predict thrombus growth, especially for threshold values greater than 0.25 Pa. However, no significant differences were found in the location of thrombus formation and its growth pattern. Nevertheless, further studies on a large cohort of patients will be required in order to test the validity of this threshold value for general applications. On the other hand, experimental evidence demonstrates that particularly high shear stress might also play an important role in thrombosis by stimulating local platelet aggregation via von Willebrand Factor (vWF), and several computational models have been proposed to simulate this process [72, 126]. The results presented in this chapter appear to indicate that low-shear thrombotic pathway is more important in FL thrombosis in Type B aortic dissection. Nevertheless, it would be desirable to also examine the role of high-shear thrombotic pathways for a more complete description of thrombus formation.

Thrombus growth. With artificially accelerated kinetics, the process has been simulated over 20 cardiac cycles, which is much shorter compared to the real time scale for thrombosis in dissection. This acceleration is possible as regions of thrombus growth are generally associated with relatively low velocities, so that growth only causes gradual changes in flow. Similar approaches have been adopted by others [109, 125, 127]. By neglecting convection and considering the time-averaged effects of hemodynamic parameters such as shear rates and residence time, regions of potential thrombosis can be identified while interactions between blood flow and thrombus growth can also be accounted for. The effects of thrombus growth on the flow field are captured through a momentum source term and changes in local porosity [50, 109]. While most of previous models assumed steady flow [78, 71, 50, 120], it was found that areas of flow recirculation and low shear could be better captured through time-averaged variables under pulsatile flow. The use of time-averaged values can also reduce the dependence of the process on inlet boundary conditions which are subject to large variations over the actual time course of thrombus growth.

Comparisons with follow-up scans taken from the patient at different time points have demonstrated that the model is able to capture the formation of thrombus and its expansion in the proximal region of FL during the initial phase (model S1); thrombosis started on the outer wall and gradually expanded towards the entry tear. The growth of thrombus on the side walls of FL during the second phase was also reasonably well predicted by including a newly-formed middle tear in model S4, which altered flow features and caused a drastic reduction in shear stress and the formation of a flow recirculation region proximal to the new tear. Also, as the CT scans for model S4 were acquired more than three months after the patient showed the first signs of thrombosis, it is reasonable to assume that, if other potentially thrombotic regions existed, coagulation factors produced within the forming thrombus and transported by the flow could have slowly built-up near the walls. This reasoning justified an initial non-zero concentration of coagulant on the walls, which was applied two cardiac cycles before running the thrombus model, in order to allow wall concentrations to drop back to zero in non-thrombotic regions. Simulated thrombus growth patterns are in good agreement with follow-up data. Some discrepancies were observed near the flap side, where the predicted distance between the thrombus and the proximal tear was larger than that measured from subsequent CT scans.

Overall, simulation results show satisfactory agreement with patient-specific follow-ups, although the present study has several limitations. The use of time-averaged variables, the rigid wall assumption, and the exclusion of aortic branches may affect the distribution of hemodynamic parameters [45, 41] thereby influencing the overall prediction of thrombus growth. In particular, the intimal flap between the TL and FL may be subject to motion driven by the pressure difference between the two chambers. The effects of wall compliance and viscoelastic behaviour of blood clots should be investigated in future studies. Other limitations involve the assumptions made in creating the model geometry. Model S4 was virtually modified by adding a second tear extracted from follow-up scans acquired three months later. During the interval between S4 and S5, the patient geometry experienced significant changes, including enlargement of the tear diameter, thrombus growth in the proximal region, and formation of micro-tears on the flap. Although these changes are likely to affect local flow patterns and shear distribution, a comprehensive wall model would be required to solve simultaneously the deformation of the TL and FL, and to predict any potential expansion or rupture, which is beyond the scope of the current study.

Lastly, this study focuses on predicting the possibility and extent of FL thrombosis rather than the duration of the process. Thrombus growth is accelerated in order to improve computational

efficiency so that simulation of FL thrombosis can be achieved in a feasible time frame (e.g. 20 cardiac cycles in the current study). A similar strategy has been adopted by others to simulate thrombosis in cerebral aneurysm [109, 125]. The relationship between the simulated time scale and real time scale was examined using the backward-facing step presented in the previous chapter under steady flow. The simulation results obtained with an augmentation factor of 150 for coagulant diffusivity were compared with experimental data [106], and there was a good agreement between predictions obtained after a simulation time of 40 s and measurements taken at 90 min, suggesting that the simulation time could be multiplied by the augmentation factor ($40 \times 150 = 6000$ s) to roughly estimate the equivalent real time (90 min = 5400 s). However, such a simple relation may not apply to pulsatile flow, as the interface between diffusion-dominated and convection-dominated domains hinders the transport of proteins and coagulation factors to the clot surface. Given that a number of patient-related and environmental factors might also affect thrombus growth rates, it is not possible to deduce what relationship exists between the simulated time scale and real-time thrombus growth from a single patient case study. Multiple patient-specific case studies and comparisons with experimentally derived biochemical models are required to elucidate the relationship between the two different time scales.

5.4 Summary

The work presented in this chapter represents the first attempt to predict FL thrombosis in patient-specific Type B aortic dissections. The hemodynamics-based model presented in Chapter 3 is applied to a patient-specific case and validated against *in vivo* data collected at 8 follow-up scans over three years. The two separate stages in thrombus growth observed from CT scans were well captured by the computational model, which was able to predict initial growth of thrombus in the proximal region and subsequent lateral thrombosis caused by the formation of a second tear. In the following chapters, this computational model will be applied to more medically and endovascularly treated dissection patients for further validation. Once fully validated, the model could be used to predict FL thrombosis based on patient-specific information at the time of initial diagnosis, which would provide great assistance in clinical decision making.

Model Validation (2) - Patient-Specific Prediction of False Lumen Thrombosis Following Thoracic Endovascular Repair[†]

Thoracic endovascular aortic repair (TEVAR) has been recently established as a viable alternative to open surgery for complicated acute Type B distal dissections [129], and has shown promising results for the treatment of both acute and chronic uncomplicated cases [28, 31]. This minimally invasive procedure involves the placement of an endovascular stent-graft in order to seal the primary entry tear in the hope of reducing pressure in the false lumen (FL), promoting remodelling of the aorta, and inducing complete FL thrombosis, thereby restoring aortic flow. However, complete FL thrombosis is not always achieved. Risk factors such as the presence of distal re-entry tears and visceral vessels arising from the FL can lead to retrograde flow along the length of the stent-graft and perpetuate FL flow leading to incomplete thrombosis [130]. The latter has been associated with higher mortality rates due to increases in FL mean and diastolic pressure, resulting in further complications, such as aortic expansion and the formation of stent graft-induced new entry tears [131]. It is therefore important to understand the hemodynamic and biomechanical consequences of TEVAR and what stent-graft designs and aortic morphologies would favour complete FL thrombosis.

The hemodynamic-based model introduced in the previous chapters has shown promising results for the application of such approach to the study of thrombosis in patient-specific Type B

[†]This chapter is adapted from: Menichini, C, Cheng, Z, Gibbs, RG and Xu, XY. *A computational model for false lumen thrombosis in Type B aortic dissection following thoracic endovascular repair. Journal of Biomechanics*, 66, 36-43. <https://doi.org/10.1016/j.jbiomech.2017.10.029> [128]

dissection. In this chapter, the model is further extended and applied to TEVAR patients showing respectively complete and incomplete false lumen thrombosis during follow-up, and to a medically treated patient with no signs of thrombosis. The model's predictive capability is validated by qualitative and quantitative comparisons with *in vivo* data.

6.1 Methodology

Two patient-specific post-TEVAR models were included in this study: (i) one for a patient who developed complete FL thrombosis following TEVAR (TEVAR-P1), (ii) one for a patient who developed partial FL thrombosis (TEVAR-P2). Both patients were classified as complicated, and were treated with TEVAR in acute phase. Patient TEVAR-P1 was treated with a Gore C-TAG device (W. L. Gore & Associates, Flagstaff, Arizona; proximal diameter: 31mm, distal diameter: 31mm, endoprosthesis length: 20 cm), while patient TEVAR-P2 was treated with a Medtronic Valiant Captivia device (Medtronic/AVE, Minneapolis, Minnesota; proximal diameter: 34mm, distal diameter: 34mm, endoprosthesis length: 20 cm). A third medically treated uncomplicated patient who only underwent medical treatments and did not show any signs of FL thrombosis during follow-up was also included as a benchmark case (BMT). All patients were kept under CT surveillance. Formal ethical approval was not required for this retrospective study, as prior agreement was made to undertake computational modelling work using totally anonymised images without requiring further specific ethics committee agreement for individual patients. All data were analysed anonymously and patient information was de-identified prior to analysis.

The patient-specific geometries were reconstructed using Mimics (Materialize HQ, Leuven) from CT images acquired within one month after TEVAR. The CT scans were performed with a Philips Mx8000 IDT 16 scanner, with voxel sizes in the range of $(0.75-0.92) \times (0.75-0.92) \times 2 \text{ mm}^3$ and FoVs between 382 and 477 mm. As the focus of this study was to predict thrombosis within the FL, all branches were excluded from the analysis. The models were meshed using ICEM 15 (Ansys Inc.), and mesh sensitivity tests were performed to ensure mesh independence for each case. As the growth of thrombus is driven by hemodynamic parameters, the sensitivity test was focused on ensuring mesh independence of the flow field. Three meshes were tested for each geometric model, and differences in peak wall shear stress and velocity below 5% were considered acceptable. The final grids represented a compromise between accuracy and computational cost and comprised

approximately 3 million elements each, with a tetrahedral core and 10 prismatic layers near the walls. A fine resolution in the boundary layer is essential to guarantee accuracy in shear stress predictions and smooth thrombus propagation. Larger element size was used in the core region away from the walls. A gradual change in mesh size was made and a mesh expansion factor below 30 was ensured for the entire domain to prevent sudden changes in mesh element size, which could compromise thrombus growth patterns.

Thrombus formation was simulated using the hemodynamics-based model presented in Chapter 3 and modified in Chapter 5. The computational model identifies regions of thrombus growth through the evaluation of time-averaged wall shear stress and shear rates, as well as the distribution of activated and resting platelets and fluid residence time. The growth of thrombus is tracked through the local concentration of a species denoted as bound platelets (BP), which is used as a surrogate for thrombus. Thrombus growth is predicted through a feedback mechanism which controls the formation of thrombus by allowing BP to accumulate in regions of high concentration of activated platelets, low shear and long residence times, and by stopping thrombus growth when these conditions are not satisfied. As in the previous chapters, the simulated rate of thrombus growth was artificially accelerated in order to allow predictions to be obtained in a feasible time frame.

The patient-specific models were implemented in Ansys CFX 15 and a high resolution spatial differential scheme was adopted. Blood was treated as a non-Newtonian fluid described by the Quemada viscosity model [94] and the flow was assumed to be laminar. A realistic flow waveform extracted from PC-MRI data with a cycle period of 0.98 s was applied at the inlet of each model with a flat velocity profile [113]. This boundary condition was deemed appropriate as the region of interest is located distal to the aortic arch [102, 113]. Realistic 3D velocity profiles at the inlet would be needed for faithful prediction of flow in the ascending aorta, as the shape of inlet velocity profile strongly affects flow predictions in this region [102]. The walls were assumed to be rigid with no slip conditions. The flow split between the iliac arteries in the two TEVAR models was regulated by a 3-element Windkessel model outlet boundary condition [41], which describes the relationship between pressure and flowrate based on the analogy between electrical circuits and the cardiovascular system [105]. For the non-thrombosed model, a pressure waveform calculated through a 3-element Windkessel model was applied at the only outlet. Values for the model parameters were extracted from the literature [132], as no patient-specific data was available.

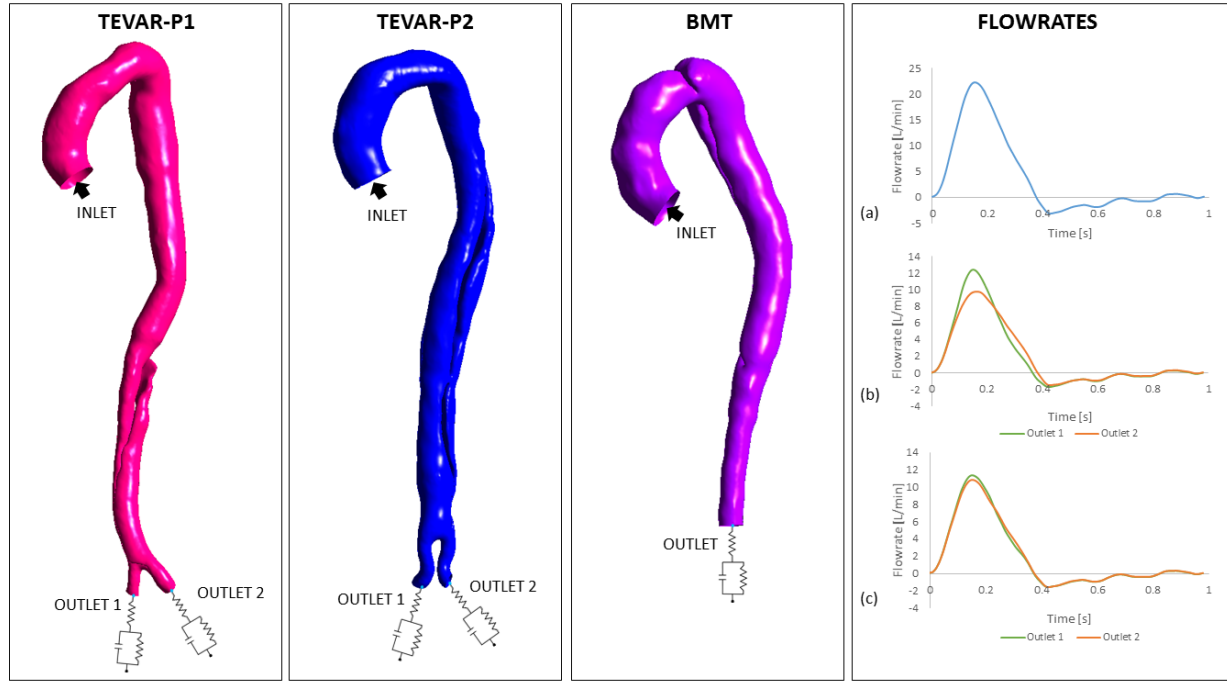


Figure 6.1: Computational models showing location of inlets and outlets, and (a) inlet flow and predicted outlet flows for (b) TEVAR-P1 and (c) TEVAR-P2. As BMT has only one outlet, the predicted outlet flow is equal to the inlet and is therefore not shown.

The boundary conditions applied in the three models are summarised in Fig. 6.1, with the respective outlet flows derived from the Windkessel models. A fixed time-step of 0.005 s was adopted based on the previous time-step sensitivity test and numerical simulations were carried out until thrombus growth stopped, which occurred after 20 cardiac cycles for TEVAR-P1, 42 cycles for TEVAR-P2, and 10 cycles for BMT. Simulation results were post-processed using CEI Ensight 10 and predictions of thrombus growth over time were validated against follow-up data.

6.2 Results

6.2.1 Model Geometries

Fig. 6.2 shows the reconstructed geometries based on initial CT scans for all three patients together with the stent-graft coverage for the TEVAR cases. In TEVAR-P1, the stent-graft starts from below the left subclavian artery and covers the entire thoracic aorta and part of the abdominal aorta up to the celiac artery (Fig. 6.2 TEVAR-P1). Below the stented region, only one re-entry tear is observed, which has an area of around 20 mm² and is located at the iliac bifurcation level.

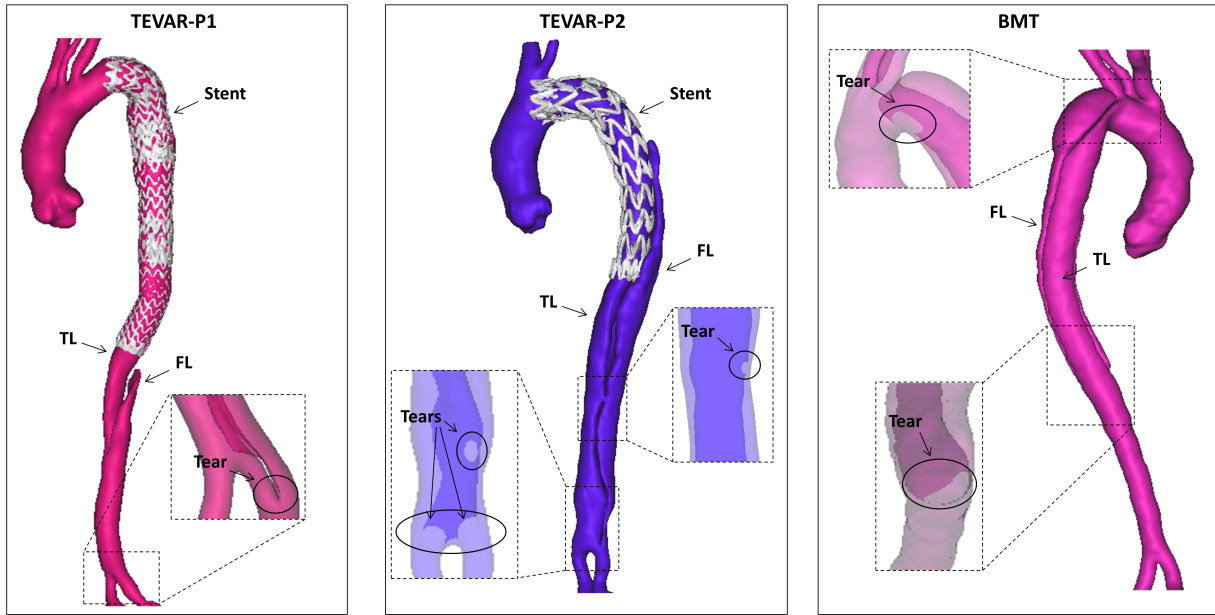


Figure 6.2: Reconstructed model geometries TEVAR-P1, TEVAR-P2 and BMT based on initial CT scans, showing the stented region for TEVAR patients.

The remaining FL extends upwards towards the celiac artery and downwards towards the iliac bifurcation. TEVAR-P2 presents a different stent configuration, with the stent-graft covering the left subclavian artery and having a shorter length limited to the thoracic aorta (Fig. 6.2 TEVAR-P2). Several small re-entry tears are observed below the stented region at the celiac and renal levels, with respective areas of 15.5 mm^2 and 20.5 mm^2 , and two larger tears at the iliac bifurcation level, with respective areas of 44.5 mm^2 and 95 mm^2 . In the non-stented BMT patient the FL extends upwards reaching the top of the aortic arch and downwards to the celiac artery level (Fig. 6.2 - BMT). Two main tears can be observed, one is located on the outer curve of the aortic arch with an area of 192 mm^2 , and another right above the celiac artery with a 124 mm^2 area. In all models, smaller tears could not be measured due to the limited image resolution, and all the measurements taken were subject to uncertainty determined by the voxel size.

6.2.2 Flow Patterns and Wall Shear Stress

Instantaneous streamlines at three different points of the cardiac cycle are shown in Fig. 6.3 for all three patients. For TEVAR-P1, particularly low velocities are observed in the FL, with slow flow recirculation in the tear region and almost static flow in the entire FL at all phases of the cardiac cycle. Extended recirculation areas exist in the FL for TEVAR-P2 where the presence of

multiple distal tears allows for flow recirculation between the tears. For this patient, high velocities are observed in proximity of the tears during systole (Fig. 6.3a and b), while highly disturbed flow patterns are observed in the FL during mid-deceleration and diastolic phase (Fig. 6.3c) as the distal tears allow blood to alternatively enter or exit the FL.

The different morphological features of the BMT model, characterised by an open entry tear located in the distal aortic arch and larger tear areas, are reflected in different flow patterns. High velocities are observed near the entry tear at all times with a larger volume of blood entering the FL, and flow recirculation is observed in the top FL region. The large distance between the tears in this case allows the flow to become more developed in the FL than in TEVAR-P2, with well organised flow patterns in the region between the tears during systolic acceleration. Disturbed flow patterns are observed in the FL in mid-deceleration and diastolic phase, when the two tears invert their roles as entry to and exit of the FL.

The aforementioned flow patterns dictate the distribution of time-averaged WSS (TAWSS) (Fig. 6.4). Very low TAWSS is observed in the entire FL in TEVAR-P1. For TEVAR-P2, the flow jets passing through the uncovered re-entry tears cause increases in local shear stress on the opposite wall, whereas shear stress in the rest of the FL is low, with particularly low values in the top FL region and between the tears, corresponding to areas of slow velocities and flow recirculation. In the BMT case, high TAWSS is observed near the entry and re-entry tears while lower values are seen in the region between the tears and at the top of the FL, but the magnitude of TAWSS is above 0.5 Pa.

6.2.3 Thrombus Growth

Predicted thrombus growth patterns were compared with follow-up clinical data. For TEVAR-P1, thrombus started forming on the FL walls and expanded uniformly towards the centre of the FL (Fig. 6.5). As the thrombus approached the distal tear, the growth rate was significantly reduced and eventually stopped after approximately 15 s, at which point the FL was completely thrombosed. As no further change was predicted thereafter, the simulation was stopped at 20 s. These results compare well with clinical follow-ups showing complete thrombosis of the FL after approximately four months following TEVAR.

For TEVAR-P2, thrombus formation was initiated in the top FL region as can be seen by comparing Fig 6.6a and 6.6b where the top part of the FL has disappeared. The thrombus continued

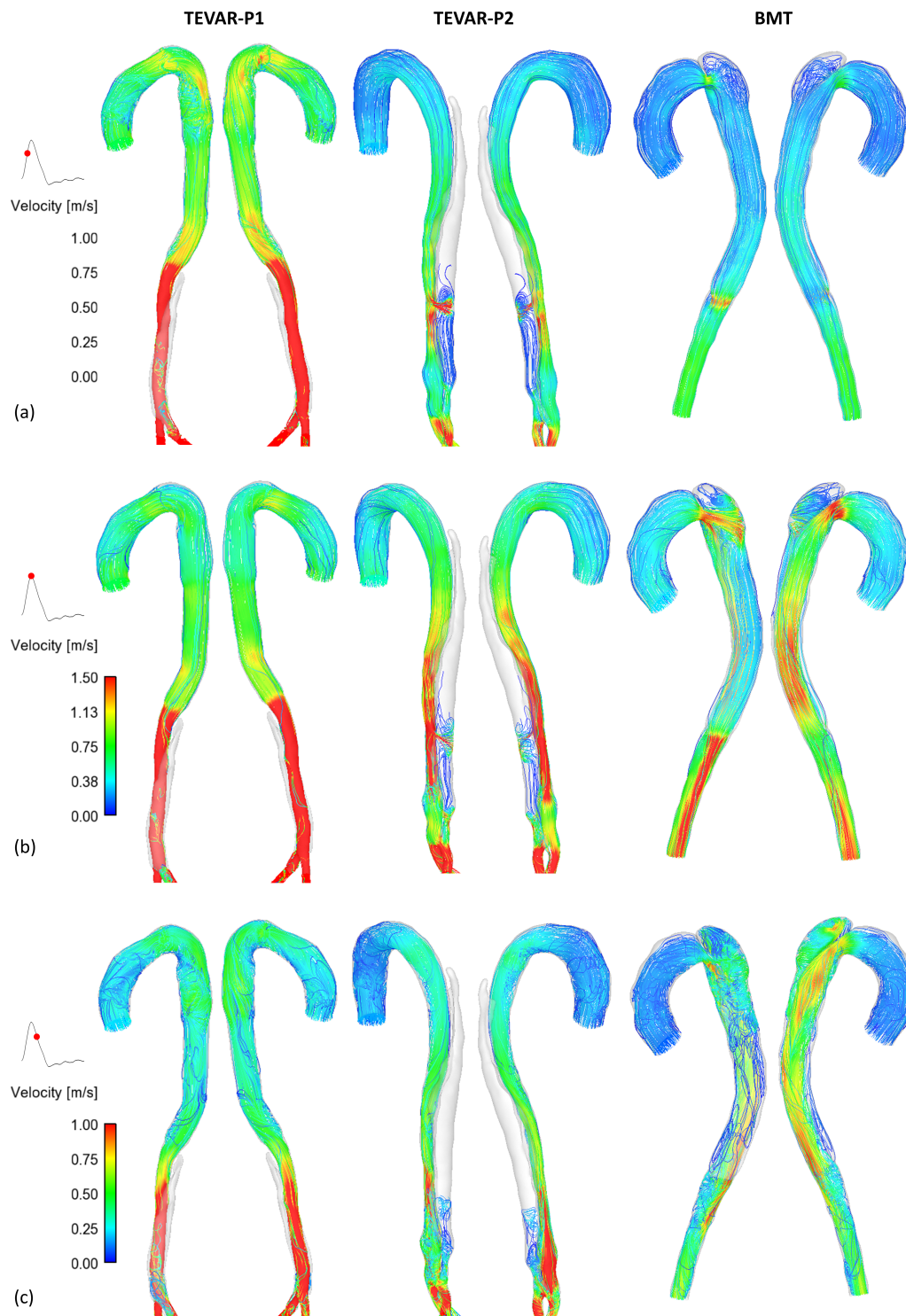


Figure 6.3: Instantaneous streamlines in the three patient models, calculated at (a) mid-systolic acceleration, (b) peak systole, and (c) mid-deceleration.

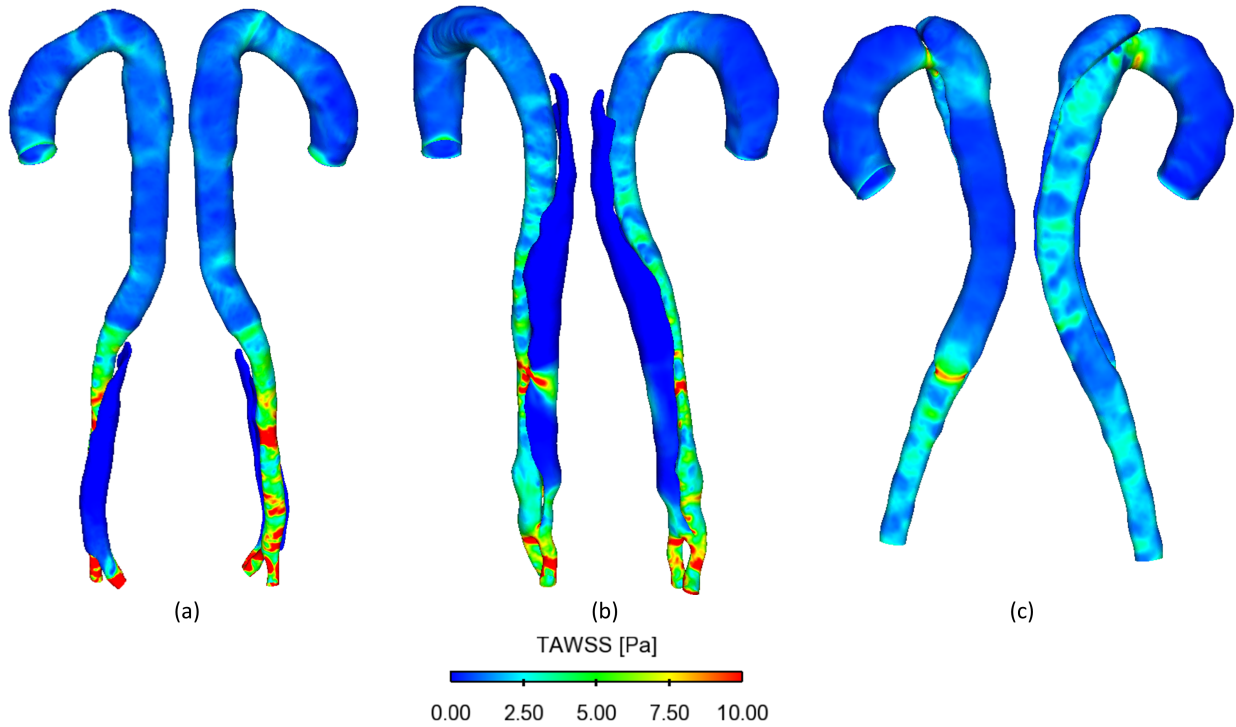


Figure 6.4: TAWSS distributions in the three patient models: (a) TEVAR-P1, (b) TEVAR-P2, and (c) BMT.

to expand towards the first tear, which is located near the celiac artery, and at 20 s (Fig. 6.6c) almost all the FL above the first tear was thrombosed. At some point between 8 and 20 s, a second region of thrombosis formed between the first and second tears, which grew very slowly until about 40 s when no further change could be predicted. Comparing the FL volume at 42 s with its initial volume indicated a predicted FL volume reduction of 93.8%. These results are in good agreement with the follow-up data collected at 1 and 4 years after TEVAR (Fig. 6.6e and f). The first follow-up scan acquired at 1 year (Fig. 6.6e) showed partial thrombosis in the top FL region, which was well captured by the simulation result shown in Fig. 6.6b. After 4 years the top FL region was completely thrombosed (Fig. 6.6f), while the area between the tears remained partially patent, with a measured FL volume reduction of 86.2% over the entire follow-up period.

The thrombosis model was also used to simulate thrombus formation in the BMT case. A periodic flow solution was obtained after 3 cardiac cycles, and no thrombus formation was predicted over 10 cycles, after which the simulation was stopped as the results would not change anymore. The predicted outcome of no FL thrombosis in this case is consistent with the corresponding follow-up data.

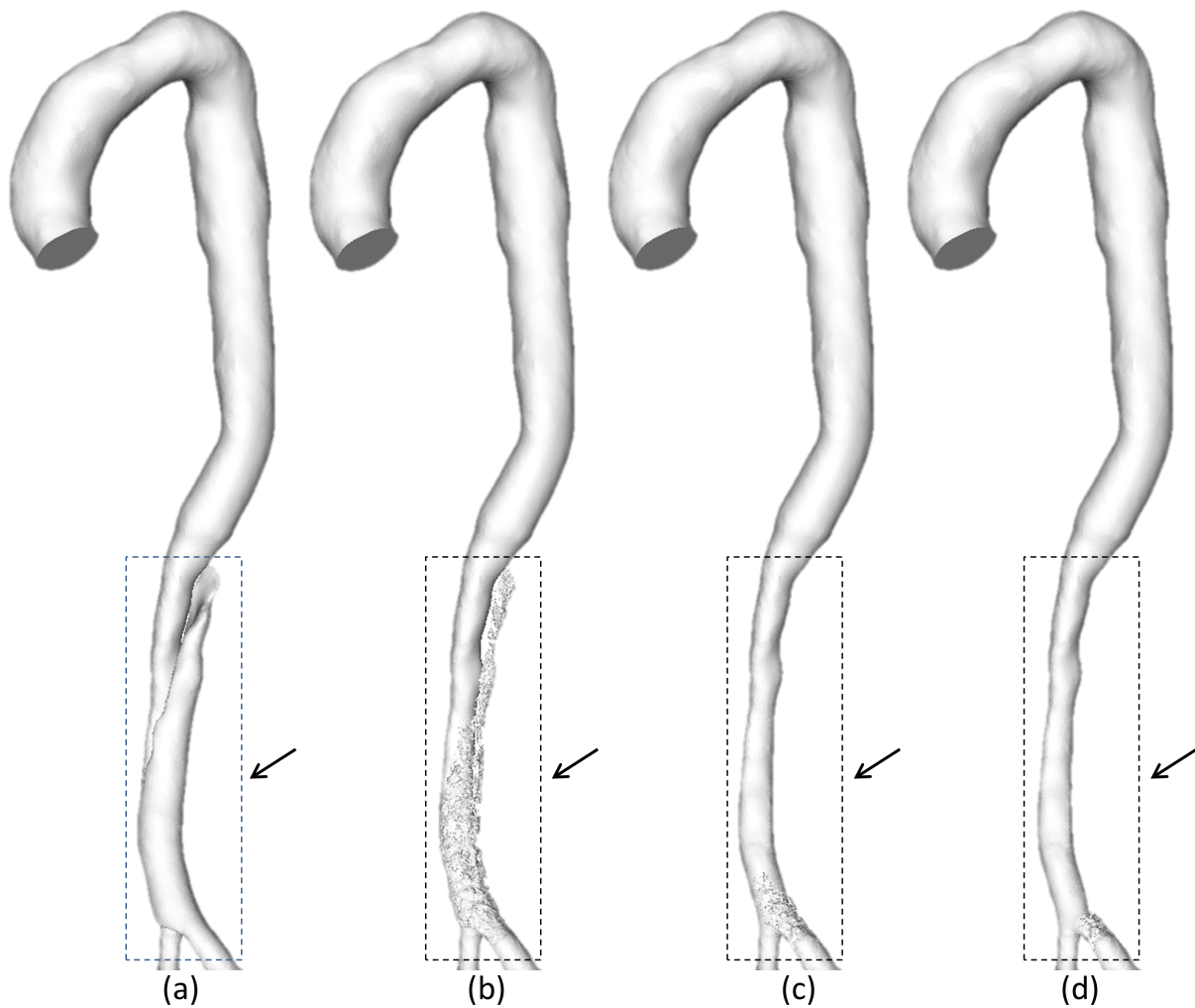


Figure 6.5: Evolution of FL surface in TEVAR-P1 following thrombus growth. (a) Reconstructed lumen surface in TEVAR-P1 based on the initial scan, and predicted FL surface following thrombus growth at (b) 7.5 s, (c) 11 s, and (d) 20 s.

6.3 Discussion

As discussed in the previous chapters, the extent of FL thrombosis has been identified as a key parameter to evaluate endovascular and medical treatment outcomes for aortic dissection [46, 5]. The use of a computational model to predict FL thrombosis could help identify which anatomical features and stent-graft related factors would favour complete FL thrombosis. This information could potentially be used to guide initial treatment plans and improve stent-graft design.

In the previous chapters, an efficient computational model was presented for the prediction of thrombus growth over time through the evaluation of blood flow patterns and hemodynamic

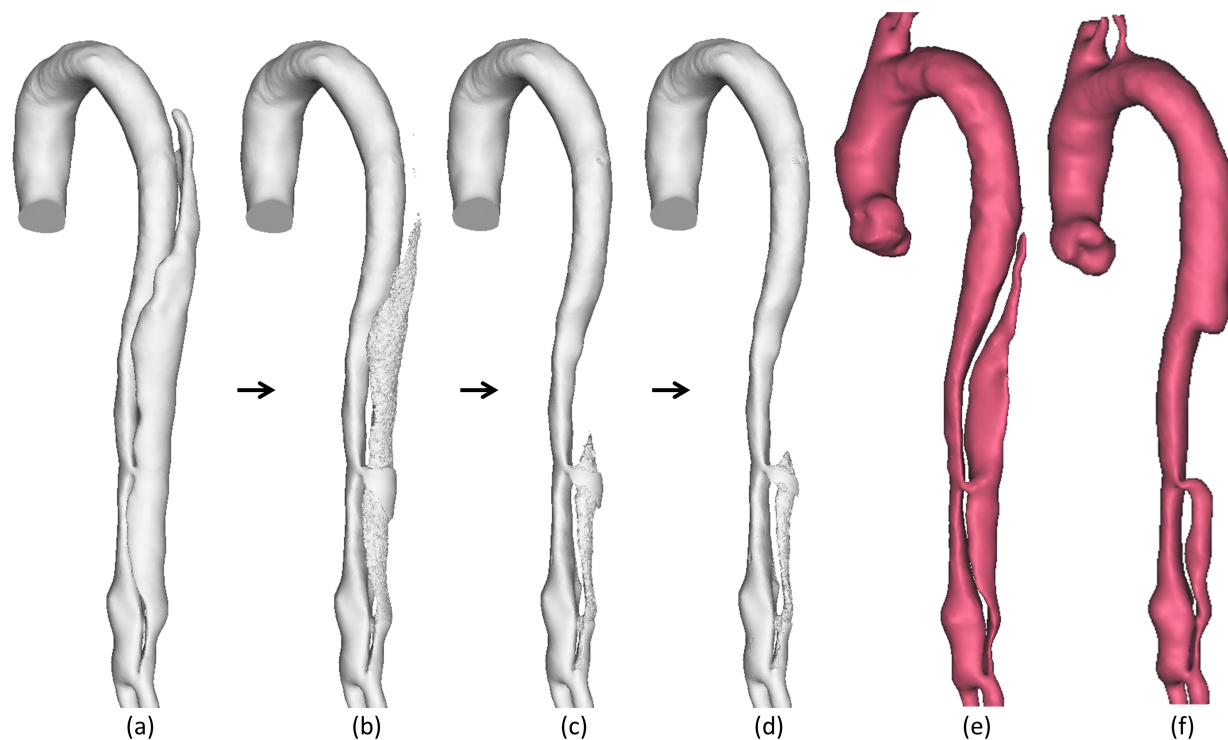


Figure 6.6: Evolution of FL surface in TEVAR-P2 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in TEVAR-P2, and predicted FL surface following thrombus growth at (b) 8 s, (c) 20 s, and (d) 42 s, in comparison with the reconstructed lumen surface based on follow-up scans acquired at (e) 1 year, and (f) 4 years after TEVAR.

parameters [91, 118]. This model allows us to predict which regions of the FL are most likely to be thrombosed and how this would affect blood flow patterns and hence further growth of thrombus. In the present study, the same model was applied to two dissection patients treated with TEVAR in order to test its capability of predicting complete and incomplete device-induced FL thrombosis. A third medically treated patient showing no thrombosis was also included as a benchmarking case.

The results demonstrated that the computational model is capable of predicting both spontaneous and device-induced thrombosis. In TEVAR-P1, complete FL thrombosis was predicted within a simulation time of 15 cardiac cycles. Thrombosis started from the FL walls and expanded rapidly in the initial stage, which was followed by a period of slow growth until thrombi reached the uncovered tear when thrombosis eventually stopped. In TEVAR-P2, thrombus formation was initially observed in the top FL region with a rapid growth rate, but its growth slowed down dramatically as the thrombus propagated towards the first uncovered tear. Thrombus formation in the upper FL caused a significant reduction in TAWSS in the region between the two tears, initiating partial thrombosis in this area. These findings are consistent with clinical studies which show that

the presence of distal tears and branching vessels arising from the FL are risk factors for incomplete FL thrombosis [133, 130, 134]. Similar results were also observed in the study reported in Chapter 5, where the formation of a second tear in a medically treated patient caused lateral thrombosis in the region between the two tears [118]. However, the BMT case included in the present study showed no sign of thrombosis in the computational predictions or follow-up scans, even though a distal tear is present in the descending aorta. This was possibly due to the relatively large distance between the two tears, which helped reduce the level of flow disturbance in the FL. The organised flow patterns produced WSS in the normal physiological range, thereby preventing the formation of thrombi. These results suggest that the distance between tears may be an important factor in determining FL thrombosis, although many more cases will be needed to elucidate its role. Additionally, contrary to TEVAR-P1 and TEVAR-P2, the BMT case showed no FL thrombosis in the top FL region. As the BMT patient presented a much shorter retrograde expansion in the upper FL as compared to the TEVAR patients studied, it is plausible to speculate that the distance between the primary entry tear and the top of the FL could be an important determinant of FL thrombosis in the proximal region.

Limitations in computational power and data storage space currently hinder the simulation of real-time thrombosis on the true time scale of months or even years typical of FL thrombosis in aortic dissection [125]. Our strategy is to use a computationally efficient model that is capable of providing fast and reliable information on thrombus formation and growth, with a view to identifying aorta or stent-graft related factors that may promote complete FL thrombosis after TEVAR. The use of accelerated kinetics allows us to predict growth patterns and final outcomes, without simulating the real-time evolution of thrombi. For TEVAR-P1, complete thrombosis was observed four months after TEVAR and the simulation of 15 cardiac cycles was sufficient to reproduce clinical observations. A much longer simulation time was required to reproduce the *in vivo* results observed on TEVAR-P2 at four-year follow-up (Fig. 6.6f). It may be possible that a relationship exists between the simulated time-scale and the effective growth rate. As many environmental and patient-specific factors relating to the patient's health conditions, medication and lifestyle are likely to affect the time scale of thrombus growth in each patient, only the analysis of a large cohort of patients will allow us to explore the possibility of scaling from the simulated time to real time thrombosis.

This work is presented as a pilot study to demonstrate the potential applicability of the model to the prediction of thrombosis following TEVAR. In order to minimize computational costs, the

model geometries adopted here do not include the aortic branches and rigid wall behaviour is assumed. This choice is partially due to the lack of availability of patient-specific flow and pressure information, which hinders the calibration of additional Windkessel models. The study carried out by Cheng et al. [113] showed satisfactory agreement between simulation results and velocities measured with phase-contrast MRI, demonstrating that the exclusion of arch branches had a minor effect on flow in the proximal descending aorta in Type B aortic dissection. However, the influence of visceral branches is unclear and it appears that their exclusion may have resulted in an over-prediction of the iliac flow in TEVAR-P2, where the celiac and one of the renal arteries arise from the FL. This may be responsible for the $\sim 8\%$ difference in FL thrombus volume between predictions and *in vivo* data for this patient. As there are no side branches arising from the FL in the TEVAR-P1 and BMT cases, no obvious differences were observed between the predicted and observed patterns of thrombosis. While in this study it seems that the exclusion of visceral branches had only a minor effect due to their specific locations, dissection geometries can vary considerably from patient to patient, and in cases where multiple branches are attached to the FL their effects could be significant. Future work will address the effects of visceral branches and compliant walls so as to improve the accuracy of predicted thrombus formation and growth, and to provide physiologically realistic pressure within the FL; the latter is required to predict potential future complications, such as aortic expansion or the formation new entry tears.

Once fully validated, the model will be applied to a large cohort of patients and used as a tool to identify which parameters have the strongest effect on thrombus formation. These findings will hopefully help surgeons to more consciously select their treatment strategy. The long term objective is to develop a powerful decision making tool to determine optimal treatments for each patient. However, at the current stage of research these computations are intensely time-consuming, which will be a major barrier for the intended clinical application. Hence, more efforts are needed to further improve the computational efficiency of the thrombosis model.

6.4 Summary

In this chapter, the hemodynamic-based model developed for thrombus predictions was applied to the study of false lumen thrombosis in three patient-specific cases of Type B aortic dissection, showing complete, partial and no thrombosis, respectively. In all three cases, the model was able

to predict the same outcome and thrombus growth patterns as observed *in vivo*, demonstrating its applicability to the study of both spontaneous and device-induced thrombosis in aortic dissection. It is hoped that the model can be used to identify anatomical or stent-graft related factors that are associated with incomplete false lumen thrombosis following TEVAR, which may help clinicians develop personalised treatment plans for dissection patients in the future.

Understanding the Progression of Type B Aortic Dissection: Predictors of False Lumen Thrombosis, Aortic Growth and Remodelling[†]

In the previous chapters, a computational model for thrombus prediction in aortic dissections was proposed and validated against *in vivo* data. Although the results shown in Chapters 5 and 6 are promising, the number of patients studied is very limited. Moreover, the geometric models are simplified, without including the thoracic and abdominal branches, which are known to affect aortic flow and thrombus growth patterns. The objectives of this chapter are twofold: (i) to extend the model to more complex geometries including all the major aortic branches, and (ii) to identify morphological factors correlated with changes in true and false lumen volumes as a result of thrombus formation, true lumen remodelling and aortic growth. This is done through a hemodynamics-based computational study focused on thrombus predictions, and an anatomical data analysis based on available clinical data.

7.1 Methodology

7.1.1 Patient Information

A total of 29 patients treated in acute phase for Type B aortic dissection were included in this study. Twenty-one of these patients (12 BMT and 9 TEVAR+BMT) were received from the ADSORB (Acute Dissection: Stent graft OR Best medical therapy) trial, which is the largest European trial

[†]This Chapter is adapted from: *Menichini, C, Milinis, K, Gibbs, RGJ, Xu, XY. The effect of FL perfusion on aortic remodelling in type B aortic dissection. (Manuscript in preparation)*

aimed at comparing different strategies for the treatment of acute uncomplicated Type B dissection [31]. Also included were eight additional Type B dissection patients (3 BMT and 5 TEVAR+BMT) treated at St. Mary's hospital in London. During the analysis phase, two of the BMT patients from the ADSORB data set had to be excluded due to the development of complications (multiple aneurysms in the abdominal aorta) and the incompleteness of the follow-up data. The 27 patients analysed were divided into two groups: TEVAR+BMT (N=14), and BMT (N=13).

7.1.2 Geometric Measurements and Anatomical Data Analysis

All the patient-specific geometries were reconstructed from CT scans using the software Mimics (Materialise HQ, Leuven), based on a semi-automated, threshold-based algorithm. Manual refinement was performed in order to accurately separate the region of interest from the surroundings. For each patient, 3 models were reconstructed: the initial geometry (baseline), 3-month follow-up (whenever available), and 1-year follow-up. However, as the 3-month follow-up was not available for all patients, only baseline and 1-year follow-up were used for analysis. Volumes of the true lumen (TL) and false lumen (FL) were calculated separately by using the following expressions:

$$Vol_{TL} = \sum_{i=1}^N \frac{(S_{i,TL} + S_{i+1,TL}) \cdot h}{2} \quad (7.1)$$

$$Vol_{FL} = \sum_{i=1}^N \frac{(S_{i,FL} + S_{i+1,FL}) \cdot h}{2} \quad (7.2)$$

where $S_{i,TL}$ and $S_{i,FL}$ are respectively the cross-sectional area of TL and FL for each axial slice i , N is the total number of axial slices, and h is the slice thickness. Changes in TL and FL volumes at each follow-up were then quantified. As shown in Fig. 7.1, the dissected aorta was subdivided into four regions of interest: subclavian to celiac artery (region A), celiac artery to renal arteries (region B), renals to aortic bifurcation (region C), and aortic bifurcation to common iliac bifurcation (region D). For each patient, a number of morphological measurements were taken at baseline and 1-year follow-up, which are summarised in Table 7.1. All the measurements were taken in collaboration with Dr. Kristijonas Milinis (Imperial College NHS trust, London, UK), who also provided clinical advice on designing this part of the study. Lengths, distances and best-fit diameters were measured from the centerline of each lumen. Pearson's and Spearman rho coefficients were calculated for the two groups to test correlations between each parameter and overall and regional changes in true

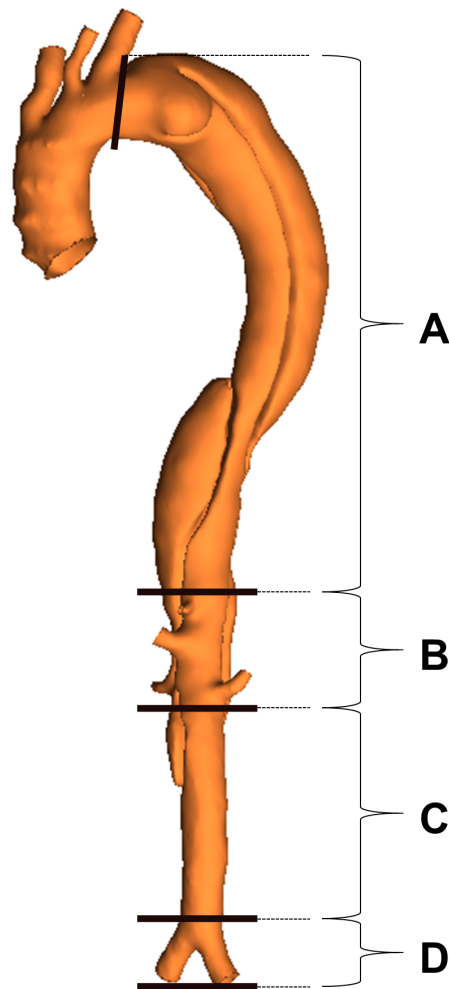


Figure 7.1: Schematic overview of the four aortic regions where measurements were taken for each patient.

and false lumen volumes, as well as changes in maximum diameter and length. Pearson's coefficient evaluates linear relationships between variables, while Spearman Rho coefficient tests the existence of monotonic relationships. Correlations with $p < 0.05$ were considered statistically significant.

7.1.3 Computational Models

Seven patient-specific geometries, 3 TEVAR+BMT (TEVAR-P1, TEVAR-P2, TEVAR-P3) and 4 BMT (BMT-P1, BMT-P2, BMT-P3, BMT-P4), were selected for further analysis (Fig. 7.2). These were chosen among the cases considered most suitable for simulations in terms of image resolution, and were considered to be the most interesting morphologies, in terms of thrombus formation, location and number of tears and FL branches. The patient-specific geometries extracted from the

Table 7.1: List of parameters measured for each patient group.

Parameter	BMT	TEVAR+BMT
Age	×	×
Total volume	×	×
Volume of each region	×	×
Total length	×	×
Length of each region	×	×
Total number of tears	×	×
Furthest distance tear-to-tear	×	×
Number of tears per region	×	×
Large vessels branching off the FL - overall	×	×
Large vessels branching off the FL per region	×	×
Total vessels branching off the FL - overall	×	×
Total vessels branching off the FL per region	×	×
Inlet Diameter (d_1)	×	×
Arch Diameter (d_2)	×	
Curvature ratio (d_1/d_2)	×	
Total tear-to-vessel component	×	×
Tear-to-vessel component per region	×	×
Distance first tear to LSA	×	
Distance first tear to top of FL	×	×
Maximum diameter - overall	×	×
Maximum diameter per region	×	×
Length of stent		×
Ratio between length of stent and length of region A		×
Ratio between length of stent and overall length		×
Distance first tear to stent		×
Distance between coeliac artery and stent		×
Maximum distance tear to major vessels in the FL	×	×
Distance tear to major vessels in the FL per region	×	×

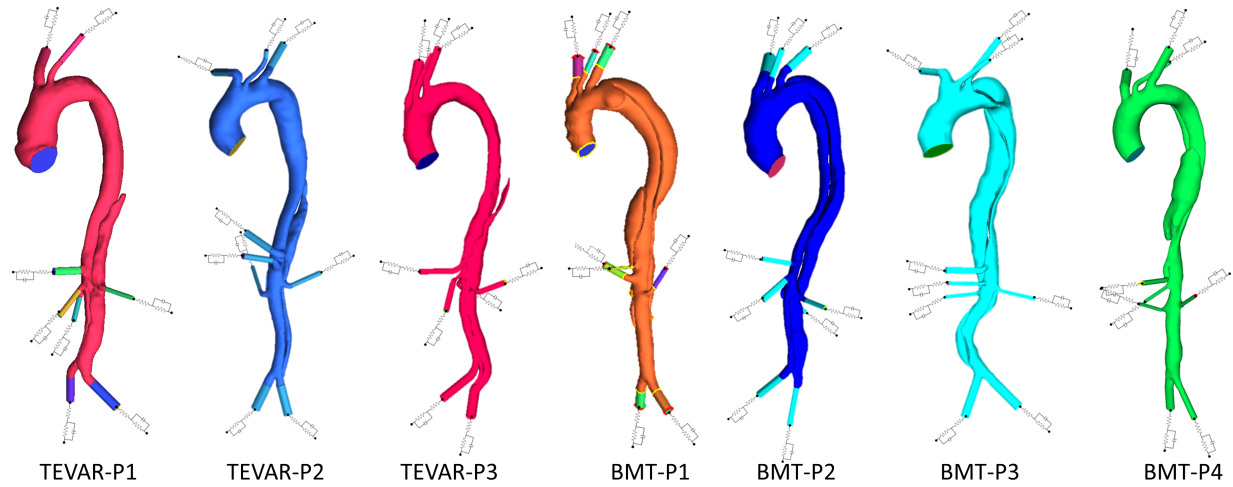


Figure 7.2: Patient-specific models reconstructed from CT images and analysed in CFD.

first scan for BMT patients and first post-TEVAR scan for TEVAR+BMT patients were imported into ICEM (Ansys Inc) and discretised into unstructured meshes of 5-10 million elements depending on the geometry. The discretised models were imported into Ansys CFX for simulation. A pulsatile inlet flow waveform [41] was applied at the inlet of each model, which included 8-9 outlets (Fig. 7.2), namely: brachiocephalic artery (BC), left common carotid artery (LCC), left subclavian artery (LSA, occluded for TEVAR-P1), coeliac (CEL) and superior mesenteric (SM) arteries, left and right renals (LR and RR) and left and right iliac (LI and RI) arteries (Fig. 7.2). A 3-element Windkessel model was applied at each outlet (Fig. 7.2). Details on model calibration are provided in the Appendix. Each model was simulated for 4 cardiac cycles to ensure a periodic solution. Results from the last cardiac cycles were used for analysis.

The hemodynamics-based thrombosis model developed and validated in the previous chapters was also applied to each geometry. Predicted thrombus patterns were compared with *in vivo* data extracted from follow-up scans in order to further validate the model's capability to predict thrombus formation in dissection patients.

From the analysis of patient-specific geometries it is difficult to assess how a single parameter may affect the predicted outcomes. In order to vary the parameters of interest in a controlled manner and to study their individual effects on pressure and flow distributions, 10 additional 3D phantom models were built for this study. These models were based on the design proposed in Chapter 4 by varying curvature ratio, entry tear diameter, distance between entry tear and the top of the FL, and the maximum distance between tears as summarised in Table 7.2.

Table 7.2: Geometric features of the phantom models analysed in this study.

	No. of tears	Tear Diameter (mm)			Distance PT to FL top (mm)	Curvature Ratio (-)	Distance PT to DT (mm)	Distance MT to DT (mm)
		PT	MT	DT				
PH-1	2	10	-	10	34	0.78	270	-
PH-2	2	10	-	10	22	0.78	282	-
PH-3	2	10	-	10	10	0.78	294	-
PH-4	2	5	-	10	34	0.78	270	-
PH-5	2	15	-	10	34	0.78	270	-
PH-6	2	10	-	10	34	0.61	270	-
PH-7	2	10	-	10	34	0.44	270	-
PH-8	2	10	5	10	34	0.78	270	236.25
PH-9	2	10	5	10	34	0.78	270	202.5
PH-10	2	10	5	10	34	0.78	270	135

PT = Proximal tear, MT = middle tear, DT = Distal tear, FL = False lumen.

7.2 Results: Anatomical Data Analysis

7.2.1 Endovascularly Treated (TEVAR+BMT) Patients

All the raw data collected for this study is available in a separate CD. Measured percentage volume changes over 1-year follow-up period for the TEVAR+BMT group are summarised in Table 7.3 and Fig. 7.3. Significant TL remodelling was observed in the TEVAR+BMT group, with an average TL volume increase of 114% at 1-year follow-up. In particular, all patients presented a TL volume increase above 20%, with 85% showing > 50% increase. The most significant changes were observed in region A, where the stent is located. Within this region all patients presented a TL volume increase above 50%. Only 43% of patients presented a TL volume increase above 20% and 23% above 50% in the abdominal region (B+C+D).

Table 7.3: Percentage change in TL and FL volumes over 1-year follow-up period for the two patient groups.

Region	TEVAR+BMT		BMT	
	TL	FL	TL	FL
Overall	114 ± 45 %	-65 ± 27 %	5 ± 28 %	14 ± 46 %
Thoracic (Reg. A)	146 ± 61 %	-84 ± 22 %	12 ± 32 %	9 ± 42 %
Abdominal (Reg. B+C+D)	27 ± 44 %	4 ± 49 %	-5 ± 28 %	1 ± 37 %

Table 7.4: Statistically significant correlations found for the TEVAR+BMT group.

Correlation (Region affected)	Pearson's (p value)	Spearman Rho) (p value)
<i>Parameters related to TL volume changes</i>		
Age (reg. B+C+D)	-	0.60 (0.022)
Age (reg. C)	0.54 (0.042)	0.68 (0.0063)
Maximum diameter in abdominal region (reg. B+C+D)	-	0.58 (0.026)
<i>Parameters related to FL volume changes</i>		
Total number of FL branches (overall)	0.71 (0.0036)	0.68 (0.0059)
Total number of FL branches (reg. A)	0.72 (0.0027)	0.73 (0.0025)
Total number of FL branches (reg. B+C+D)	0.60 (0.021)	0.67 (0.0069)
Total number of FL branches in region A (overall)	0.80 (0.00050)	0.74 (0.0020)
Total number of FL branches in region A (reg. A)	0.83 (0.00010)	0.78 (0.00060)
Total number of tears (reg. C)	0.56 (0.033)	0.66 (0.0090)
Total number of tears in region A (overall)	0.62 (0.016)	0.74 (0.0017)
Total number of tears in region A (reg. A)	0.54 (0.041)	0.82 (0.00024)
Total number of tears in region A (reg. B+C+D)	0.53 (0.049)	0.69 (0.0052)
Maximum distance between tears (overall)	0.64 (0.013)	-
Maximum distance between tears (reg. A)	0.68 (0.0060)	-
Length of region B (overall)	0.54 (0.043)	0.55 (0.040)
Length of region B (reg. A)	0.53 (0.048)	0.60 (0.020)
Length of region B (reg. B)	0.70 (0.0044)	0.57 (0.031)
Length of region B (reg. B+C+D)	-	0.56 (0.033)
Distance between FET ^a and FL top (overall)	-0.60 (0.022)	-
Distance between FET ^a and FL top (reg. A)	-0.63 (0.013)	-0.66 (0.0091)
Distance between FET ^a and FL top (reg. C)	-0.55 (0.037)	-0.62 (0.016)
Distance between FET ^a and EOS ^b (reg. A)	-	-0.54 (0.040)
Distance between FET ^a and EOS ^b (reg. C)	-	-0.58 (0.025)
Distance between FET ^a and LSA ^c (overall)	-0.66 (0.026)	-0.53 (0.046)
Distance between FET ^a and LSA ^c (reg. A)	-0.68 (0.017)	-0.59 (0.025)
Distance between FET ^a and LSA ^c (reg. C)	-	-0.58 (0.026)
Total number of tears in region B (reg. B+C+D)	-0.63 (0.013)	-0.59 (0.023)
Total number of tears in region B (reg. C)	-0.72 (0.0032)	-0.57 (0.031)
Tear-to-vessel component in region B (reg. B)	-0.65 (0.0095)	-0.61 (0.016)

^a First post-stent entry tear^b Distal end of stent-graft^c Left subclavian artery

- p>0.05



Figure 7.3: Bar charts showing (a) overall, (b) thoracic (reg. A), and (c) abdominal (reg. B——++C+D) percentage changes in TL and FL volumes for the TEVAR+BMT patient group over 1-year follow-up period.

Major changes in volume were also observed in the FL during the 1-year follow-up period, with an average FL volume reduction of 65% and over 86% of patients presenting a FL volume reduction above 20% and 79% above 50%. Once again, the region most affected was the thoracic one, where over 86% of patients presented $> 50\%$ FL volume reduction. Changes in the abdominal region (B+C+D) were less pronounced, with 36% of patients presenting a volume decrease above 20%, but over 43% presenting a volume increase above 20% and 23% above 50%.

Statistically significant correlations found for the TEVAR+BMT group are summarised in Table 7.4. Several parameters were found to correlate with overall FL growth, but the most important parameters were the total number of branches originating from the FL ($p=0.0059$) and the number of tears in region A ($p=0.0017$). Other parameters associated with overall FL growth were the maximum distance between tears ($p=0.013$) and the length of region B ($p=0.040$). In region A, the most statistically significant factor was the number of tears in region A, affecting local growth ($p=0.00024$). The length of region B was associated with FL growth in this specific region ($p=0.0044$), while the total number of tears was related to FL growth in region C ($p=0.0090$).

The distance between the first post-stent tear (FET) and the end of the stent, the distance between the FET and the top of the FL and the distance between the FET and the LSA were identified as statistically significant predictors of FL thrombosis ($p<0.05$). In particular, these parameters appeared to be correlated with thrombosis in both region A ($p=0.040$, $p=0.0091$ and $p=0.017$) and region C ($p=0.025$ and $p=0.016$ and $p=0.026$). The number of tears in region B and the presence of a tear-to-vessel component (defined as the presence of a tear in close proximity to an abdominal branch coming off the FL) also demonstrated a positive correlation with FL reduction and thrombosis in the abdominal region ($p=0.013$ and $p=0.017$). Age ($p=0.022$) and maximum diameter in the abdominal region ($p=0.026$) were found to be correlated with TL growth in the entire abdominal region (B+C+D).

7.2.2 Medically Treated (BMT) Patients

All the raw data collected for this study is available in a separate CD. Measured percentage volume changes over 1-year follow-up period for the BMT group are summarised in Table 7.3 and Fig. 7.4. An average 5% TL volume increase was observed for the BMT group at 1-year follow-up. In particular, an average 12% TL volume increase was found in region A, while a 5% TL volume decrease was observed on average in the abdominal region (B+C+D). 23% of patients presented

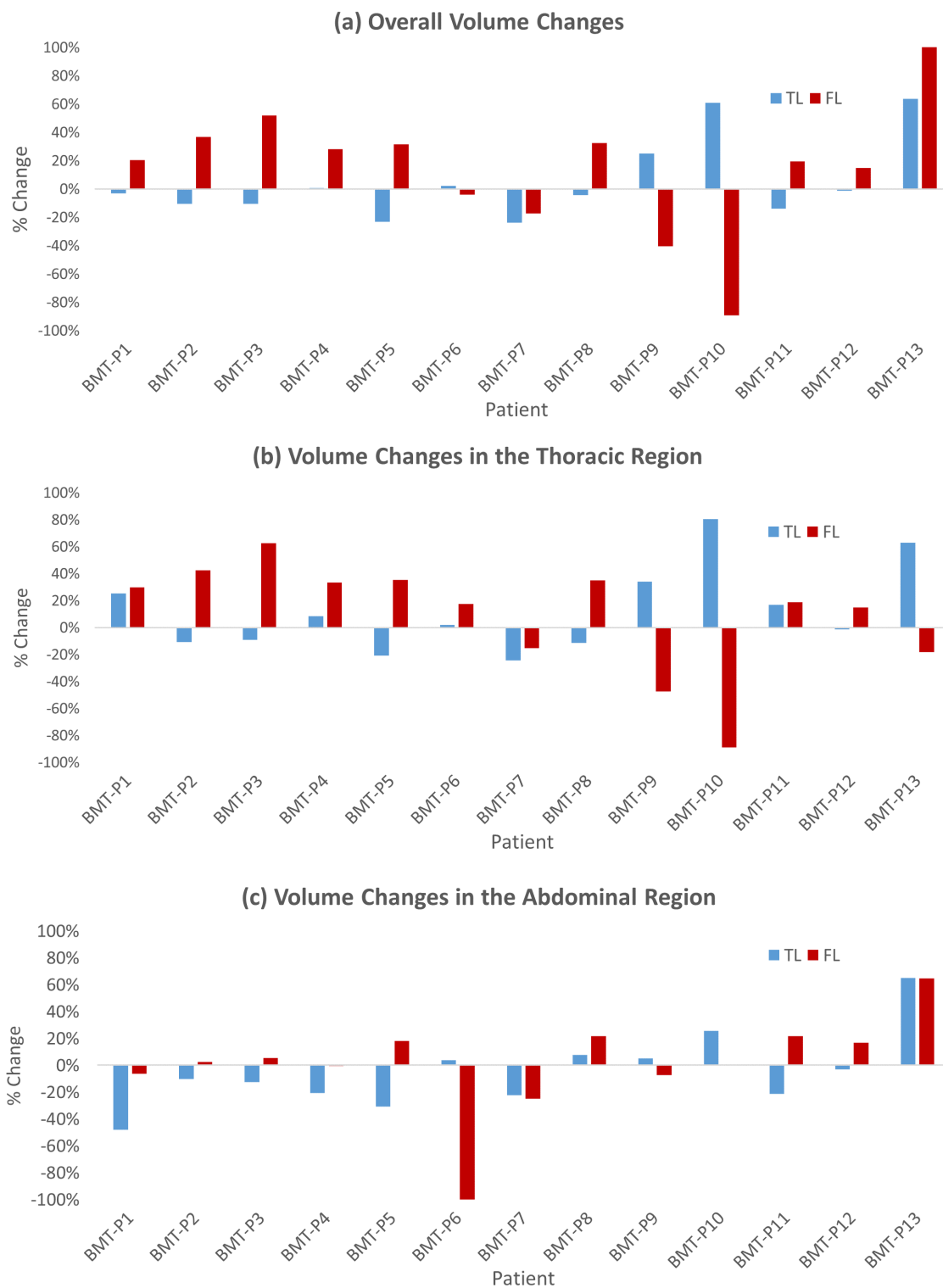


Figure 7.4: Bar charts showing (a) overall, (b) thoracic, and (c) abdominal percentage changes in TL and FL volumes for the BMT patient group over 1-year follow-up period.

an overall TL volume increase above 20% and 15% of patients presented an overall TL decrease above 20%, while 8% of patients presented a TL volume decrease above 50%. In particular, 31% of patients presented a TL volume increase above 20% in the thoracic region, and 15% above 50%.

For the FL, an average 14% FL volume increase was observed for the BMT group at 1-year follow-up, with 54% of patients presenting a FL volume increase above 20% and 15% above 50%. The most significant changes were observed once again in region A, where 46% of patients presented a FL increase above 20% and 8% showing above 50% FL volume increase. 15% of patients also presented a FL volume decrease above 20% in the abdominal region (B+C+D), and the same percentage presented a FL volume increase above 20% in the same region.

Several parameters were associated with overall TL volume changes, but the strongest correlations were found for the number of tears in region C ($p=0.0042$) and the maximum distance between tears ($p=0.00088$). The number of tears in region A was also associated with overall TL growth ($p=0.011$), while the diameter of the first entry tear and the length of region B were both associated with overall TL volume reduction ($p=0.018$ and $p=0.011$). In region A, a statistically significant correlation was found between the presence of a tear-to-vessel component in region B and local TL growth ($p=0.043$), while the maximum distance between tears, the maximum aortic diameter and the length of region B were associated with local TL reduction ($p=0.00039$, $p=0.014$ and $p=0.0024$). A statistically significant correlation was found in region B between the presence of FL branches and local TL reduction (0.00040). Curvature ratio was associated with TL growth in region C ($p=0.017$), while the total number of FL branches and the number of FL branches in regions B and C were associated with TL reduction in region C ($p=0.032$, $p=0.011$ and $p=0.00070$).

The most statistically significant parameters associated with overall FL volume changes were the maximum tear diameter in region C ($p=0.0042$) and curvature ratio ($p=0.0043$). The total number of large vessels in the FL and the maximum distance between tears were associated with overall FL growth ($p=0.040$ and $p=0.037$), while the distance between the first entry tear (FET) and the FL top and the distance between the FET and the LSA were associated with overall FL reduction/thrombosis ($p=0.023$ and $p=0.013$). FET diameter and maximum distance between tears correlated with FL expansion in region A ($p=0.0066$ and $p=0.0013$), and the presence of a tear-to-vessel component in region B was associated with FL reduction/thrombosis in region A ($p=0.0043$). The latter was also correlated with FL reduction/thrombosis in region B ($p=0.0043$) and diameter growth ($p=0.018$). FL growth in region C was observed in patients with large branches in this region ($p=0.0081$).

Table 7.5: Statistically significant correlations found for the BMT group.

Correlation (Region affected)	Pearson's (p value)	Spearman Rho (p value)
<i>Parameters related to TL volume changes</i>		
Total number of tears tears (reg. B+C)	0.57 (0.038)	-
Curvature ratio (reg. C)	0.64 (0.017)	-
Number of tears in region A (overall)	-	0.68 (0.011)
Tear-to-vessel component in region B (reg. A)	-	0.56 (0.043)
Number of tears in region C (overall)	0.66 (0.012)	0.72 (0.0042)
Maximum tear diameter in region C (reg. B+C)	0.59 (0.032)	0.57 (0.038)
Diameter of first entry tear (overall)	-0.59 (0.030)	-0.63 (0.018)
Maximum distance between tears (overall)	-0.69 (0.0071)	-0.79 (0.00088)
Maximum distance between tears (reg. A)	-0.75 (0.0023)	-0.82 (0.00039)
Maximum distance between tears (reg. B+C+D)	-	-0.55 (0.045)
Length of region B (overall)	-0.68 (0.0089)	-0.62 (0.011)
Maximum aortic diameter (reg. A)	-	-0.65 (0.014)
Length of region B (reg. A)	-0.75 (0.0024)	-0.67 (0.023)
Total number of FL branches (reg. C)	-0.59 (0.032)	-
Total number of FL branches in region B (reg. B)	-0.82 (0.00040)	-0.66 (0.012)
Total number of FL branches in region B (reg. C)	-0.67 (0.011)	-
Total number of FL branches in region C (reg. C)	-0.54 (0.010)	-0.80 (0.00070)
Total number of FL branches in region C (reg. B+C+D)	-0.67 (0.050)	-0.69 (0.0072)
Maximum tear diameter in region B (overall)	-0.59 (0.030)	-
<i>Parameters related to FL volume changes</i>		
Total number of large vessels in FL (overall)	0.63 (0.019)	0.57 (0.040)
Total number of FL branches in region C (reg. B+C+D)	0.63 (0.019)	0.57 (0.040)
Inferior mesenteric artery branching off FL in region C (reg. C)	0.59 (0.032)	0.69 (0.0081)
Diameter of first entry tear (reg. A)	-	0.70 (0.0066)
Maximum distance between tears (overall)	0.57 (0.037)	-
Maximum distance between tears (reg. A)	0.73 (0.0036)	0.77 (0.0013)
Maximum tear diameter in region C (overall)	0.55 (0.047)	0.70 (0.0042)
Curvature ratio (overall)	-	-0.72 (0.0043)
Distance between FET ^a and FL top (overall)	-0.61 (0.023)	-0.56 (0.041)
Distance between FET ^a and LSA ^b (overall)	-0.65 (0.013)	-0.55 (0.047)
Tear-to-vessel component in region B (reg. A)	-	-0.56 (0.0043)
Tear-to-vessel component in region B (reg. B)	-	-0.72 (0.0043)
<i>Parameters affecting diameter changes</i>		
Maximum diameter (reg. A)	-	-0.55 (0.045)
Maximum tear diameter in region B (overall)	-0.66 (0.012)	-0.58 (0.033)
Tear-to-vessel component in region B (overall)	0.63 (0.018)	-
Curvature ratio (overall)	-	-0.66 (0.011)

^a First entry tear^b Left subclavian artery

- p>0.05

7.3 Results: Patient-Specific Study

7.3.1 Flow Patterns, Pressure and TAWSS

Flow Distribution and Flow Patterns. All the models except for BMT-P4 presented at least one major branch in the FL, or being perfused by both TL and FL, as shown in Fig. 7.2 and Table 7.6. Predicted flow distribution among the aortic branches is presented in Table 7.6. Flow in the brachiocephalic (BC), left common carotid (LCC) and left subclavian (LSA) arteries were respectively 16.9-23.6%, 4.3-11.3% and 11.5-14.2% of the inlet flow. The highest percentage values for BC and LCC were found in TEVAR-P1, whose LSA was occluded by the stent-graft. Flow percentages between 12.4-15% and 10.7-12.6% were calculated for coeliac (CEL) and superior mesenteric (SM) arteries, while 8-9.4% of the inlet flow was distributed to each renal artery (LR and RR). Flow in each iliac artery (LI and RI) was between 9.9-10.7% of the inlet flow. All these values were within previously reported ranges [135], except for the arch branches (BC, LCC and LS) where the total calculated percentage was slightly above normal values (reported to be approximately up to 30% of the inlet). However, as no flow information was provided, results could not be validated against patient-specific data. The major differences among the 7 models were observed for the renal arteries, which often branched off the FL. In particular, the average flow in the right renal artery in TEVAR-P2 and TEVAR-P3 was lower than that in the left renal artery, which was perfused by

Table 7.6: Percentage of inlet flow diverted to each arterial branch in the patient-specific models.

	TEVAR			BMT			
	P1	P2	P3	P1	P2	P3	P4
BC	23.6%	16.9%	19.8%	18.4%	19.6%	18.9%	20.1%
LCC	11.3%	4.3%	7.2%	5.8%	5.6%	8.0%	5.0%
LSA	n/a	11.9%	11.0%	14.0%	11.5%	12.2%	14.2%
CEL	13.9%	15.0%	13.0%	12.4%	13.3%	12.5%	12.7%
IM	11.9%	12.8%	11.0%	11.7%	12.0%	11.0%	10.7%
RR	9.0% (T)	8.0% (T)	8.6% (T)	8.6% (F)	9.0% (T)	8.2% (TF)	8.2% (T)
LR	9.2% (F)	9.8% (TF)	9.3% (TF)	9.1% (T)	9.4% (TF)	8.3% (T)	8.9% (T)
RI	10.6%	10.6%	10.0%	10.0%	9.9%	10.4%	10.0%
LI	10.6%	10.7%	10.0%	10.1%	9.9%	10.4%	10.2%

BC= brachiocephalic artery, LCC = Left common carotid artery, LSA = Left subclavian artery, CEL = coeliac artery, SM = superior mesenteric artery, RR and LR = Right and left renal arteries, RI and LI = right and left iliac arteries, T = True lumen perfusion, F = False lumen perfusion, TF = True and false lumen perfusion.

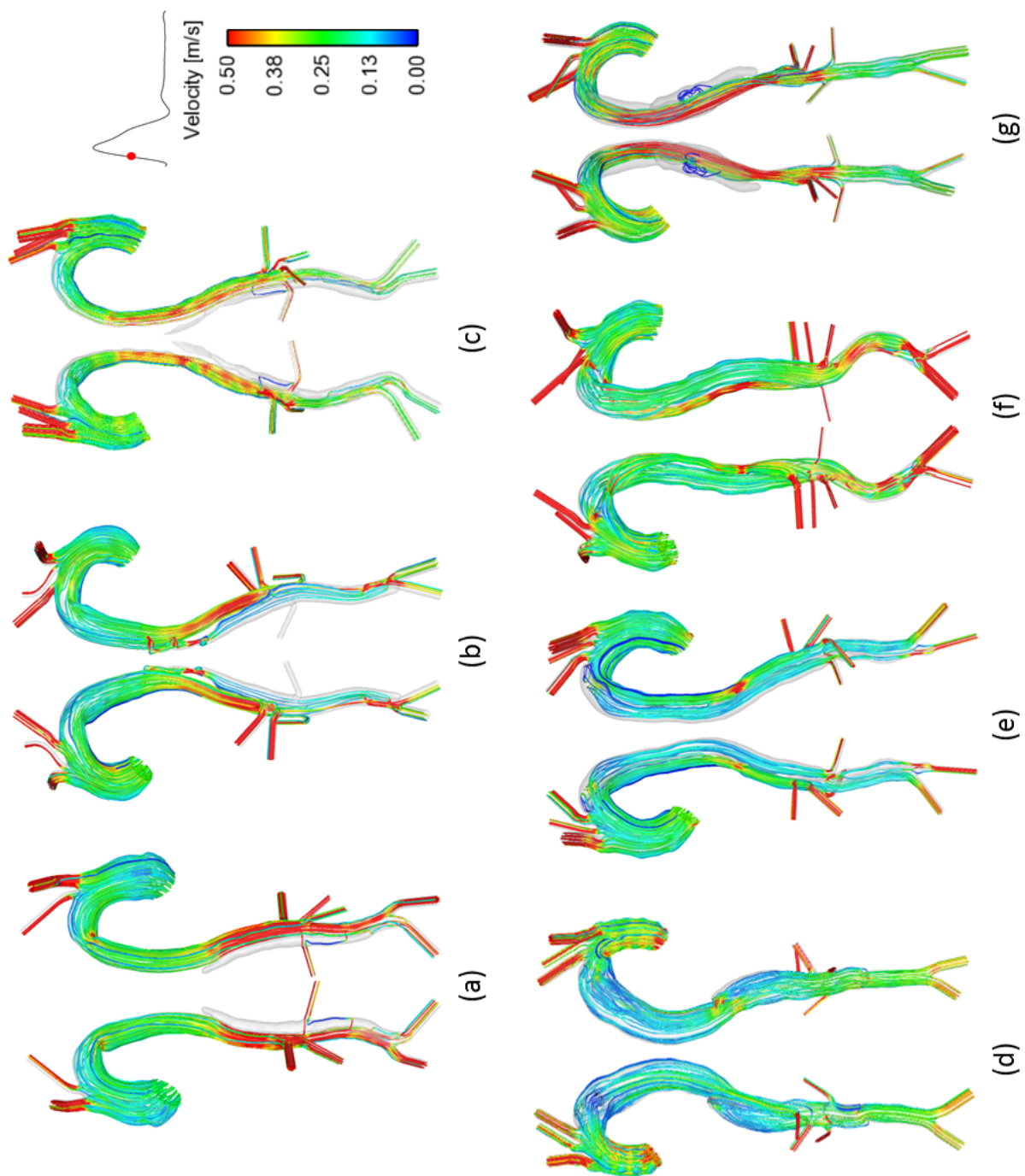


Figure 7.5: Instantaneous velocity streamlines during mid-systolic acceleration in (a) TEVAR-P1, (b) TEVAR-P2, (c) TEVAR-P3, (d) BMT-P1, (e) BMT-P2, (f) BMT-P3 and (g) BMT-P4.

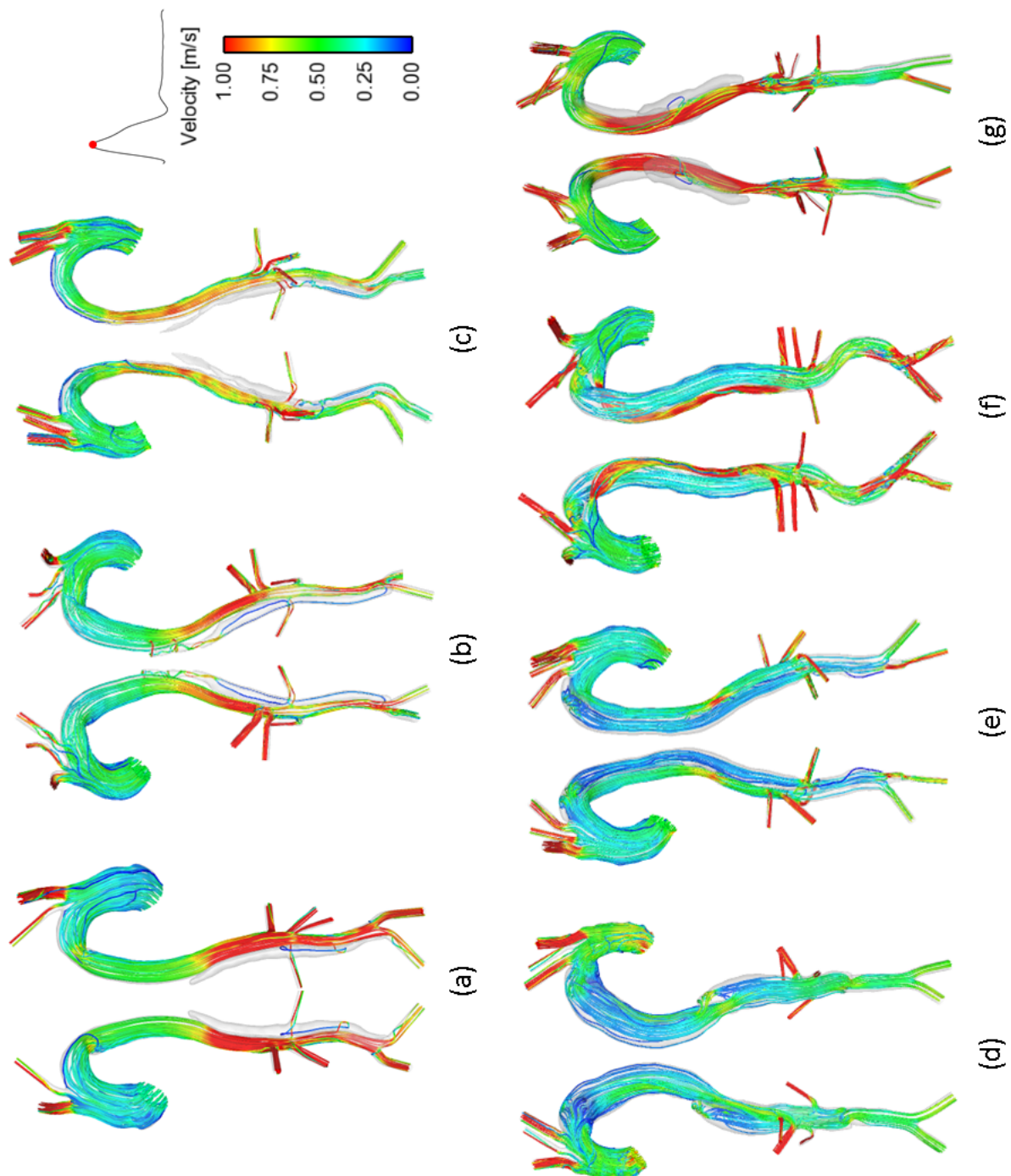


Figure 7.6: Instantaneous velocity streamlines at peak systole in (a) TEVAR-P1, (b) TEVAR-P2, (c) TEVAR-P3, (d) BMT-P1, (e) BMT-P2, (f) BMT-P3 and (g) BMT-P4.

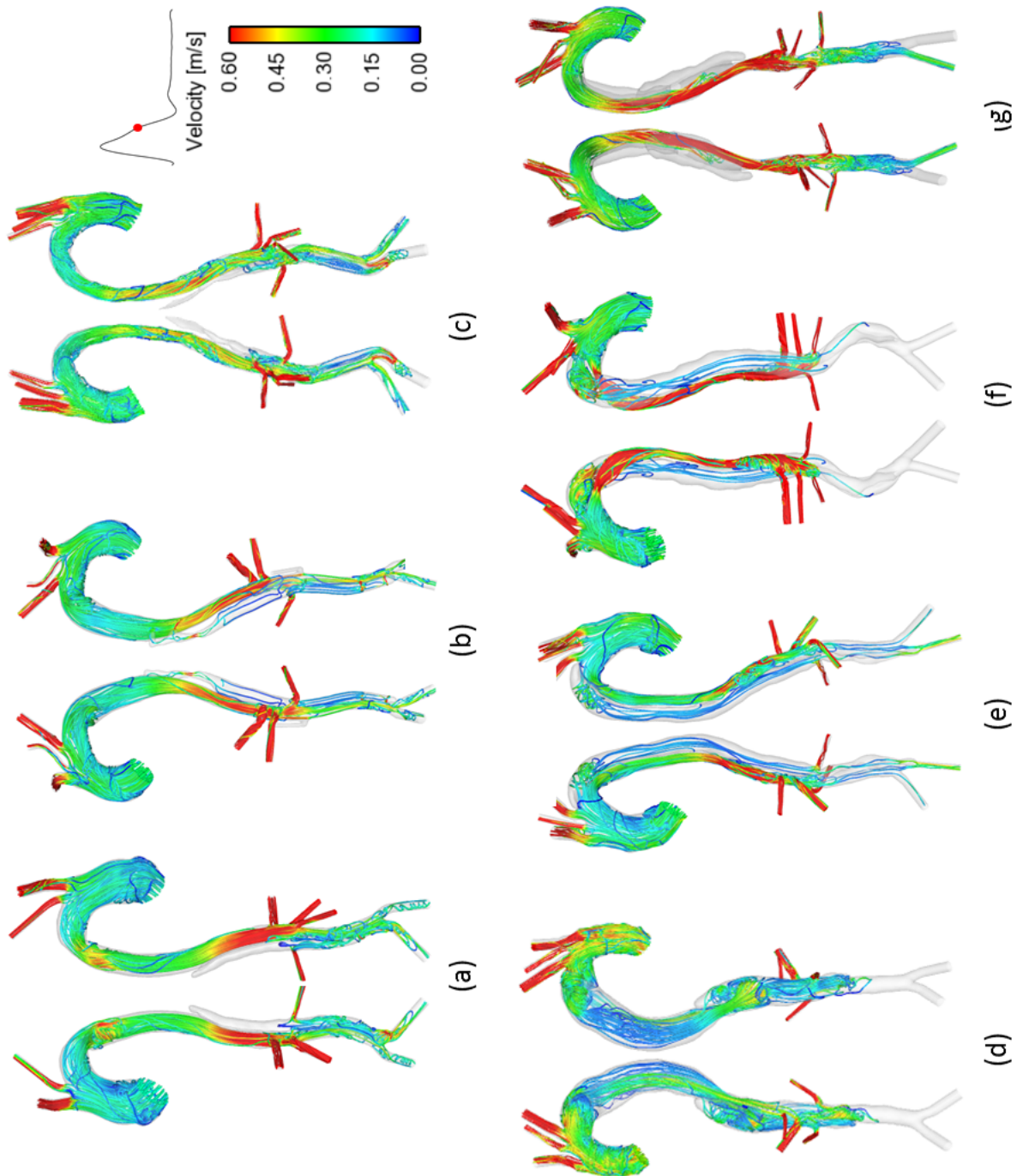


Figure 7.7: Instantaneous velocity streamlines during mid-systolic deceleration in (a) TEVAR-P1, (b) TEVAR-P2, (c) TEVAR-P3, (d) BMT-P1, (e) BMT-P2, (f) BMT-P3 and (g) BMT-P4.

both TL and FL. Likewise, the flow in the left renal artery was higher than that in the right renal in patient BMT-P1, where the right renal artery was perfused only by the FL.

Instantaneous velocity streamlines at three different time points in the patient-specific models are shown in Fig. 7.5, 7.6 and 7.7. Very low flow was observed in the FL for the TEVAR patients and in particular for patients TEVAR-P1 and TEVAR-P3, who presented a large distance between the distal end of the stent-graft and the first post-stent tear. This means that little flow could enter the top region of the FL. Disturbed flow with flow recirculation between the tears was observed in the distal FL during the deceleration phase in all three TEVAR patients.

For the BMT patients disturbed flow was observed in the FL proximally to the entry tears with local flow recirculation, and velocities in the FL were lower than in the TL at all time points. Much higher velocities were observed near the tears and in the narrowest regions of the FL. The lowest FL velocities were observed in patient BMT-P2, presenting the smallest entry tear diameter (approx. 8 mm), and almost static flow was observed in patient BMT-P4, having only one major tear located in the descending aorta.

Pressure. Fig. 7.8 shows the average pressure distributions in all the patient-specific models. It is clear that the different anatomies determined very different pressure distributions. Generally the TEVAR patients showed lower pressures in the FL, as a large distance existed between the first post-stent tear and the aortic arch. TEVAR-P2 had slightly higher FL pressure as compared to the other TEVAR models, and the patient had a short distance between the first post-stent tear and the distal end of the stent-graft. For the BMT patients, the highest FL pressure was observed in BMT-P3, whose entry tear was located at the LSA level, with zero distance between the tear and the top of the FL. BMT-P4 had the lowest FL pressure, who also had a large distance between the first tear and the aortic arch. These results confirmed the findings of the anatomical data analysis, where a shorter distance between the first entry tear (primary for BMT and post-stent for TEVAR) and the top of the FL, the distance between the first entry tear (primary for BMT and post-stent for TEVAR) and the LSA and the presence of uncovered tears in region A for TEVAR patients were predictors of FL expansion.

TAWSS. The TAWSS distributions in the patient-specific models are presented in Fig. 7.9. Again, the patient-specific anatomy affected the TAWSS pattern. The highest shear stress was observed proximally to the tears and in the regions of high velocity. Very low TAWSS in the FL was observed in patients TEVAR-P1 and TEVAR-P3, where a larger distance existed between the

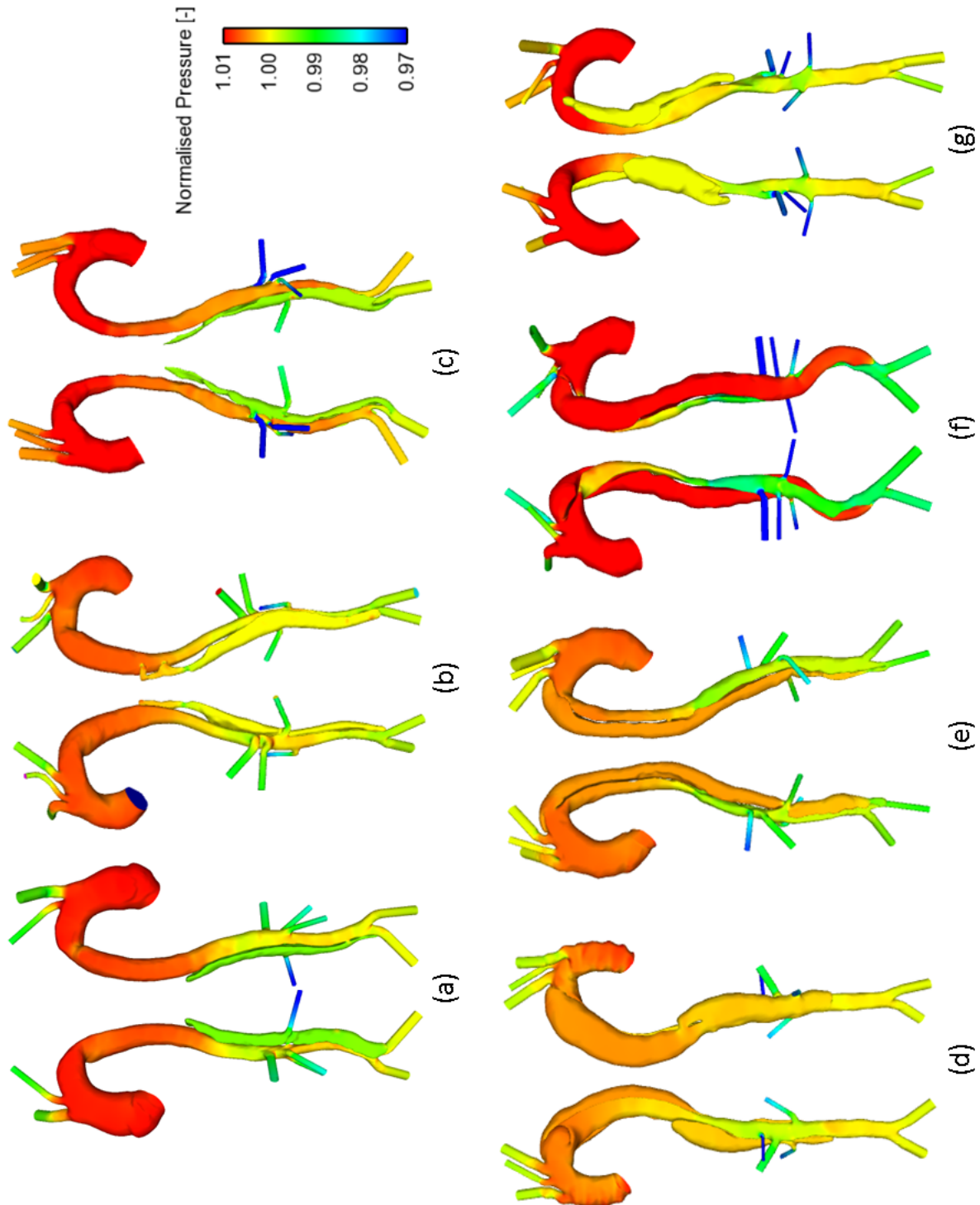


Figure 7.8: Time-averaged pressure distributions, normalised by the average pressure for each model. (a) TEVAR-P1, (b) TEVAR-P2, (c) TEVAR-P3, (d) BMT-P1, (e) BMT-P2, (f) BMT-P3 and (g) BMT-P4.

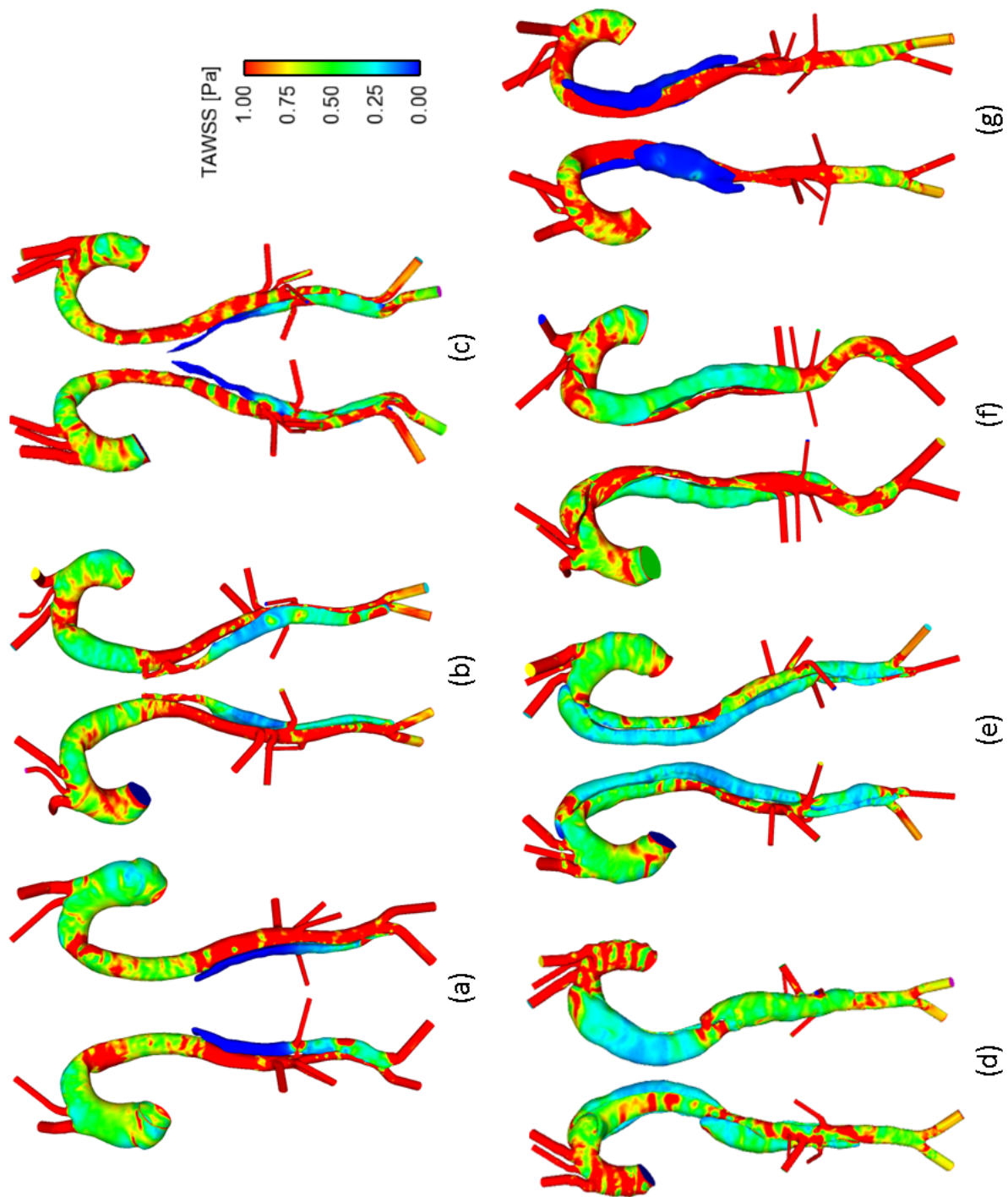


Figure 7.9: Time-averaged wall shear stress (TAWSS) distribution in the seven patient-specific models. (a) TEVAR-P1, (b) TEVAR-P2, (c) TEVAR-P3, (d) BMT-P1, (e) BMT-P2, (f) BMT-P3 and (g) BMT-P4.

first post-stent entry tear and the top of the stent-graft as compared to TEVAR-P2. For the BMT patients, the lowest TAWSS in the FL was observed in BMT-P4, having only one tear located in the descending aorta, and in BMT-P2, having the smallest entry tear diameter (approx. 8 mm). Interestingly, these two patients were the only BMT patients analysed who developed FL thrombosis during follow-up.

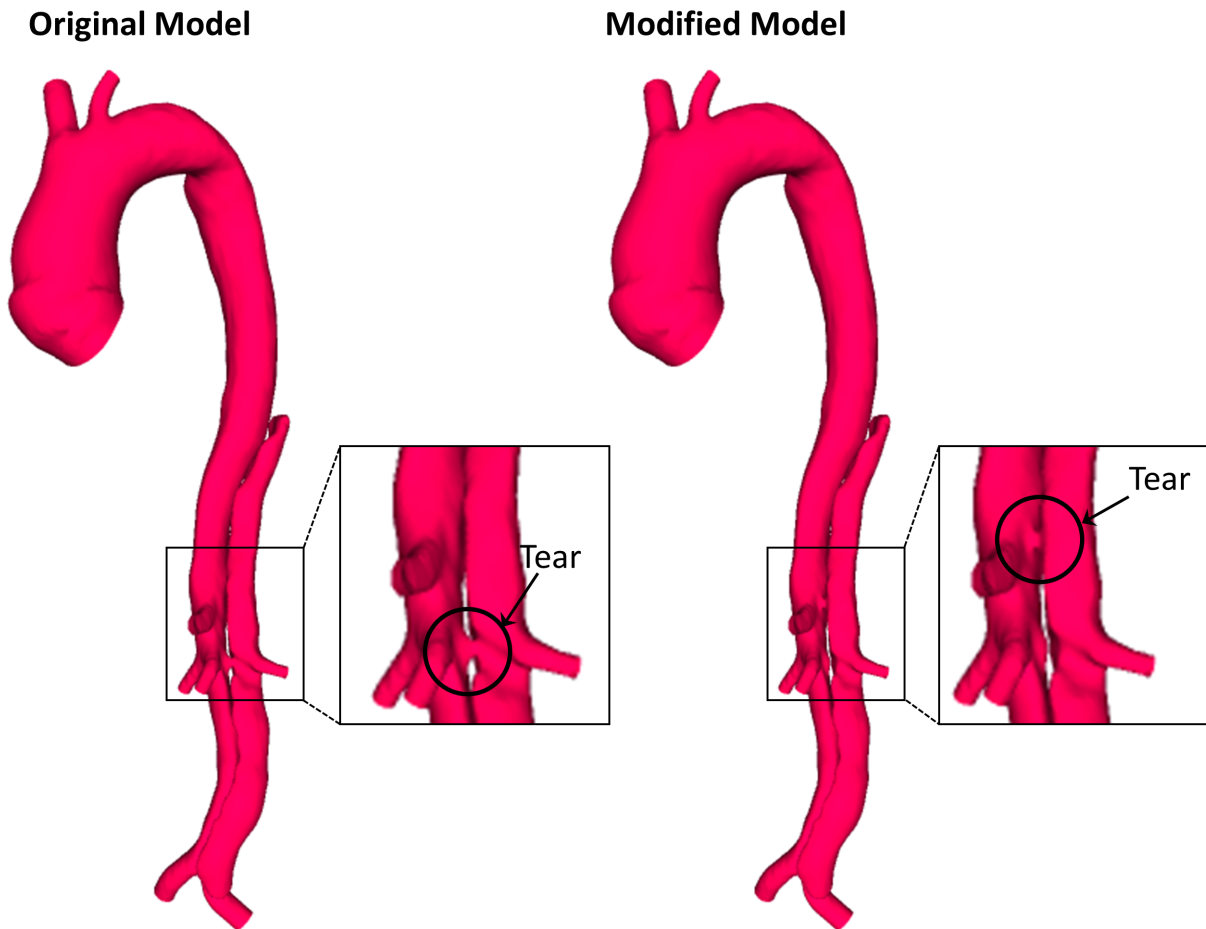


Figure 7.10: Original and modified TEVAR-P1 models, showing the location of the first post-stent tear.

Tear-to-vessel component. In order to understand the correlations found in the anatomical data analysis concerning tear-to-vessel component and distance between first post-stent tear and top of the FL, one of the patient-specific models (TEVAR-P1) was artificially modified. The first post-stent entry tear, originally located at the level of the left renal artery branching off the FL, was artificially moved up by 30 mm towards the stent, right above the celiac trunk (Fig. 7.10). Results from this case are reported in Figure 7.11. It can be clearly observed that the change of

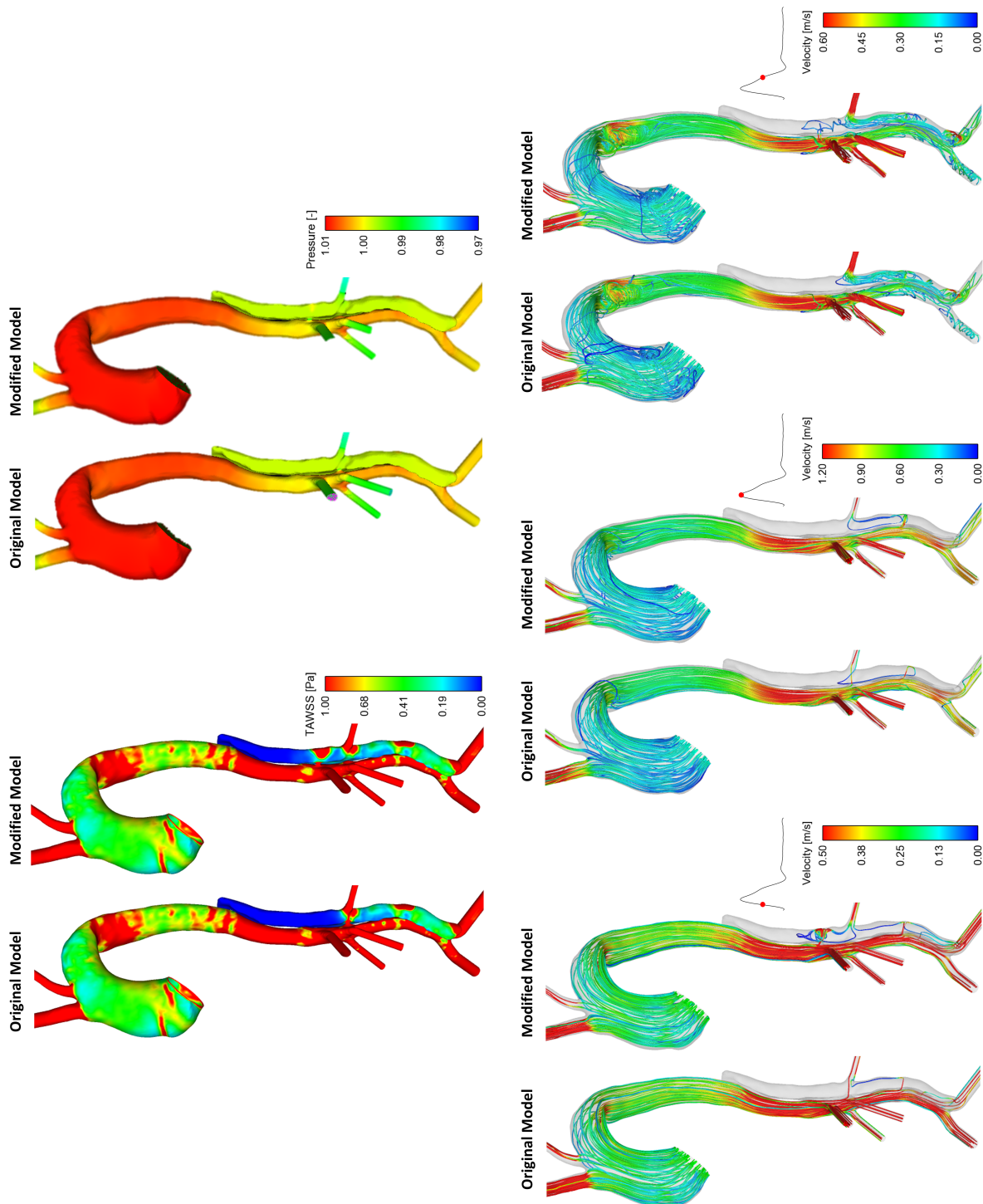


Figure 7.11: TAWSS, Average pressure distribution and flow patterns at different time points for the original geometry and the one obtained by moving the first post-stent tear up by 30 mm.

location of the tear had repercussions on FL flow, pressure and TAWSS, in particular in the region surrounding the tear. While almost no FL flow was observed above the renal arteries in presence of a tear-to-vessel component (i.e. the existence of a tear in close proximity to a major vessel branching off the FL), increasing the distance between the first post-stent tear and the FL branch resulted in an appreciable amount of flow in this region. Significantly higher TAWSS and slightly higher pressure were also observed in proximity of the relocated tear. These imply a much lower probability for thrombus formation in this region and potentially a local increase in FL volume.

7.3.2 Thrombus Predictions

In order to extend the thrombosis model to more complex geometries, this was applied to the patient-specific models described above. The predicted thrombus growth patterns were also compared with follow-ups for validation purpose. Results for the three TEVAR patients are shown in Fig. 7.12, 7.13 and 7.15. For all three patients, partial thrombosis was predicted in the FL. Thrombus formation started from the top region of the FL and continued to expand towards the

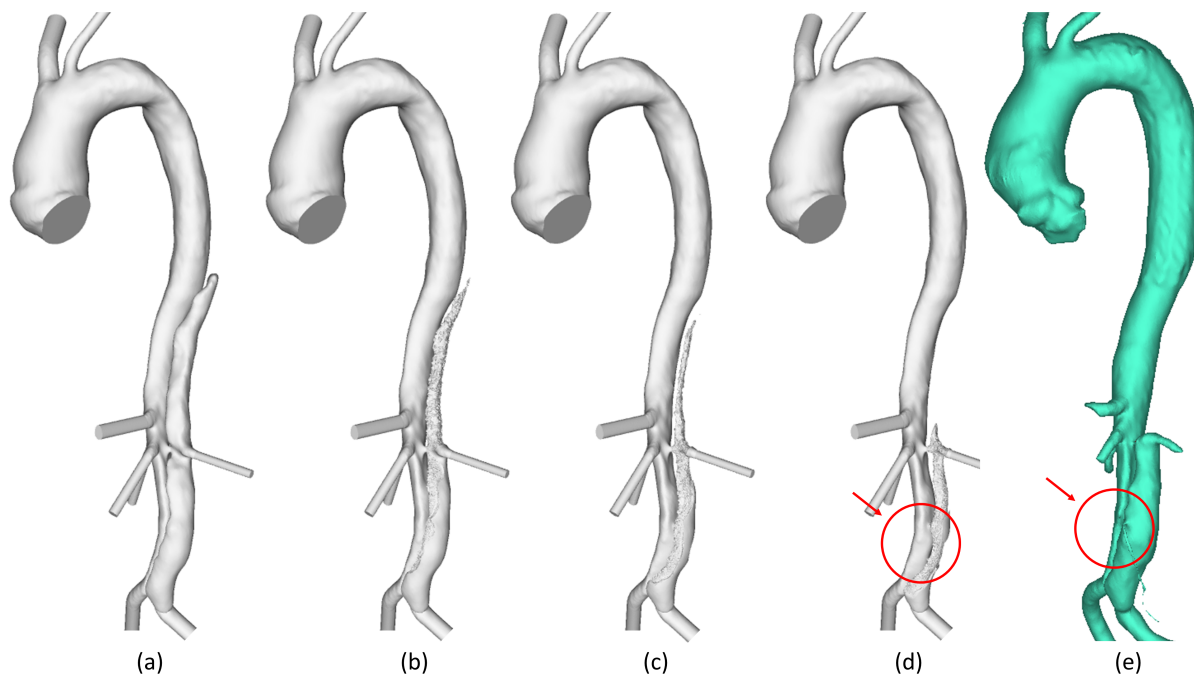


Figure 7.12: Evolution of FL surface in TEVAR-P1 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in TEVAR-P1, and predicted FL surface following thrombus growth at (b) 8 s, (c) 15 s, and (d) 26 s, in comparison with (e) the reconstructed lumen surface based on follow-up scans acquired at 3 years after TEVAR.

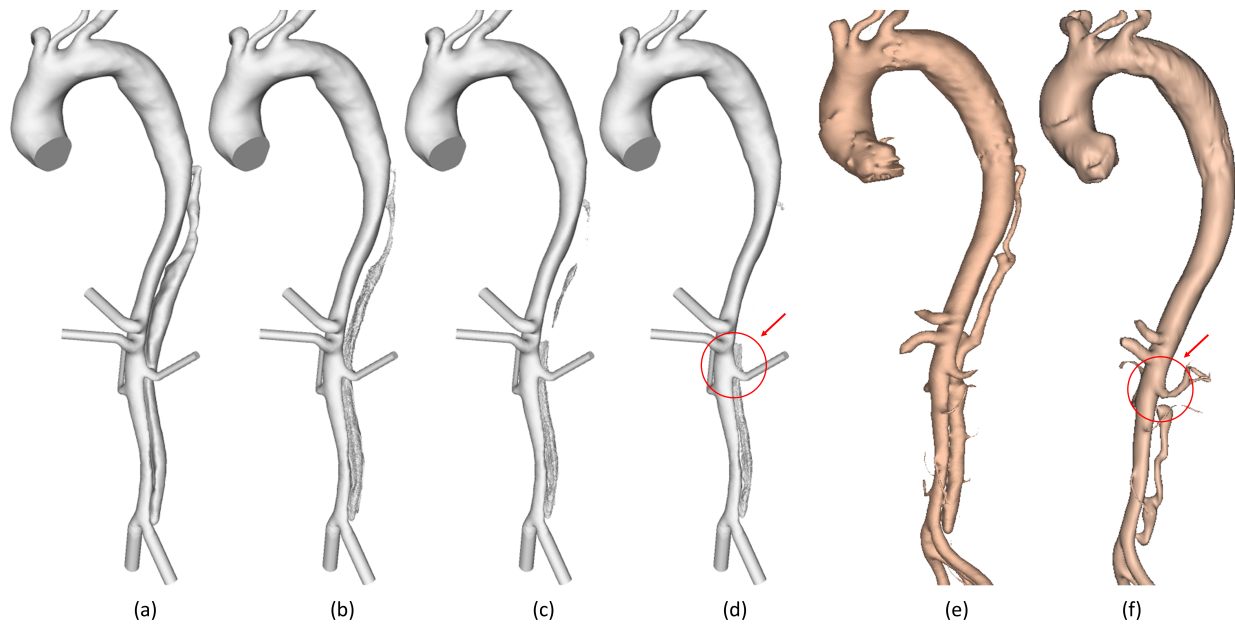


Figure 7.13: Evolution of FL surface in TEVAR-P2 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in TEVAR-P2, and predicted FL surface following thrombus growth at (b) 15 s, (c) 22 s, and (d) 28 s, in comparison with the reconstructed lumen surface based on follow-up scans acquired at (e) 1 year, and (f) 2 years after TEVAR.

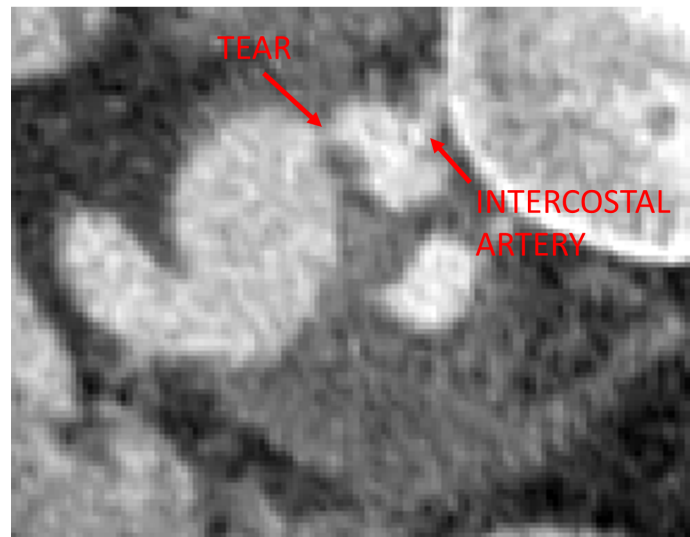


Figure 7.14: Cross-sectional plane of TEVAR-P2 showing the relative locations of the entry tear located above the celiac trunk and an intercostal artery.

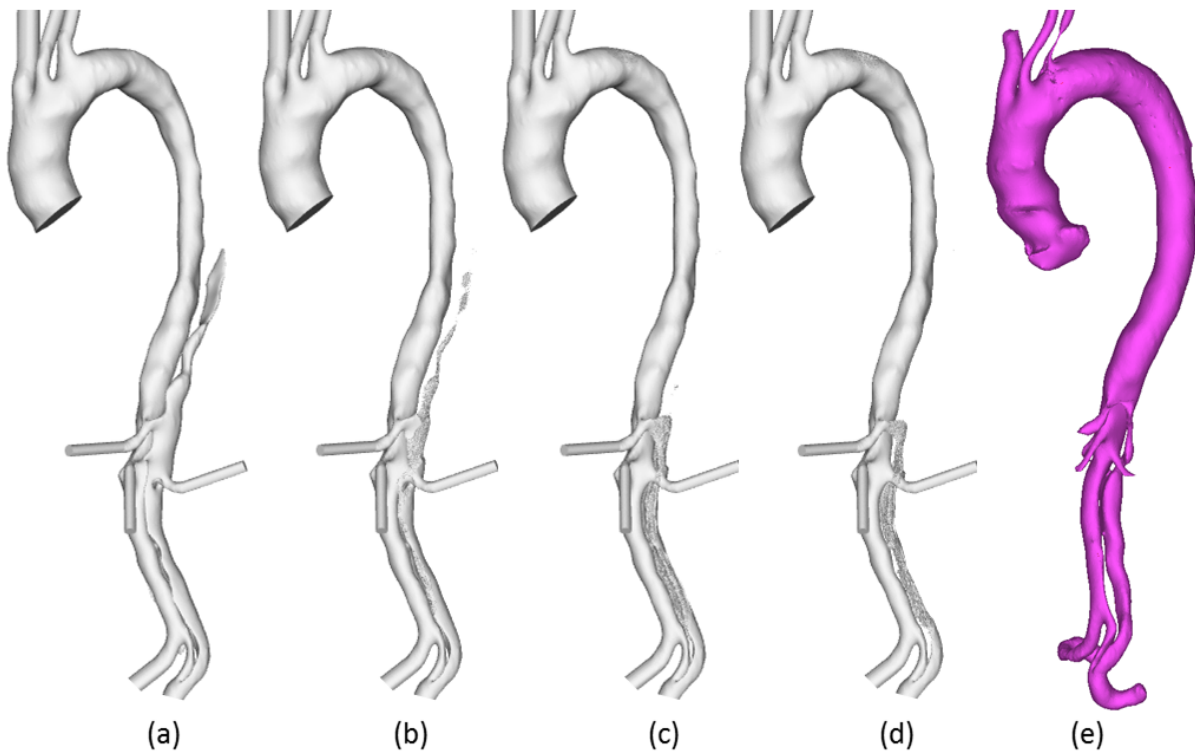


Figure 7.15: Evolution of FL surface in TEVAR-P3 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in TEVAR-P3, and predicted FL surface following thrombus growth at (b) 8 s, (c) 15 s, and (d) 26 s, in comparison with (e) the reconstructed lumen surface based on follow-up scans acquired at 1 year after TEVAR

first post-stent tear. A second region of partial thrombosis was also observed in-between the first post-stent and the distal tears. For all TEVAR patient, thrombus growth slowed down after about 20 s, until stopping after 26-28 s (Fig. 7.12-7.15).

Results for BMT-P2 and BMT-P4 are shown in Fig. 7.16 and Fig. 7.18 respectively. Results for BMT-P1 and BMT-P3 are not shown here as no significant thrombus growth occurred, apart from small patches of thrombus in sharp corners and locations where a small branch had been artificially occluded. For patient BMT-P2, partial thrombosis was predicted in the abdominal region of the FL. Thrombus formation started in the region below the renal arteries, and slowly proceeded upwards towards the thoracic FL and downwards towards the aortic bifurcation. After approximately 50 s of simulation time the region below the abdominal branches was almost completely thrombosed, while partial FL thrombosis was observed in the thoracic region between the first and the second tears (Fig. 7.16). BMT-P4 only presented one entry tear in the descending aorta and no visible distal tears could be observed. In this patient, thrombus formation started

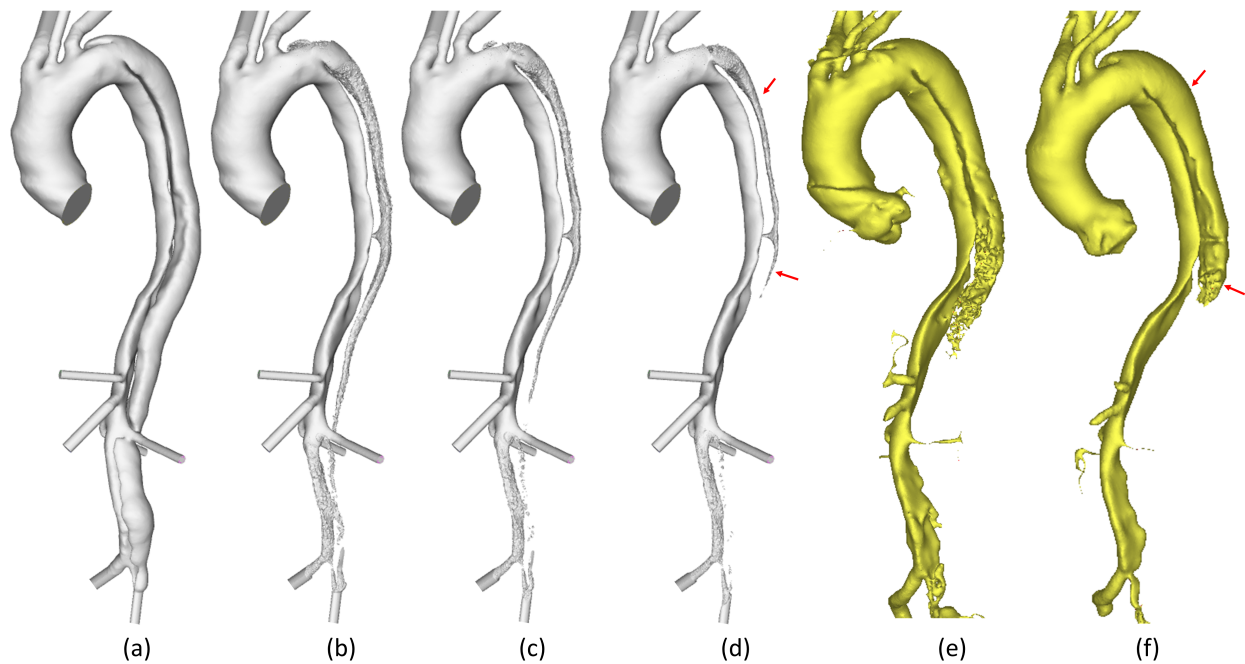


Figure 7.16: Evolution of FL surface in BMT-P2 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in BMT-P2, and predicted FL surface following thrombus growth at (b) 30 s, (c) 40 s, and (d) 52 s, in comparison with the reconstructed lumen surface based on follow-up scans acquired at (e) 1 year, and (f) 2 years after TEVAR.

at the proximal and distal ends of the FL and, as the thrombus approached the tear, growth was significantly slowed down. After a simulation time of approximately 26 s the FL was almost completely thrombosed (Fig 7.18).

For all TEVAR patients, good overall agreement was achieved between predicted thrombus growth and actual clinical observations. The model was able to capture the location of thrombus growth, and correctly predicted incomplete thrombosis within a simulated time frame of less than 30 s. Some disagreements can be observed in TEVAR-P1 and TEVAR-P2. In TEVAR-P1, the model overpredicted thrombus growth in the region between the renal arteries and the aortic bifurcation (Fig. 7.12). This was due to the inferior mesenteric artery and one of the intercostal arteries, which were not included in the computational models, branching off the FL (Fig. 7.12). In TEVAR-P2, the region between the superior mesenteric artery and the right renal artery was predicted to remain patent, while thrombosis was observed during follow-up (Fig. 7.13). Thrombosis of this region in the computational model was hindered by the presence of a tear at the level of the superior mesenteric artery which allowed flow into the FL. In the CT scan an intercostal artery can be seen at the same level of the tear (defined before as tear-to-vessel component, Fig. 7.14). Most of the

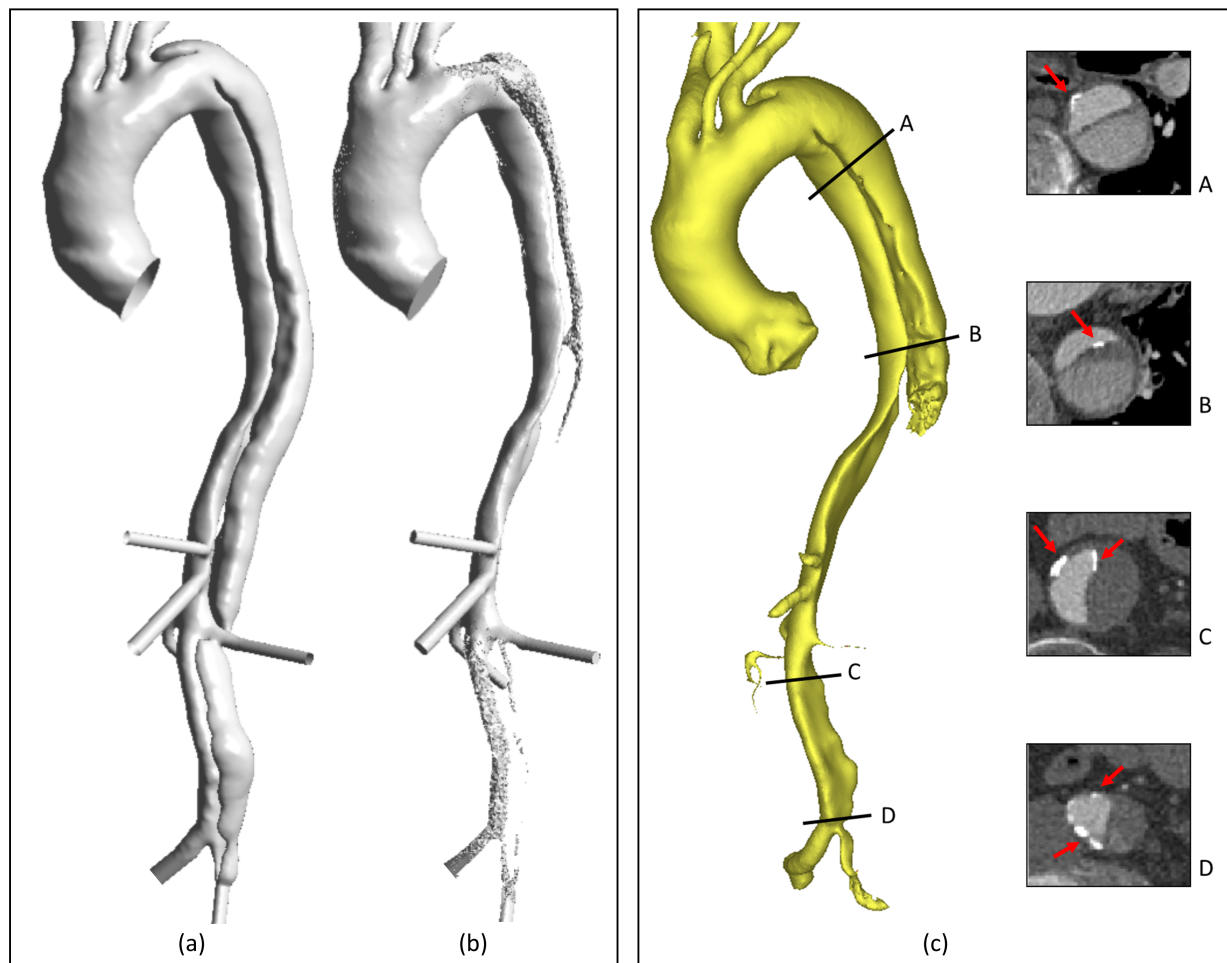


Figure 7.17: (a) Initial geometry, (b) predicted FL surface following thrombus growth after 40 cardiac cycles and (c) reconstructed lumen surface based on follow-up scans acquired 2 years after TEVAR. The planes A, B, C, D have been extracted from the CT data and show some of the locations where calcifications formed in the true lumen, indicated by the red arrows.

flow crossing the tear was hence diverted to the branch, reducing the amount of blood circulating in this region of the FL.

Also for the BMT cases, the model identified well the location of thrombus growth, and correctly predicted complete or incomplete thrombosis within a simulated time frame of 52 s. Some disagreements were found for patient BMT-P2, where the thoracic FL was predicted to be partially thrombosed while no major thrombosis was observed during follow-up (Fig. 7.16). Interestingly, when looking at the original geometry it is possible to identify 11 intercostal arteries branching off this region, which are likely to hinder the deposition of platelets and the formation of thrombus. Some thrombus formation was also observed in the abdominal TL, where calcifications

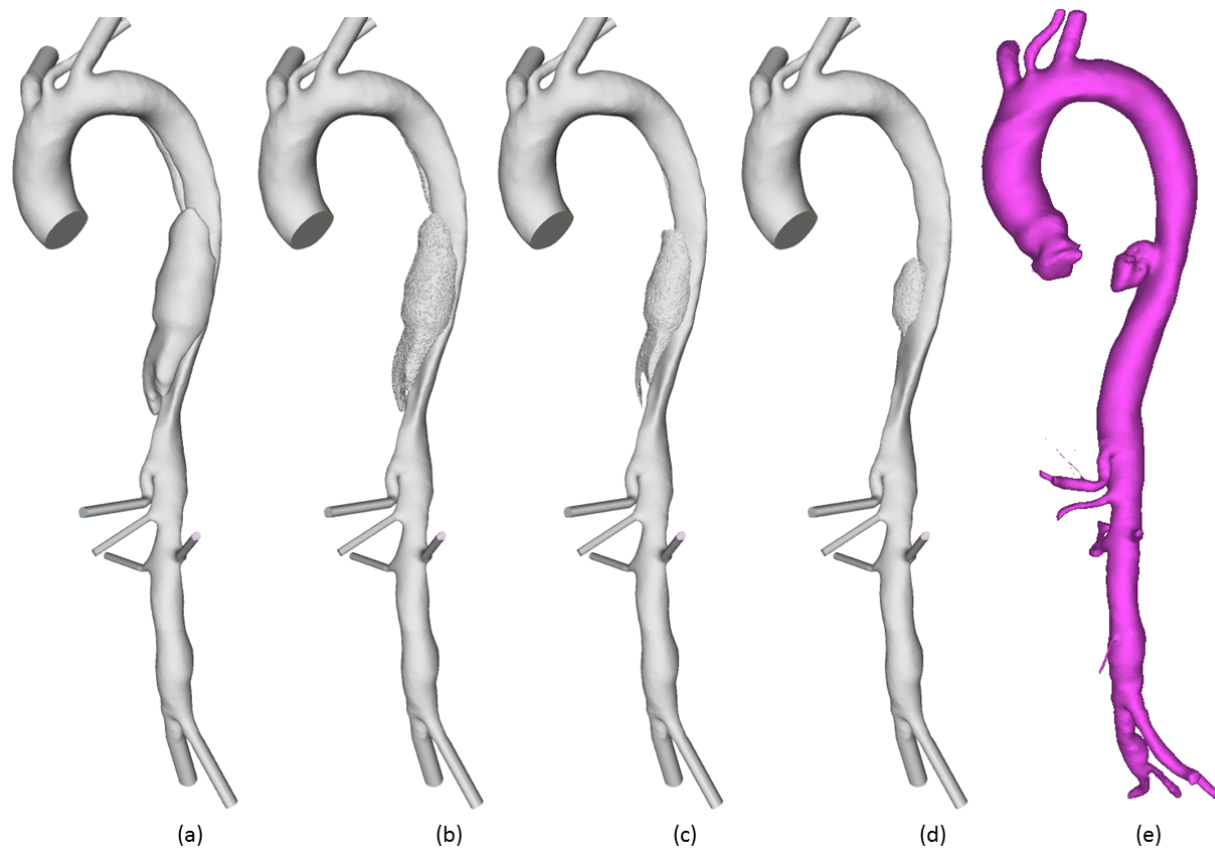


Figure 7.18: Evolution of FL surface in BMT-P4 following thrombus growth. (a) Reconstructed lumen surface based on the initial scan in BMT-P4, and predicted FL surface following thrombus growth at (b) 7 s, (c) 15 s, and (d) 26 s, in comparison with (e) the reconstructed lumen surface based on follow-up scans acquired at 1 year after TEVAR.

were observed during follow-up, as shown in Fig. 7.17. Good overall agreement between predicted thrombus growth and follow-up data was observed for patient BMT-P4.

The findings presented in this section further demonstrate that parameters like the existence of a tear-to-vessel component and the presence of branches in the FL, including small arteries such as intercostal arteries and inferior mesenteric, play an important role in determining the evolution of FL thrombosis, as indicated by the strong correlations found in the anatomical data analysis.

7.4 Results: Analysis of Phantom Models

The average pressure and TAWSS distributions in the 10 different phantom models are shown in Fig. 7.19 and 7.20, where the geometries are grouped according to the geometric parameter

changed. Also, pressure differences between TL and FL were evaluated and their variations with time at three locations are reported in Fig 7.21 and 7.22. All the chosen geometric parameters had an effect on the magnitude of pressure and shear stress in the FL. Reducing the distance between the primary entry tear and the top of the FL (and hence the distance between the primary entry tear and the LSA, not included in the phantom models) appeared to increase both FL pressure and local TAWSS. Increasing the entry tear diameter appeared to increase both TL and FL pressure, to increase TAWSS in the middle region of the FL and to reduce TAWSS in the top of the FL. Reducing the curvature ratio led to an increase in FL pressure, but did not show any major effects on TAWSS. Reducing the distance between middle and distal tears seemed to increase the difference between TL and FL pressure, to increase TAWSS on the external wall of the FL proximally to the middle tear, and to lower TAWSS just below the first entry tear, near the flap.

From the results reported in this section, the diameter of the first tear appears to be the geometric parameter having the strongest effect on both pressure and TAWSS. The size of the entry tear determines the velocity and the amount of blood entering the FL: a larger tear diameter allows more blood to be diverted into the FL and hence higher pressure. The reduction of the inlet diameter also causes a drastic decrease in TAWSS in the region in-between the tears, increasing the likelihood for thrombus formation. The second most important parameters appeared to be the distance between the first entry tear and the top of the FL. A smaller distance from the top is associated with a more direct jet of blood entering the FL, and hence more FL flow and higher pressure. This also affects TAWSS in the region above the first tear, with a larger distance between tear and top of the FL corresponding to a significantly lower TAWSS and hence a higher likelihood for thrombus formation. The effect of the curvature ratio on pressure was milder but still noticeable. A smaller curvature ratio, hence a larger curvature width and/or a smaller inlet diameter, leads to an increase in FL flow and pressure. The distance between middle and distal tears had a mild effect on TAWSS and almost negligible effects on average pressure. Nonetheless, when looking at the time-varying pressures (Fig. 7.22), a slightly increased difference between TL and FL pressures both in the proximal and distal descending aorta can be seen when reducing the distance between tears.

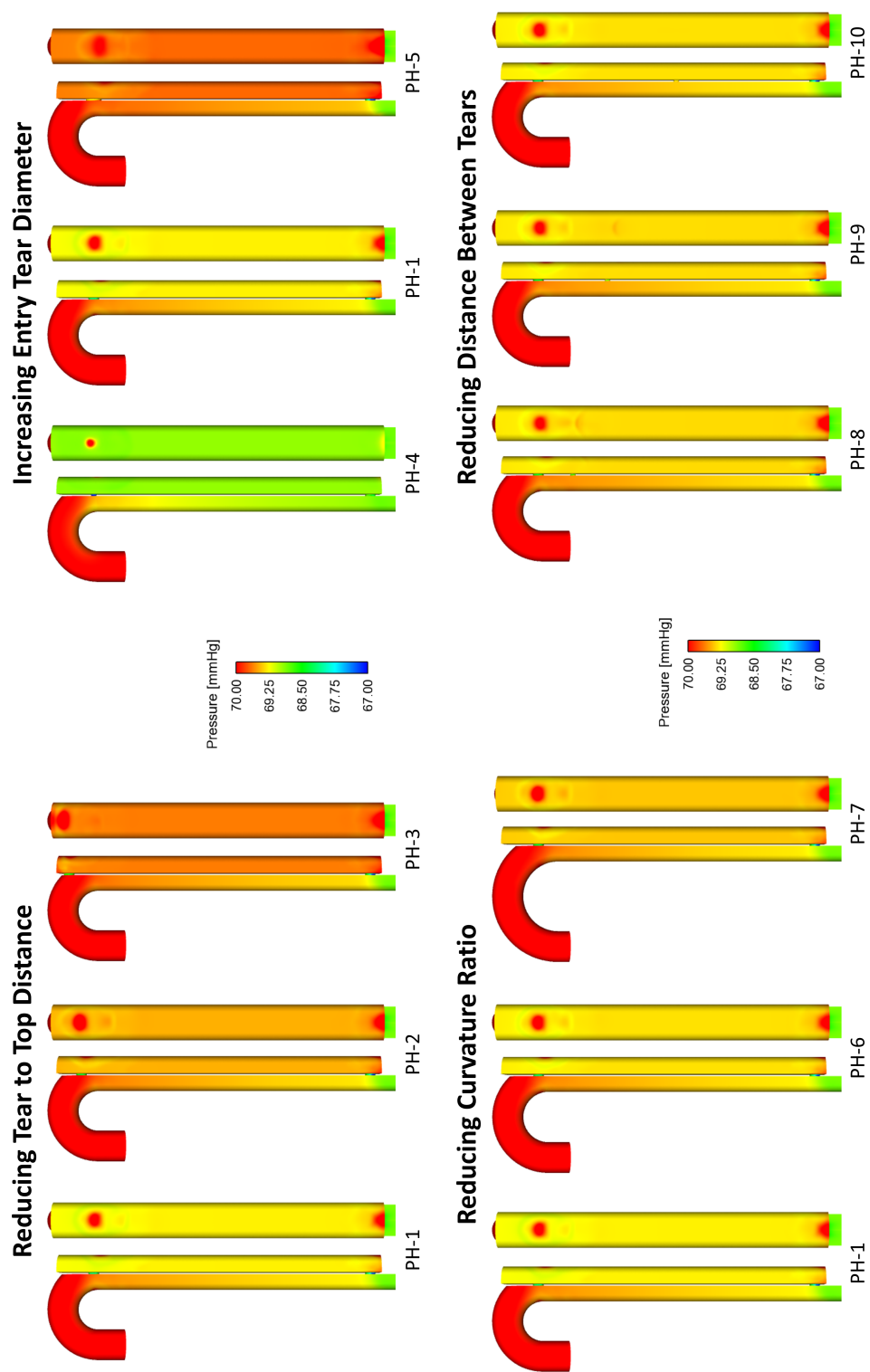


Figure 7.19: Cycle-averaged pressure distribution in the 12 phantom models.

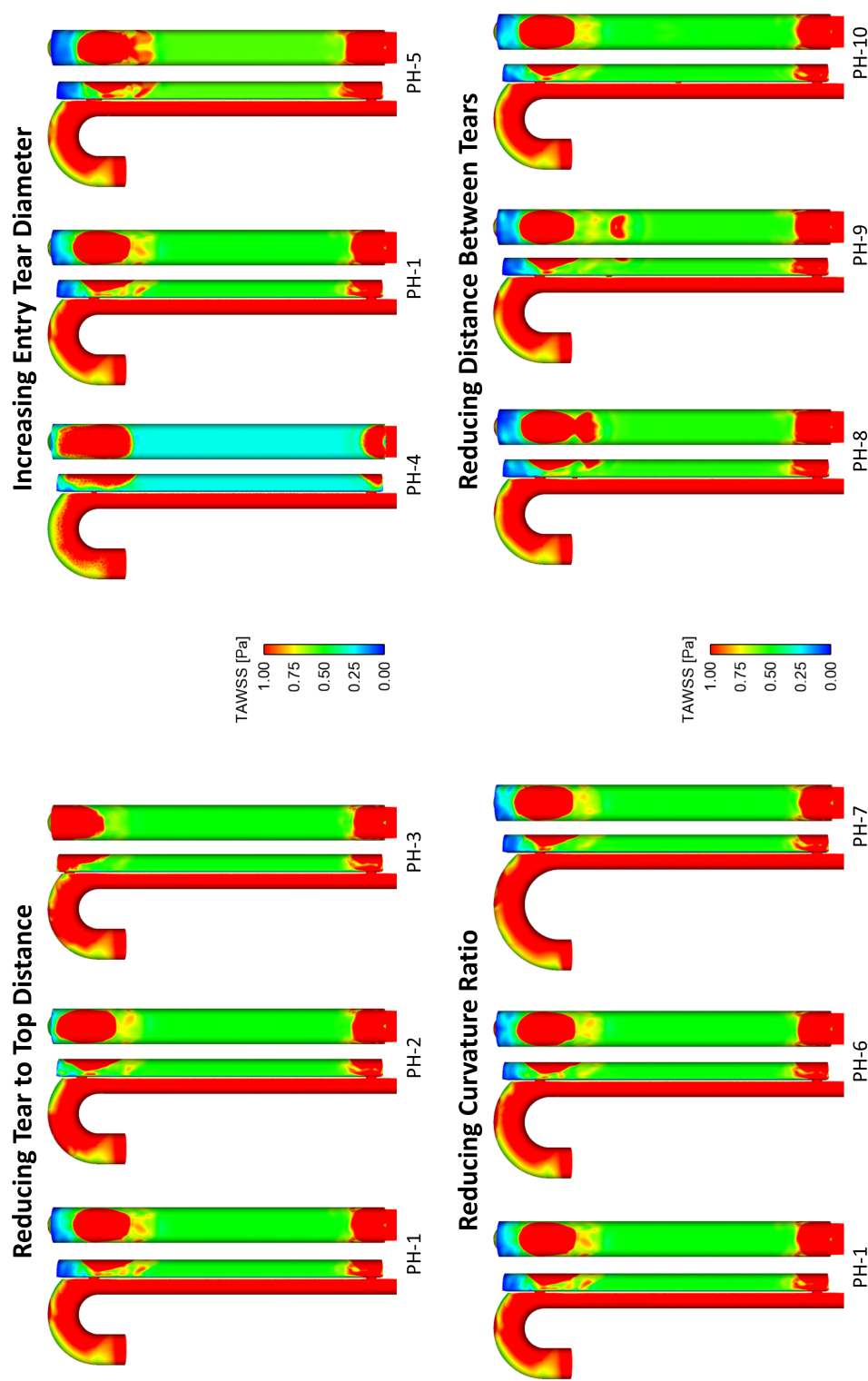


Figure 7.20: Time-averaged shear stress distribution in the 12 phantom models

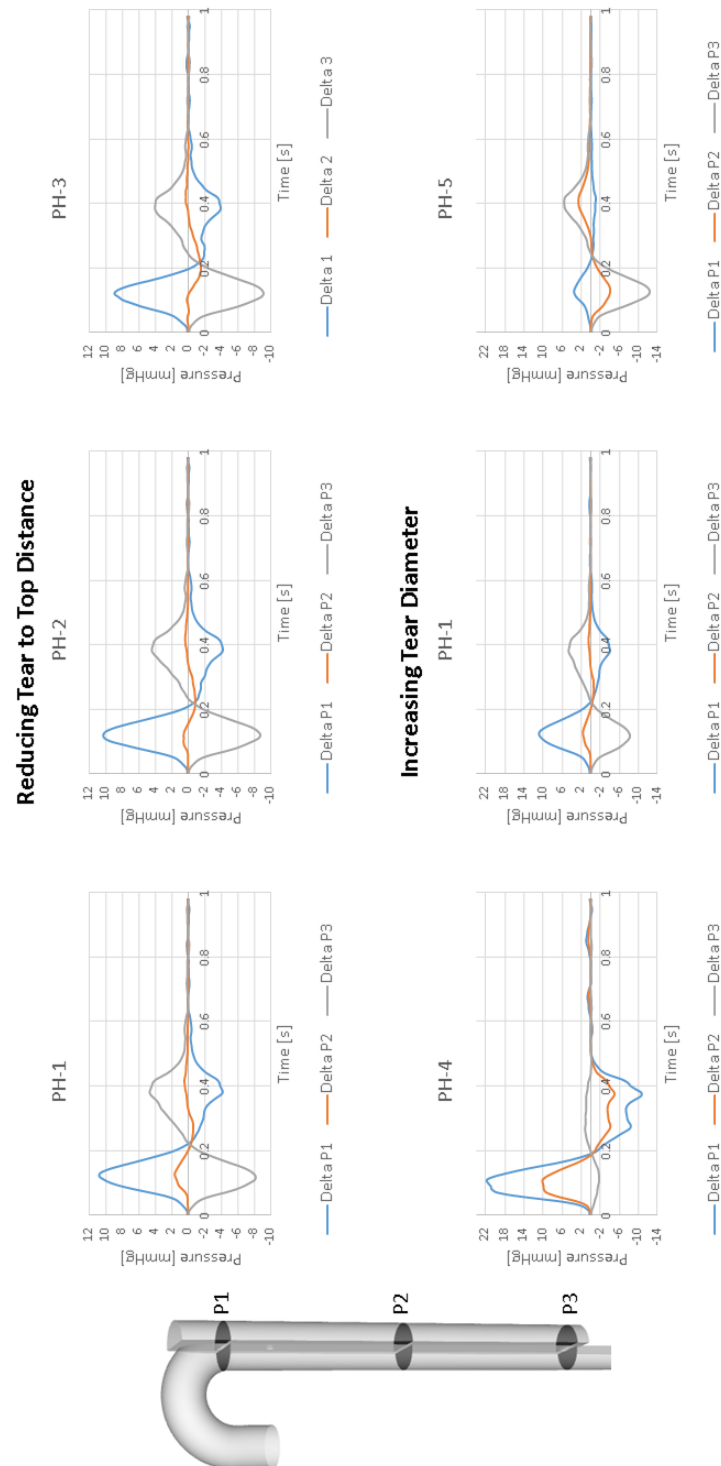


Figure 7.21: Difference between true and false lumen pressure plotted over time, and calculated as mean pressure over a cross sectional plane P1 at the top of the false lumen (Delta P1), in the middle descending aorta at location P2 (Delta P2), and at the bottom of the false lumen at location P3 (Delta P3) [part 1].

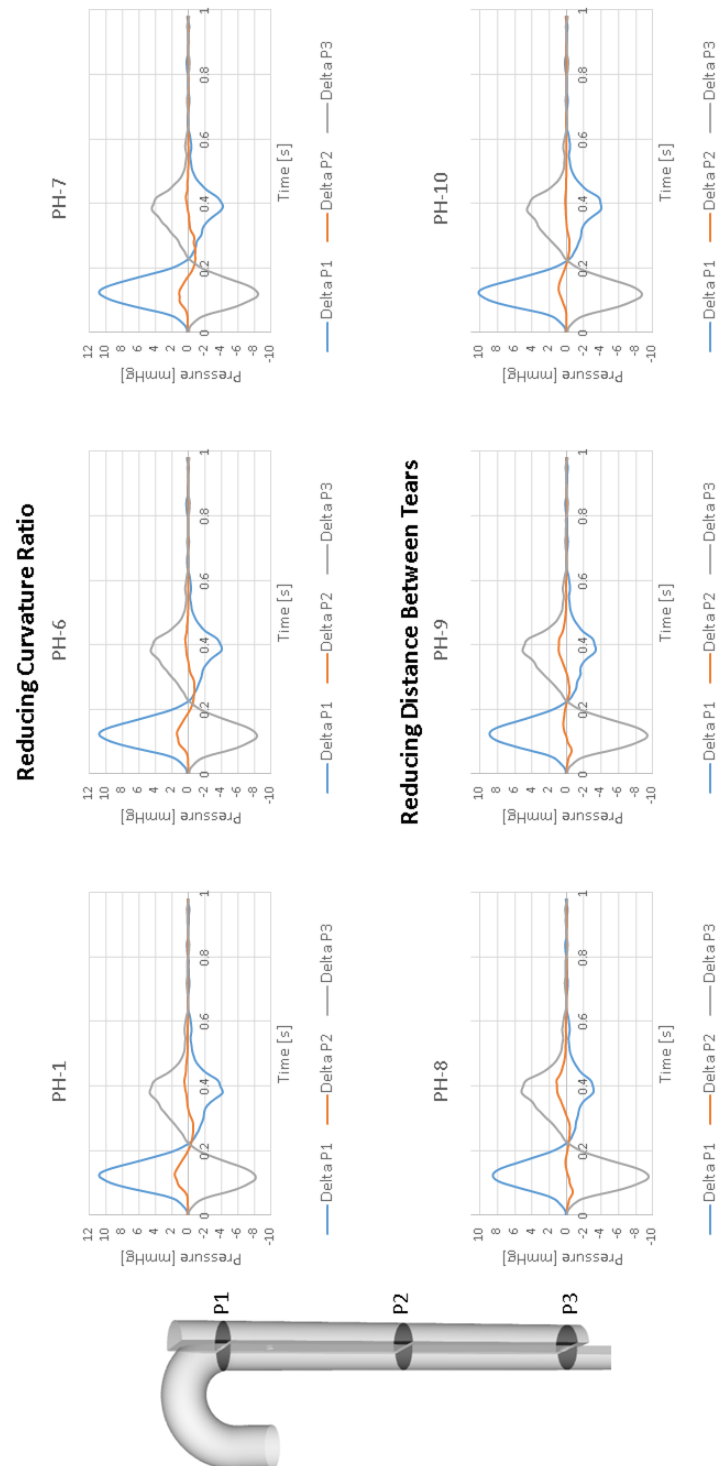


Figure 7.22: Difference between true and false lumen pressure plotted over time and calculated as mean pressure over a cross sectional plane P1 at the top of the false lumen (Delta P1), in the middle descending aorta at location P2 (Delta P2), and at the bottom of the false lumen at location P3 (Delta P3) [part 2].

7.5 Discussion

Although in-hospital survival rates are high for Type B aortic dissection patients, post-discharge prognosis is highly variable and uncertain. Extensive studies have been carried out trying to assess the efficacy of TEVAR against BMT treatments [129, 31], and to identify predictors of FL thrombosis and aortic growth [34, 37, 12, 36, 32, 130, 134, 136, 137]. Nonetheless, it is still unclear which are the key parameters driving the progression of this disease and determining the outcome of treatments. The main aim of this study was therefore to elucidate the role of morphological features in determining FL growth and/or thrombosis. A morphological analysis was carried out on 27 patients in order to identify correlations between changes in TL and FL volume and anatomical features. The choice of the parameters analysed in this study was inspired by the findings presented in the previous chapters, which indicated a potential influence of variables such as the distance between tears and the position of the entry tear on flow and FL thrombosis.

For the TEVAR+BMT group, an overall positive TL remodelling and FL thrombosis were observed. While significant remodelling and thrombosis were observed in the thoracic region, outcomes in the abdominal region varied. In particular, 43% of patients presented substantial FL volume increase ($> 20\%$) in this region (B+C+D). Several statistically significant correlations were found for the TEVAR+BMT group. The number of pre-operative FL branches was identified as a predictor of FL growth and an obstacle for FL thrombosis, as also reported by Ge et al. [137]. The presence of FL branches creates an additional pressure drop which drives flow within the FL and hinders the deposition of platelets and the formation of thrombus. In regions where small branches were artificially occluded, the model over-predicted thrombus formation, demonstrating that the presence of the branches clearly affected outcomes. Although the presence of FL branches was found to be associated with aortic growth and/or negative TL remodelling, the presence of a tear-to-vessel component was identified as a positive predictor for FL thrombosis. When a tear is located proximally to a FL branch, the flow driven to the FL by the presence of this vessel is diverted directly into the branch, limiting the amount of blood circulating within the rest of the FL. An example of this correlation was found in patient TEVAR-P2, where there were noticeable differences between the predicted thrombus formation and follow-up CT data in the region proximally to the first post-stent tear. Close inspection of the initial post-TEVAR CT scans revealed the presence of an intercostal artery at the tear level (Fig. 7.14), which was not included in the computational

model. Further evidence was provided by artificially relocating the first post-stent tear in TEVAR-P1. When moving the tear away from the branch, higher TAWSS and pressure were observed directly opposite the first post-stent tear. Also, as the flow crossing the tear and directed to the left renal artery had to travel a longer distance to reach the branch, higher velocities were observed in the region between the tear and the branch, previously characterised by almost stasis of blood. This finding also applies to patients presenting a branch perfused by both TL and FL, who are more likely to develop local thrombosis in the FL. The presence of tears in region A was also found to be correlated with FL growth, while the distance between the first post-stent tear and the top of the FL and the distance between the first post-stent tear and the arch were identified as predictors for FL thrombosis. Significantly higher pressure was in fact observed in patient TEVAR-P2 as compared to the other TEVAR patients, as the first post-stent tear was located immediately after the distal end of the stent-graft. The total number of tears and the maximum distance between tears were also found to be correlated with FL growth and negative remodelling. More flow is diverted into the FL in presence of multiple tears which contributes to pressurizing the FL, in particular when a large distance exists between tears. As shown in Chapter 5, tears close to one another may promote local recirculation and low TAWSS, contributing to the formation of thrombus.

Variable outcomes were observed for the BMT group in terms of volume changes. While on average no major TL volume changes were observed, a 14% average increase in FL volume was measured across the group over a 1-year follow-up period. Significant FL volume increases were observed in region A, where 54% of patients presented an increase in volume above 20%. From the anatomical data analysis, diameter and location of the primary entry tear were identified as predictors of FL growth. Evidence of these correlations can be found from the pressure distributions in the patient-specific geometries. The highest FL pressure was observed in patient BMT-P3, presenting the entry tear at the LSA level, while the lowest was observed in patient BMT-P2, presenting the smallest entry tear diameter, and in patient BMT-P4, with the entry tear being furthest from the arch. Similar findings were also observed from the phantom models, where the diameter of the entry tear and the distance between the first tear and top of the FL were identified as the parameters having the strongest effect on FL pressure. The number of FL branches, as also reported by Kamman et al. [134], was also found to be positively correlated with FL growth. As mentioned before, the presence of aortic branches affects local TAWSS and the pressure drop determined by the presence of aortic branches in the FL drives additional flow in the FL. In patient

BMT-P2, a comparison between predicted thrombus growth and *in vivo* data showed thrombus over-prediction in region A, where 11 small branches could be identified from the CT data. Although these branches are known to have negligible effects on the overall flow predictions, excluding them from the models affected local predictions of TAWSS and flow patterns, resulting in an over-prediction of thrombus growth. As for the TEVAR+BMT group, the maximum distance between tears was also found to be correlated with FL volume changes, so was the curvature ratio. From the analysis of the phantom models, it was possible to observe higher FL pressure for lower curvature ratios: a lower curvature ratio determines a more direct jet of blood into the FL, with higher FL flow and hence pressure. Nonetheless, the effects of varying the maximum distance between tears and curvature ratio were weaker than those of varying diameter and location of the primary entry tear.

Although much work has been done to identify the effects of changing morphological features on aortic flow and changes in diameter, little had been done prior to this work to assess the direct effect of these parameters on changes in aortic volume, especially looking at specific regions of the aorta. Our aim was not just to identify predictors of aortic growth and remodelling, but also to understand the physics behind these correlations. It is hoped that these findings will help us elucidate the dynamics driving the progression of Type B aortic dissection for both medically and endovascularly treated patients, and will help clinicians plan treatments.

Several limitations affect the work presented in this chapter. Firstly, the number of patients included in the anatomical data analysis was limited, and a multi-variate analysis to study the simultaneous effect of morphological parameters could not be performed. The analysis of a larger cohort of patients is recommended as future work in order to validate findings. The patient-specific geometries analysed in this study assumed rigid wall behaviour. It is known that, especially during the early stages of dissection and for BMT patients, the intimal flap is subject to movement, and this could affect predictions of flow and thrombus growth. By coupling the flow model with a wall model, it will be possible to run fluid-structure-interaction (FSI) simulations and to assess the effect of this assumption on predictions. Finally, the phantom models used to assess the impact of anatomical features on flow and pressure distribution were very simplified. The use of more realistic phantom geometries including abdominal and thoracic branches and the stent-graft will allow us to study the direct effect of FL branches on aortic growth and remodelling for both BMT and TEVAR patients.

7.6 Summary

In this chapter the effects of morphological features on the progression of Type B aortic dissections were investigated in terms of aortic growth, remodelling and thrombosis. Correlations between anatomical features and the evolution of TL and FL volume were analysed in terms of Pearson's and Spearman Rho coefficients. Statistically significant correlations were further investigated in order to understand the physical meaning of these findings through an in-depth flow analysis on patient-specific and phantom models, and through the application of the thrombus model developed in the previous chapters. Thrombus predictions in patient-specific geometries were also validated against *in vivo* data.

The results obtained in this chapter demonstrate that anatomical factors such as size and location of entry tears, the presence of branches in the FL and the distance between tears play an important role in aortic expansion and FL thrombosis. The shape of the arch in terms of curvature ratio was also found to be an important parameter to predict the risk of FL expansion in BMT patients. These findings could potentially help clinicians select the most appropriate treatments for individual patients and to predict which patients would be most likely to benefit from endovascular treatments, and which ones are at low risk for FL expansion. Future studies of a larger cohort of patients and the use of multi-variate analysis are warranted, which will determine which anatomical factors play the most important role in the progression of aortic dissection and will allow us to assess the simultaneous effects of changing these parameters.

Patient-Specific Prediction of Stent Graft-Induced New Entry Tears Following Thoracic Endovascular Repair: A Pilot Study[†]

As seen in the previous chapters, thoracic endovascular repair has become the preferred option for the treatment of complicated aortic dissection, and recent studies have shown its efficacy for the treatment of uncomplicated Type B dissections. The placement of a stent-graft which covers the primary entry tears favours the development of thrombosis in the false lumen (FL), helping to restore normal aortic flow. However, complete thrombosis is not always achieved and complications such as the formation of stent graft-induced new entry tears (SINE) have been reported. The formation of SINE is potentially life-threatening and often requires re-intervention. The SINE can cause retrograde dissection, pressurization of the FL leading to aneurysmal expansion, and can potentially lead to the formation of a second FL, aggravating the patient's conditions. Stent-graft oversizing, spring-back force (the inherent tendency of the stents to return to its initial straight status) and the pathologic fragility of the aortic wall are considered among the main risk factors associated with the formation of SINE [131].

In this chapter, a computational approach based on a combination of Finite Element (FE) modelling and CFD is tested for the prediction of SINE location. For the FE analysis, the results from a patient who developed SINE during follow-up are compared with a non-SINE patient in order to examine the differences between the two and to identify potential causes for SINE formation.

[†]This Chapter is adapted from: *Menichini, C, Pirola, S, Guo, B, Dong, Z, Fu, W, Xu, XY. Patient-specific prediction of stent graft-induced new entry tears following thoracic endovascular repair: A pilot study, and Pirola, S, Menichini, C, Guo, B, Dong, Z, Fu, W, Xu, XY. Deriving patient-specific boundary conditions for aortic flow simulation based on 4D-MRI. (Manuscripts in preparation)*

A complete flow analysis is also performed on the SINE patient, using a patient-specific set of boundary conditions based on 4D PC-MRI data and Dopplerwire pressure measurements.

8.1 Methodology

Two dissection patients treated with a Medtronic Valiant Captivia device (Medtronic, Minneapolis) in acute phase at the Zhongshan Hospital in Shanghai were analysed in this study. Both patients, a 59-year old (Patient 1 - Medtronic Valiant Captivia 32-200 mm) and a 44-year old (Patient 2 - Medtronic Valiant Captivia 28-150 mm) females, presented aneurysmal dilatation in the thoracic FL, more pronounced in the first patient. In both cases the left subclavian artery (LSA) was covered by the stent and a separate left carotid-subclavian artery bypass operation was performed for revascularization of the LSA. The thoracic FL appeared almost completely thrombosed during the first follow-up, taken 3 months after TEVAR for Patient 1 and 4 months after TEVAR for Patient 2, with thrombus formation extending up to the celiac trunk in Patient 1, and just below the distal end of the stent in the second. After 14 months, the formation of a SINE was observed in Patient 1 near the distal end of the stent-graft, which led to aneurysmal growth and the formation of a second FL. The conditions of Patient 2 remained stable, with no significant changes in FL volume. Both patients were kept under CT surveillance and 4D MRI scans were acquired before stenting and at the second follow-up. Dopplerwire pressure measurements were taken pre-TEVAR and at each follow-up.

8.1.1 Anatomical Measurements

Pre- and post-TEVAR geometries were reconstructed from the corresponding CT images using Mimics (Materialise HQ, Leuven) by segmenting the aortic geometry with a semi-automated threshold-based algorithm and then smoothing the surfaces. In order to assess morphological changes following TEVAR, key geometric parameters were measured in Mimics. These included inlet, arch and maximum diameters, curvature ratio, length of the thoracic aorta, tortuosity index and TL and FL volumes. The curvature ratio was calculated as the ratio between the inlet diameter and the internal width of the aortic arch, while the thoracic aortic length was measured from the centerline. The tortuosity index was calculated as L_1/L_2 , where L_1 is the distance between the initial and end point on the centerline, and L_2 is the linear distance between the two points. The volumes were calculated based on segmented area and slice thickness, as described in Chapter 7.

Table 8.1: Material properties used in the FE simulations.

Parameter	Value	Reference
Wall Thickness - Aorta [<i>mm</i>]	1.4	Van Puyvelde et al. [138]
Young's Modulus - Aorta [<i>MPa</i>]	2	Chen et al. [140]
Poisson Ratio - Aorta [—]	0.45	Chen et al. [140]
Wall Thickness - Stent Graft [<i>mm</i>]	0.9	Pasta et al. [139]
Young's Modulus - Stent Graft [<i>MPa</i>]	8.4	Pasta et al. [139]
Poisson Ratio - Stent Graft [—]	0.3	Pasta et al. [139]

8.1.2 Finite Element Modelling

Wall models were built for the first post-TEVAR follow-ups. In order to build the wall geometry including the flap, the inner and outer wall surfaces were created separately. The geometries created in Section 8.1.1 were used as the inner wall surface, while the outer wall surface was created by uniformly extruding the undissected equivalent of the inner wall by 1.4 mm for the aorta [138] and by 2.3 mm for the stent-wall region [139]; the latter was treated as a composite material. The computational models were meshed in ICEM (Ansys Inc.) and discretized into unstructured tetrahedral grids comprising approximately 2 million elements each. A linear elastic model was used to describe the aortic wall and the stent-graft. Material properties were extracted from the literature, which are reported in Table 8.1.

Three uniform pressure loads were tested: 50 mmHg (the pulse pressure of Patient 1), 42 mmHg (the pulse pressure of Patient 2), and 46 mmHg (the average value). Static pressure loads were applied perpendicularly to the internal surface of each model and displacement constraints were applied at the inlet and at each outlet. The models were resolved with the Ansys Static Structural solver (Ansys Inc.).

8.1.3 Flow Model

The first post-TEVAR geometry of the SINE patient (Patient 1) was discretized into an unstructured mesh comprising approximately 4 million elements, with a tetrahedral core and 10 prismatic layers at the walls. Eight outlets were included in the model, namely brachiocephalic trunk, left common carotid artery, celiac and superior mesenteric arteries, renal and iliac arteries. 3D patient-specific time-varying velocity profiles reconstructed from the pre-TEVAR 4D PC-MRI images were imposed at the inlet (Fig. 8.1), with a period of 0.7 s. A 3-element Windkessel model was used

at each outlet. Proximal and distal resistances and vessel compliance were calculated through the pre-TEVAR Dopplerwire pressure and flow measurements extracted from the pre-TEVAR 4D PC-MRI data available. The post-TEVAR 4D PC-MRI data could not be used for the extraction of boundary conditions due to image artefacts caused by the stent.

In order to obtain a full set of patient-specific boundary conditions, the pre-TEVAR 4D PC-MRI data was converted into an Ensight file through an in-house Matlab code developed by Miss Selene Pirola. In Ensight, five planes perpendicular to the flow were defined (Fig. 8.1) and the average flowrate through each plane was then calculated. For the two arch branches, the flow split was calculated according to their cross-sectional areas. Once the average flow through each outlet $\overline{Q}_i$ was determined, the total resistance R_{t_i} of each outlet i was obtained as:

$$R_{t_i} = \frac{\overline{P}_i}{\overline{Q}_i} \quad (8.1)$$

The compliance of each vessel was calculated as:

$$C_i = \frac{\tau}{R_{t_i}} \quad (8.2)$$

where τ is the time constant of the exponential fall-out of pressure and is equal to 1.79 [132]. Characteristic impedance (R_{c_i}) and peripheral resistance (R_{p_i}) for each outlet were then calculated as follows [132]:

$$R_{c_i} = \frac{\rho c_i}{A_i} \quad (8.3)$$

$$c_i = \frac{a_2}{(2R_i)^{b_2}} \quad (8.4)$$

$$R_{p_i} = R_{t_i} - R_{c_i} \quad (8.5)$$

where ρ is the blood density and c_i , A_i and R_i are respectively the local pulse-wave velocity, the area and the radius of outlet i [132]. The two empirical coefficients a_2 and b_2 are respectively equal to 13.3 and 0.3 [141]. An additional plane was extracted at the inlet of the pre-TEVAR set of data in order to obtain 3D time-varying velocity profiles for inlet boundary condition. All this procedure was carried out in collaboration with Miss Selene Pirola.

The boundary conditions were implemented in Ansys CFX via a user-defined CEL functions and Fortran subroutine. Blood was modelled as an incompressible Newtonian fluid, with viscosity

of 0.004 Pa/s and density of $1060 \text{ m}^3/\text{s}$. A high resolution scheme was used to solve the system of differential equations, with a time step of 0.001 s . Blood flow was simulated for five cardiac cycles in order to ensure periodic flow and pressure solutions. Results from the fifth cycle were used for analysis.

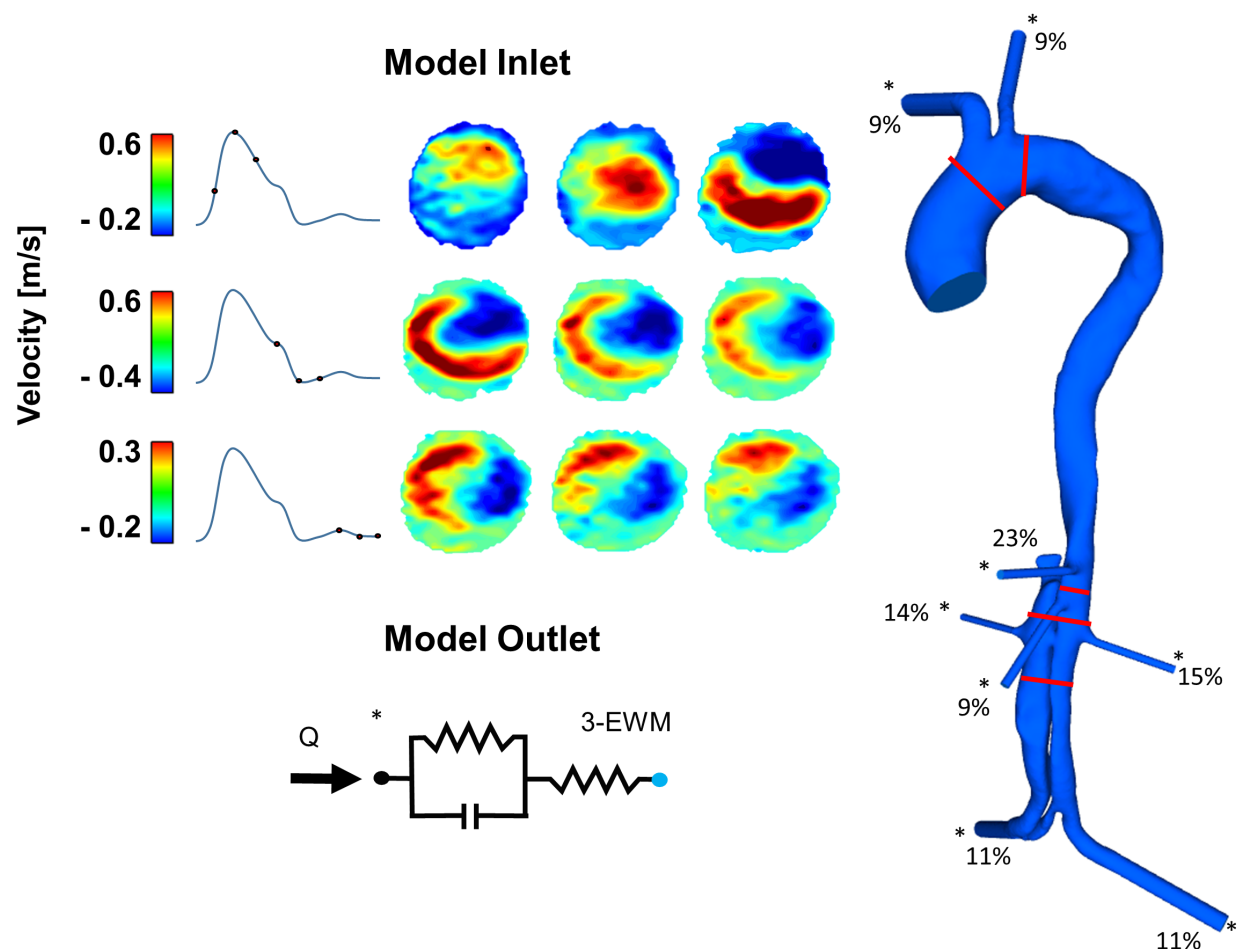


Figure 8.1: CFD model with boundary conditions. The red lines show the location of the planes extracted from the 4D-MRI images and used to build the outlet boundary conditions.

8.2 Results

8.2.1 Anatomical Features

The reconstructed patient-specific geometries are shown in Figure 8.2, and all the geometric measurements are summarised in Table 8.2. Patient 1 had a very tortuous geometry pre-TEVAR, with

significant aneurysmal dilatation in the thoracic aorta and a maximum diameter of 54 mm. In the first follow-up, the entire thoracic region of the FL was completely thrombosed, with an overall FL reduction of 88% (100% in the thoracic region and 36% in the abdominal region), and 40% reduction in maximum diameter. Significant remodelling was observed in the thoracic TL, with a 74% measured increase in volume. Almost no remodelling was observed in the abdominal TL. The length of the thoracic section of the descending aorta was also reduced, with a decrease in tortuosity by 10%. The curvature ratio was reduced by 16% post-TEVAR. The examination at the second follow-up showed the formation of a large SINE (approximately 70 mm in length) on the external side of the aorta (Fig. 8.2), located at the distal end of the stent-graft, with significant aneurysmal dilatation and the formation of a second FL with a maximum aortic diameter of 91 mm.

Patient 2 presented a much shorter and less tortuous thoracic aorta, with a slight aneurysmal dilatation in the thoracic region pre-TEVAR and a maximum diameter of 36 mm (Fig 8.2). An overall FL volume reduction of 80% was measured at the first follow-up, with reductions in thoracic and abdominal FL volume by 98% and 23% respectively. TL remodelling was also observed, with an overall increase in TL volume by 30% (53% in the thoracic region and 6% in the abdominal region), but there were no significant changes in thoracic aortic length or tortuosity. The tortuosity index of the stented region was 22% lower than in Patient 1. A 34% reduction in curvature ratio at follow-up was also observed. Further TL remodelling was observed at the 1-year follow-up, with an overall volume increase by 9% (8% in the thoracic region and 12% in the abdominal region), and an increase in maximum thoracic diameter from 30 mm measured at the first post-TEVAR scan up to 32 mm. No significant changes in FL volume were observed at the 1-year follow-up, with a total deviation of 2%.

8.2.2 Wall Displacement and Torsional Deformation

FE analyses were performed on the wall models for the first post-TEVAR follow-ups. Predicted wall displacements are shown in Figure 8.3. In both patients, high displacements can be observed in the descending aorta and in particular just below the stent. Much higher displacement with values up to 3 mm are observed in Patient 1 as compared to Patient 2 near the distal end of the stent, proximally to the location of SINE. The stent itself is also subject to high displacement in its central region, which can be attributed to the tortuosity of the geometry.

Table 8.2: Morphological measurements taken in Patients 1 and 2 pre-TEVAR and at the first post-TEVAR follow-up.

Patient 1	Pre-TEVAR	Post-TEVAR (3 months)	% Change
True Lumen Volume ^a [mm ³]	71855.3	99925.5	+39%
False Lumen Volume [mm ³]	270633.3	32008.1	-88%
Diameter - Ascending Aorta (d_1) [mm]	34.0	34.0	0%
Internal Arch Width (d_2) [mm]	61.2	73.0	19%
Maximum Diameter - Descending Aorta [mm]	54.3	32.6	-40%
Curvature Ratio (d_1/d_2) [—]	0.56	0.47	-16%
Length of Thoracic Aorta ^a [mm]	236.0	203.5	-14%
Normalised Length of Thoracic Aorta ^{a,b}	0.57	0.55	-4%
Thoracic Tortuosity Index ^a [—]	1.43	1.28	-10%
Aortic Tortuosity Index ^a [—]	1.43	1.16	-19%
Stent Tortuosity Index [—]	—	1.64	—
Thoracic Region			
True Lumen Volume ^a [mm ³]	37276.6	64963.6	+74%
False Lumen Volume [mm ³]	220248.9	0.00	-100%
Abdominal Region			
True Lumen Volume ^a [mm ³]	34578.8	34961.9	+1%
False Lumen Volume [mm ³]	50384.4	32008.1	-36%
Patient 2	Pre-TEVAR	Post-TEVAR (4 months)	% Change
True Lumen Volume ^a [mm ³]	54832.6	71407.4	+30%
False Lumen Volume [mm ³]	99483.5	20179.8	-80%
Diameter - Ascending Aorta (d_1) [mm]	27.3	28.2	3%
Internal Arch Width (d_2) [mm]	37.2	57.9	56%
Maximum Diameter - Descending Aorta [mm]	36.4	30.2	-17%
Curvature Ratio (d_1/d_2) [—]	0.73	0.49	-34%
Length of Thoracic Aorta ^a [mm]	195.4	179.9	-8%
Normalised Length of Thoracic Aorta ^{a,b}	0.52	0.48	-7%
Thoracic Tortuosity Index ^a [—]	1.19	1.16	-2%
Aortic Tortuosity Index ^a [—]	1.09	1.10	+1%
Stent Tortuosity Index [—]	—	1.28	—
Thoracic Region			
True Lumen Volume ^a [mm ³]	28439.6	43537.3	+53%
False Lumen Volume [mm ³]	75184.6	18679.2	-75%
Abdominal Region			
True Lumen Volume ^a [mm ³]	26393.0	27870.1	+6%
False Lumen Volume [mm ³]	24298.9	1500.7	-94%

^a Measured from the root of the left subclavian artery.^b Normalised against the total length of the descending aorta, measured from the root of the left subclavian artery up to the aortic bifurcation.

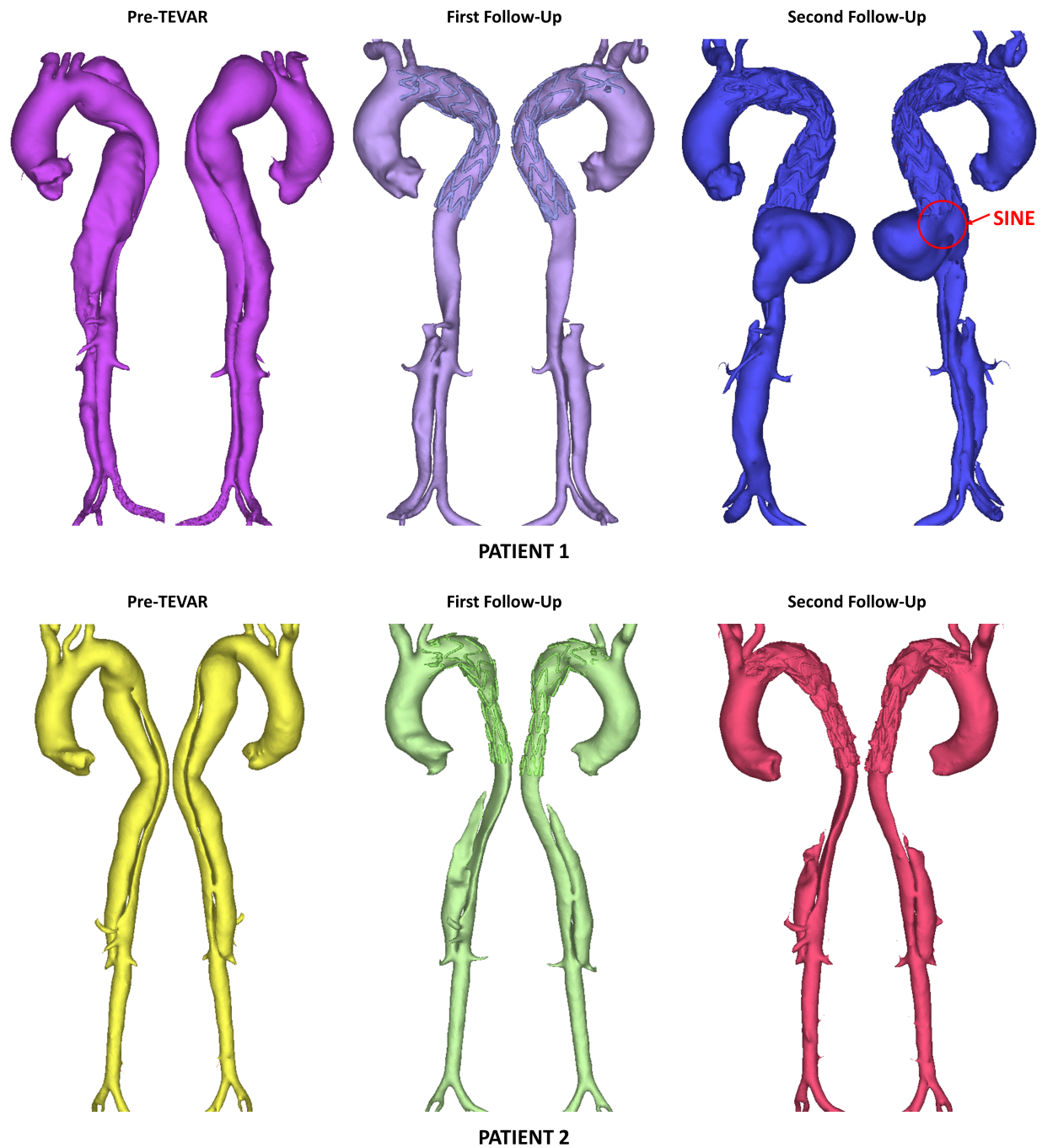


Figure 8.2: Patient-specific geometries reconstructed from pre-TEVAR data, and follow-ups taken at 3 (Patient1) and 4 (Patient 2) months, and after 1 year.

The torsional deformation of the wall models was analysed through the evaluation of radial shear elastic strains. For both patients, high shear strain values are observed before the proximal end of the stent and in the descending aorta. While in Patient 2 the highest strain values are located

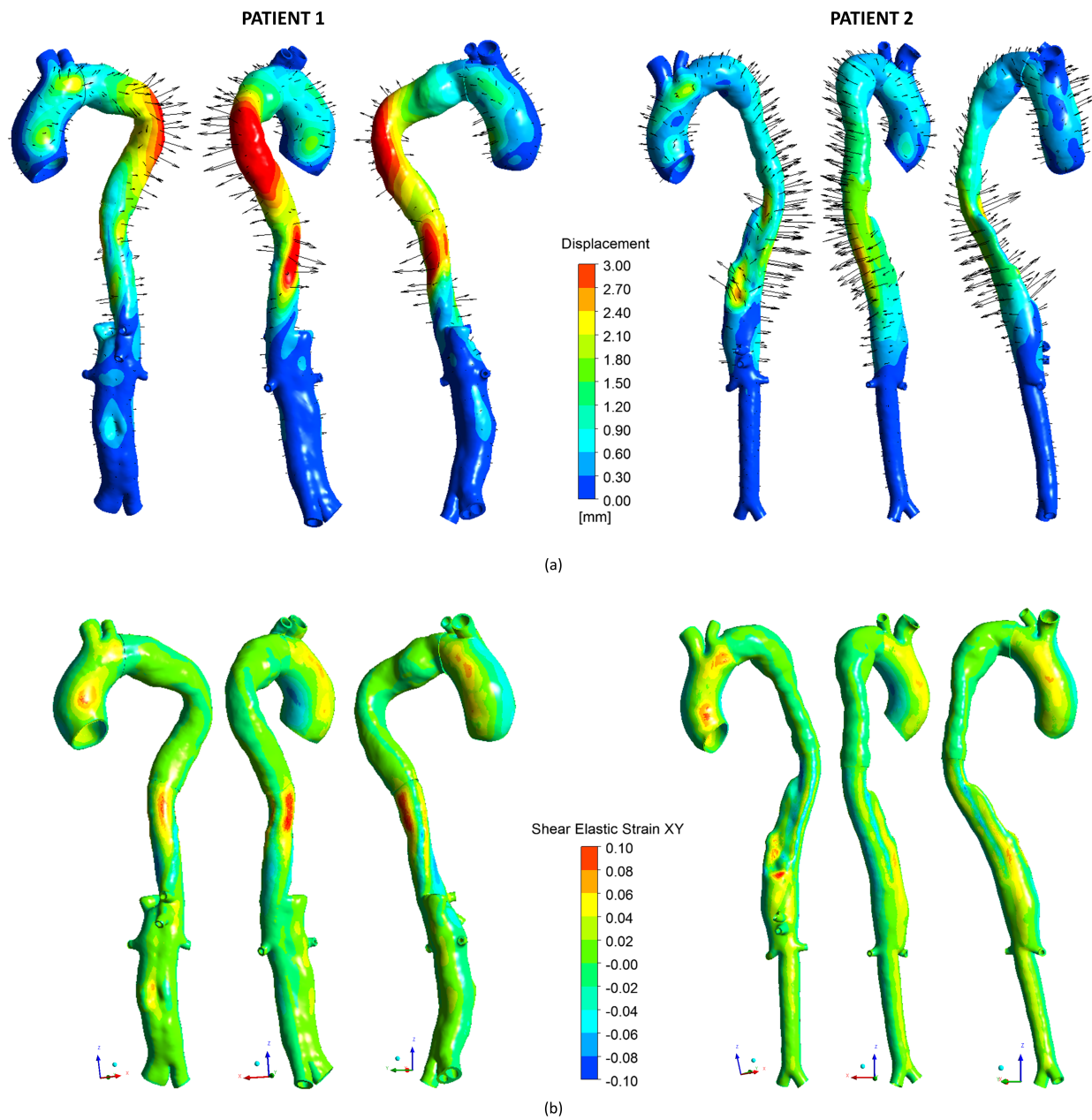


Figure 8.3: Total displacements with displacement vectors and shear strain in the radial (XY) direction in Patients 1 and 2 obtained with the highest pressure load tested (50 mmHg), corresponding to the pulse pressure in Patient 1.

right above the celiac trunk, in Patient 1 high shear strain is observed near the distal end of the stent, proximally to the location of SINE and aneurysm formation. The shear strain distribution clearly shows the existence of torsional forces acting on the wall near the distal end of the stent, proximally to the location of SINE.

Table 8.3: Maximum von Mises stress values for the post-TEVAR models.

Pressure Load [mmHg]	Peak Stress [kPa] Patient 1	Peak Stress [kPa] Patient 2
42	395	228
46	432	248
50	470	271

8.2.3 Stress Distribution

The von Mises stress distributions in the post-TEVAR models of both patients are shown in Figure 8.4. In both cases and for all loads tested, high stress values are found near the proximal and distal ends of the stent-graft, which can be attributed to the mismatch in biomechanical properties between the bare wall and the stent graft-wall composite. The peak stress is located near the distal end of the stent-graft in both patients, but Patient 1 has peak values greater than 350 kPa, which is more than 100 kPa higher than in Patient 2 (Table 8.3).

It should be noted that, due to image resolution issues, the proximal bare-stent used in the Medtronic Valiant Captivia device could not be included in the reconstructed wall geometry. For this reason, stress values calculated in this area are considered unreliable.

8.2.4 Flow Analysis and Wall Shear Stress

CFD simulation was performed on the post-TEVAR model for Patient 1 at first follow-up. Flow patterns at three different time points are shown in Figure 8.5. Disturbed flow with recirculation zones and vortical structures can be seen in the abdominal FL proximally to the first post-stent entry tear, in particular in the top region, which would favour further thrombus formation. Helical flow structures are observed in the ascending aorta, while flow patterns in the descending TL are well organised. Higher velocities can be noticed near the distal end of the stent-graft and in the right iliac artery, due to the narrow cross-sectional areas.

The wall shear stress distribution averaged over a full cardiac cycle (TAWSS) is shown in Fig 8.5d. High shear stress is located near the distal tear and the root of the aortic branches, in particular renals and celiac. The distal end of the stent-graft in the descending aorta is also exposed to elevated TAWSS, caused by a local narrowing.

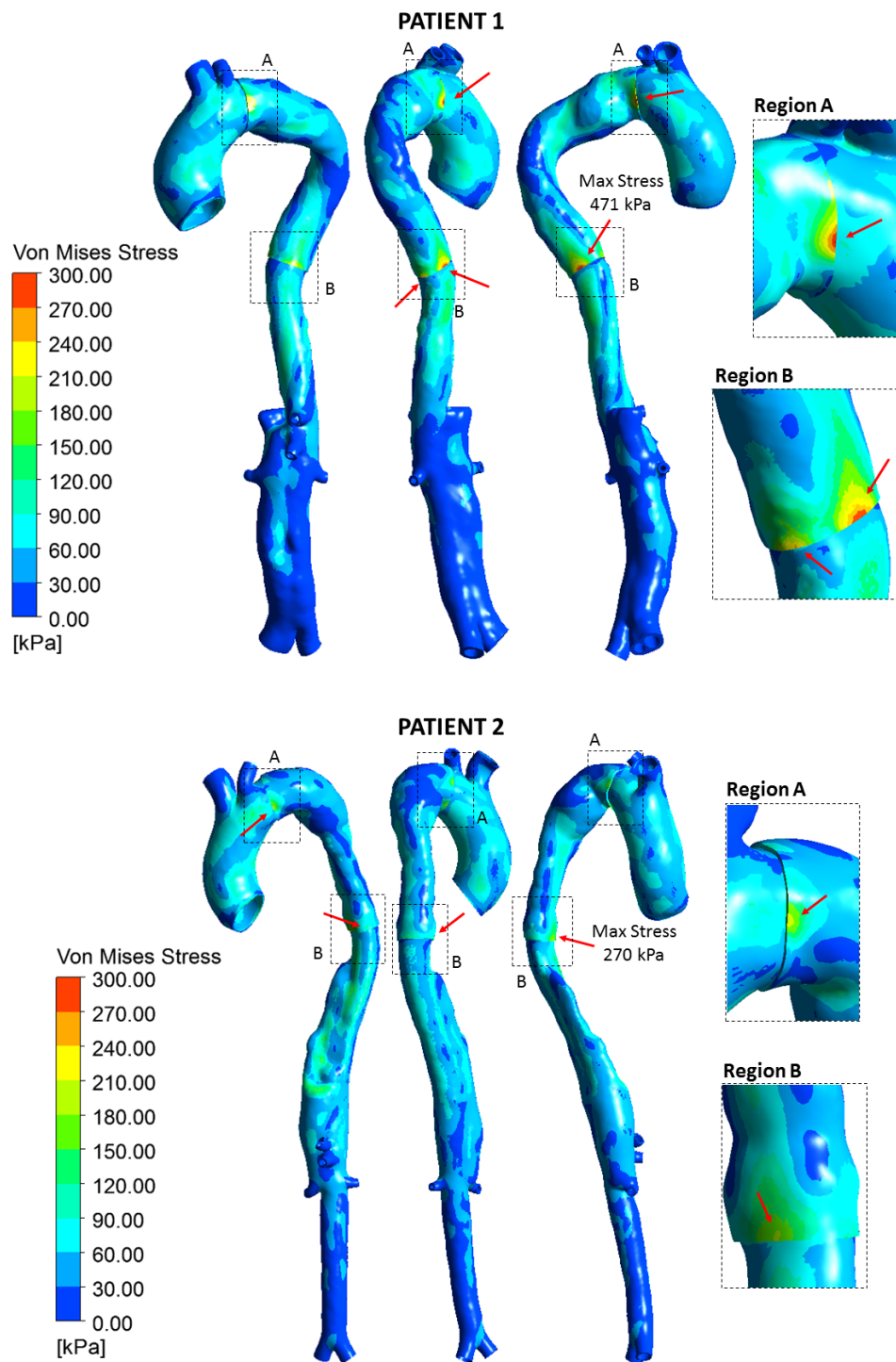


Figure 8.4: Stress distribution in Patients 1 and 2 obtained with the highest pressure load tested (50 mmHg), corresponding to the pulse pressure in Patient 1. The red arrows show the locations of highest stress in each model. Regions A and B show the points of peak stress near the proximal and distal ends of the stent-graft.

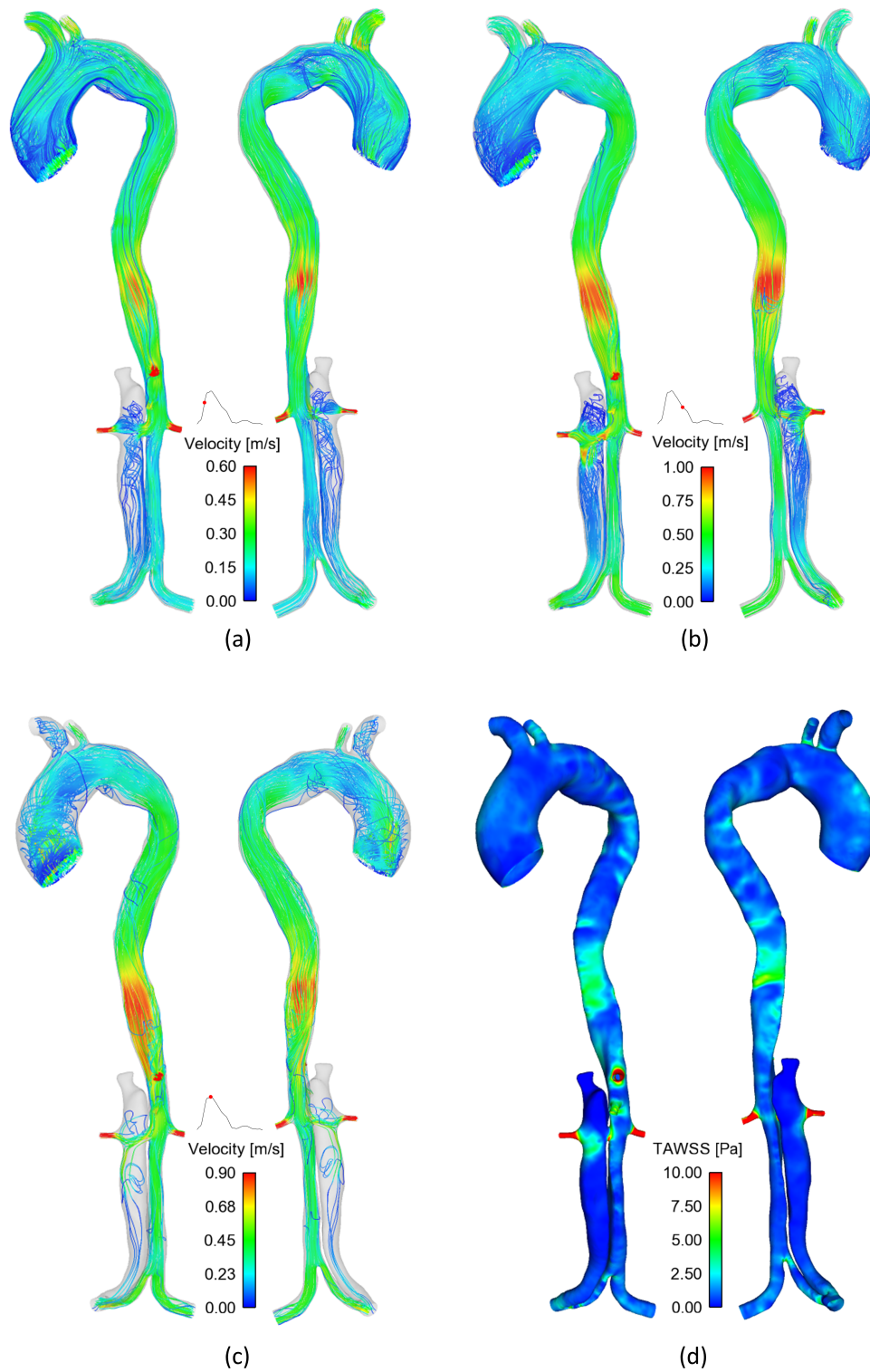


Figure 8.5: Velocity streamlines at (a) mid-systolic acceleration, (c) peak systole, and (d) mid-systolic deceleration. (d) Time-averaged wall shear stress (TAWSS) distribution. Results are for Patient 1.

8.2.5 Pressure Distribution

Pressure distributions at three different time points are shown in Figure 8.6, together with the mean wall pressure. The average pressure in the abdominal FL is lower than in the TL due to the small percentage of flow circulating in the former. While on average 16% of the aortic flow crosses the tear during a cardiac cycle, 89% of this is diverted to the right renal artery and only 11% enters the abdominal FL. Pressures in the TL are higher than in the FL at mid-systolic acceleration and deceleration, while almost equal pressures are found at peak systole, when more blood entered the abdominal FL.

8.3 Discussion

The formation of stent graft-induced new entries is considered a non-frequent but high-mortality complication which can arise from TEVAR [131, 142]. Marfan syndrome, distal oversizing, high TL taper ratio, high stent graft-aorta angle, and across-arch placement of the endograft have been identified among the risk factors [131, 142]. These can cause high stress and high spring-back force which may contribute to weakening of the aortic wall, eventually leading to rupture.

The presence of a stent-graft alters the biomechanical behaviour of the thoracic aorta, and the compliance mismatch between the stented and non-stented regions can have consequences on stress and strain distributions. Nauta et al. [143] and Nauta et al. [144] observed radial and longitudinal stiffening of the thoracic aorta in porcine models following TEVAR, together with significant strain mismatch between the stented and non-stented regions. The strain mismatch could play an important role in the development of TEVAR-related complications such as SINE formation. Nonetheless, as only 3-6% of TEVAR patients are affected by this complication [131, 142], other factors are likely to be involved in the development of SINE. A comprehensive study aimed at identifying the key risk factors responsible for SINE is still lacking.

Anatomical features play an important role in determining stress distribution and the locations at high risk of tear formation in aortic dissection. Poullis et al. [145], Shirali et al. [146], Chen et al. [147] and Craiem et al. [148] reported that parameters such as aortic length and tortuosity and arch shape and curvature were associated with the formation of initial tears and the development of complications. In this study, a longer and more tortuous aorta was observed in the SINE patient compared to the non-SINE patient, in particular in the stent region. The SINE patient

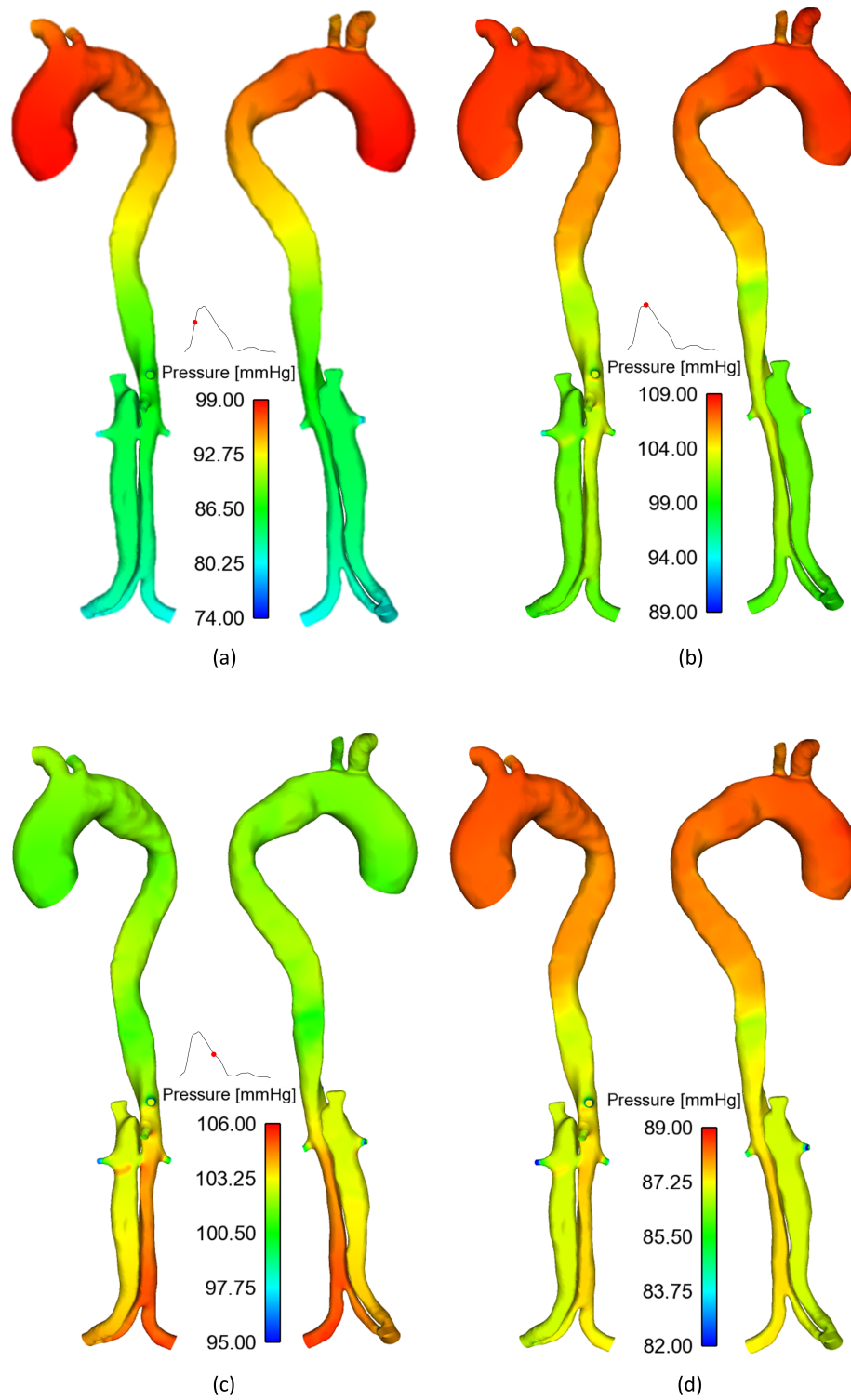


Figure 8.6: Pressure distributions at (a) mid-systolic acceleration, (b) peak systole, and (c) mid-systolic deceleration. (d) Pressure distribution averaged over a cardiac cycle. Results are for Patient 1.

also had a much wider aortic arch and a smaller curvature ratio. These factors are reflected in a different stress distribution and significantly higher stress levels than in the non-SINE patient, with values above 350 kPa concentrated near the distal end of the stent-graft. Peak stresses in the range of 290 kPa to 450 kPa have been reported for aneurysmal aortas [149]. The higher tortuosity index is also reflected in larger displacement of the stent itself. By looking at the vectors in Fig 8.3 it is possible to visualize two forces acting on the descending aorta of Patient 1: one acting on the stent curvature and determining further stent bending, while the other pulling in the opposite direction and acting proximally to the distal end of the stent. Displacements in Patient 2 were more uniformly distributed. High radial shear strain was also observed in Patient 1 just below the stent and proximally to the location of SINE and aneurysm formation. This causes the descending aortic wall to twist, increasing the risk of rupture. The SINE region also experienced slightly elevated TAWSS. Other flow features seem to be within the normal range. We therefore speculate that the formation of SINE is mainly caused by structural factors.

This pilot study demonstrates that computational flow and structural analysis can potentially offer more insights into the causes of SINE formation and predict which patients are more likely to develop this complication. A very simple proof-of-concept study was performed to demonstrate the utility of this strategy, from which it is already possible to identify clear differences between the two patients under analysis. These involve both morphological parameters and mechanical quantities such as stress, strain and wall displacement. The tortuosity of the thoracic aorta and the stent region in Patient 1 resulted in particularly high stress, wall twisting and high displacement especially in a region proximal to the distal end of the stent-graft, where the SINE was formed. All these factors determine an increased risk for wall rupture and SINE formation as compared to Patient 2.

The approach used in this pilot study involves several limitations. A constant wall thickness was assumed for the aortic wall and, due to the impossibility of reconstructing the exact stent-graft geometry from CT or MR images, a simplified stent model was adopted. The mechanical properties of the stent-graft were assumed to be homogeneous and isotropic, and the bare stent attached to the proximal end of the stent was not included in the model. As shown by Pasta et al. [139], who performed one-way FSI analysis in a patient who underwent traumatic thoracic aortic injury repair, this proximal protrusion extension has a non-negligible effect on stress distribution and flow in this region, and should therefore be considered in future models for a more complete analysis.

Also, the structural simulations performed in this study were static and decoupled from the flow field. Based on the results shown in this chapter, the formation of the new entry tear seems to be induced by structural factors rather than fluid factors. Nonetheless, as structural deformation and fluid flow are not independent from one another, a more in-depth analysis with coupled pulsatile flow and structural analysis would be required to obtain more insight into the development of SINE. Finally, the present study is limited to the analysis of two patients. Our future goal is to apply this methodology to a large cohort of SINE and non-SINE patients, in order to perform a statistical analysis aimed at further validating findings and at identifying the underlying causes of SINE formation.

8.4 Summary

In this chapter, a pilot study on the assessment of the risk of SINE formation following thoracic endovascular repair was presented. Comparisons of morphological parameters and stress analysis between a SINE and a non-SINE patient revealed noticeable differences, with the SINE patient presenting a much longer and more tortuous aorta than the non-SINE patient. FE analysis based on the first follow-up scans indicated significantly higher stress, torsional strain and wall displacement in the patient who developed SINE 11 months later than in the non-SINE patient, and the region of high stress and displacement was close to the SINE location. These findings demonstrate that anatomical features such as tortuosity, curvature and thoracic aortic length have a strong impact on stress distribution and these factors could act together to cause high stress concentration in a specific area, thereby increasing the risk for wall rupture and SINE formation in this region. This pilot study demonstrates that a methodology based on a combination of finite element modelling and patient-specific CFD analysis could potentially be used for the development of tools to predict the risk of SINE formation.

Conclusions and Recommendations

Aortic dissection is a critical clinical emergency with high morbidity and mortality. The study of thrombosis in aortic dissection is of particular importance as patient outcomes are associated with the formation of blood clots in the false lumen (FL). The extent of FL thrombosis has in fact been regarded as an indicator of the effectiveness of endovascular treatments, and improved outcomes have been observed for patients developing complete thrombosis in the FL as this event generally indicates re-absorption of the dissection. Although considerable efforts have been made to predict thrombus formation, previous models were computationally intensive and impractical for complex geometries such as patient-specific models of aortic dissections reconstructed from *in vivo* images. To the author's knowledge, no attempts had been made prior to this work to predict thrombus growth in patient-specific dissections.

This thesis proposed a novel approach for the prediction of thrombosis in aortic dissection involving the identification of zones where thrombus formation is likely to occur through the analysis of flow patterns and key variables such as shear stress and residence time. The mathematical model proposed in this thesis involves both the solution of blood flow by means of Computational Fluid Dynamics and mass transfer to model thrombus growth. Accumulation of platelets and formation of thrombus are predicted on the basis of hemodynamic parameters which drive mass transfer and permit the identification of zones with high probability for thrombogenesis. The number of species modelled is minimal as compared with models that incorporate a full representation of the coagulation cascade, and time scales have been adapted to facilitate simulation of the process in a short time period (only a few cardiac cycles), significantly reducing the computational time required.

Starting from the application to simple 2D idealised phantom geometries, the model has been tested in progressively more complex geometries, from a 3D backward facing step to more complete

patient-specific geometries including all major branches. The numerical simulations performed to date have shown satisfactory agreement with *in vivo* observations in both medically treated and stented patients, demonstrating the validity and applicability of the model for patient-specific assessment. By predicting whether and where thrombosis is likely to occur and to what extent for individual patients, this study will help clinicians in patient-specific stratification and treatment planning.

Another major contribution which has been achieved in this thesis is the identification of morphological parameters which are associated with changes in true and false lumen volume. A detailed anatomical data analysis has been performed on a cohort of 27 patients (Chapter 7), highlighting multiple correlations between geometric features and aortic growth, remodelling or FL thrombosis. For BMT patients, these geometric factors include the size and location of the entry tear, distance between tears and the presence of aortic branches in the FL. For TEVAR patients, statistically significant correlations have been found between the location of the first post-stent entry tear and FL thrombosis, and relative position of entry tears and FL branches. Several of the correlations found have been further investigated using patient-specific and phantom models, in order to understand how these parameters affect pressure distribution in the FL. These findings provide additional information which may help clinicians evaluate the risk of further expansion and rupture during patient follow-up.

Finally, a pilot study exploring the possibility of predicting stent graft-induced new entry tears (SINE) has been performed (Chapter 8). Preliminary findings based on the analysis of two patients, one with and one without SINE, demonstrate that the SINE patient presented significantly higher wall stress proximally to the SINE location 11 months before rupture. A morphological analysis revealed that this concentrated high stress could potentially be caused by the high tortuosity of the stented region.

A summary of the main contributions of this study is given below.

9.1 Summary of Contributions

- A novel computational approach to predict thrombosis in aortic dissection was developed. Predictions of thrombus formation are based on the distribution of hemodynamics parameters, platelets and residence time. Biochemical reactions are neglected in order to minimize the

computational cost of the model and allow the application to clinically relevant geometries and physiological flows. (Chapter 3)

- The model was first validated in a 3D backward-facing step geometry using experimental results reported by Taylor et al. [106]. It was then tested in 2D idealised phantom models, showing good agreement with expected trends. (Chapter 4)
- Further validations were performed on patient-specific geometries, ranging from medically treated patients with spontaneous FL thrombosis or no thrombosis to TEVAR patients with complete or incomplete thrombosis, and more complex geometries from the ADSORB trial. In all cases, the model was able to predict correctly the formation of thrombus as confirmed by follow-up scans. (Chapters 5-7)
- Based on anatomical data extracted from a cohort of 27 medically and endovascularly treated patients, statistically significant correlations were identified between morphological features and changes in true and false lumen volumes. The most important anatomical factors include the presence of FL branches, number and position of entry tears, relative location of FL branches and tears, and arch curvature ratio. Their roles in FL thrombosis and aortic growth were further investigated through CFD analysis of phantom and patient-specific models. (Chapter 7)
- In an initial attempt to identify predictors of stent graft-induced new entry tears, 4D-MRI based flow analysis and finite element structural modelling were carried out. Results revealed significantly higher wall stress in the SINE patient 11 months before rupture, which may be attributed to a significantly more tortuous geometry in the stented region, highlighting a potential correlation between tortuosity and the risk for wall rupture. (Chapter 8)

In the future, it is hoped that the hemodynamics-based model outlined in this thesis could contribute to the development of a powerful decision making tool to determine optimal patient-specific treatments for different diseases.

9.2 Limitations and Future Directions

The present study involves several limitations, which should be addressed in order to refine predictions. Some of the major limitations of this work are discussed below, with suggestions for future work.

9.2.1 Geometric Assumptions

The reconstructed patient-specific geometries are generally extracted from images which represent a snapshot of the diastolic geometry and hence appear to be static. In reality, the arterial walls are compliant and the intimal flap is subject to a movement driven by the pressure difference between TL and FL. The reconstruction of static images could potentially lead to the presence of sharp corners in the geometry which are not actually present in the patient. These can affect local flow patterns causing very low shear stress values. As the thrombus model developed in this thesis is shear-dependent, these conditions can cause thrombus formation to be predicted in these regions. An example can be found in Figure 9.1, where small patches of thrombus were observed in regions characterised by sharp corners. In such cases, the thrombus model would predict thrombus to form in the sharp corners, but as soon as these are covered and as flow patterns and local shear rates return to the normal range, thrombus growth will eventually stop. This limitation is caused by the rigid wall assumption, and could therefore be overcome with the use of compliant walls.

Another limitation which could potentially cause over-prediction of thrombus growth is related to the presence of FL branches. As highlighted in Chapter 7, the presence of both small and large aortic branches in the FL has a major effect on thrombus formation and aortic expansion. Due to the limited image resolution, it is currently not possible to include branches as small as intercostal arteries and inferior mesenteric in the reconstructed aortic models. Although these arteries have a minor influence on the overall flow structure, they have non-negligible effects on local flow patterns and shear stress. When a minor branch is artificially occluded during geometry reconstruction, the local flow proximal to the branch will not be accurately predicted, possibly causing under- or over-prediction of the local shear stress and hence thrombus formation. Examples of this limitation can be found in Fig. 9.1a and b. The model shown in Fig 9.1a presents small patches of thrombus at the origins of small branches. This is even more evident from Figure 9.1b, where final predictions are compared with the actual *in vivo* geometry. While the model is able to correctly predict complete thrombosis of the stented region, there are clear differences between predicted thrombus growth and follow-up data in the region between the renal arteries and the iliac bifurcation. Close inspection of the follow-up scans reveals the presence of multiple branches coming off the FL in this region, which would have prevented the local accumulation of platelets and clotting if included. In order to overcome this limitation, either all the minor branches should be included in the model, or the regions where small branches have been ignored should be defined

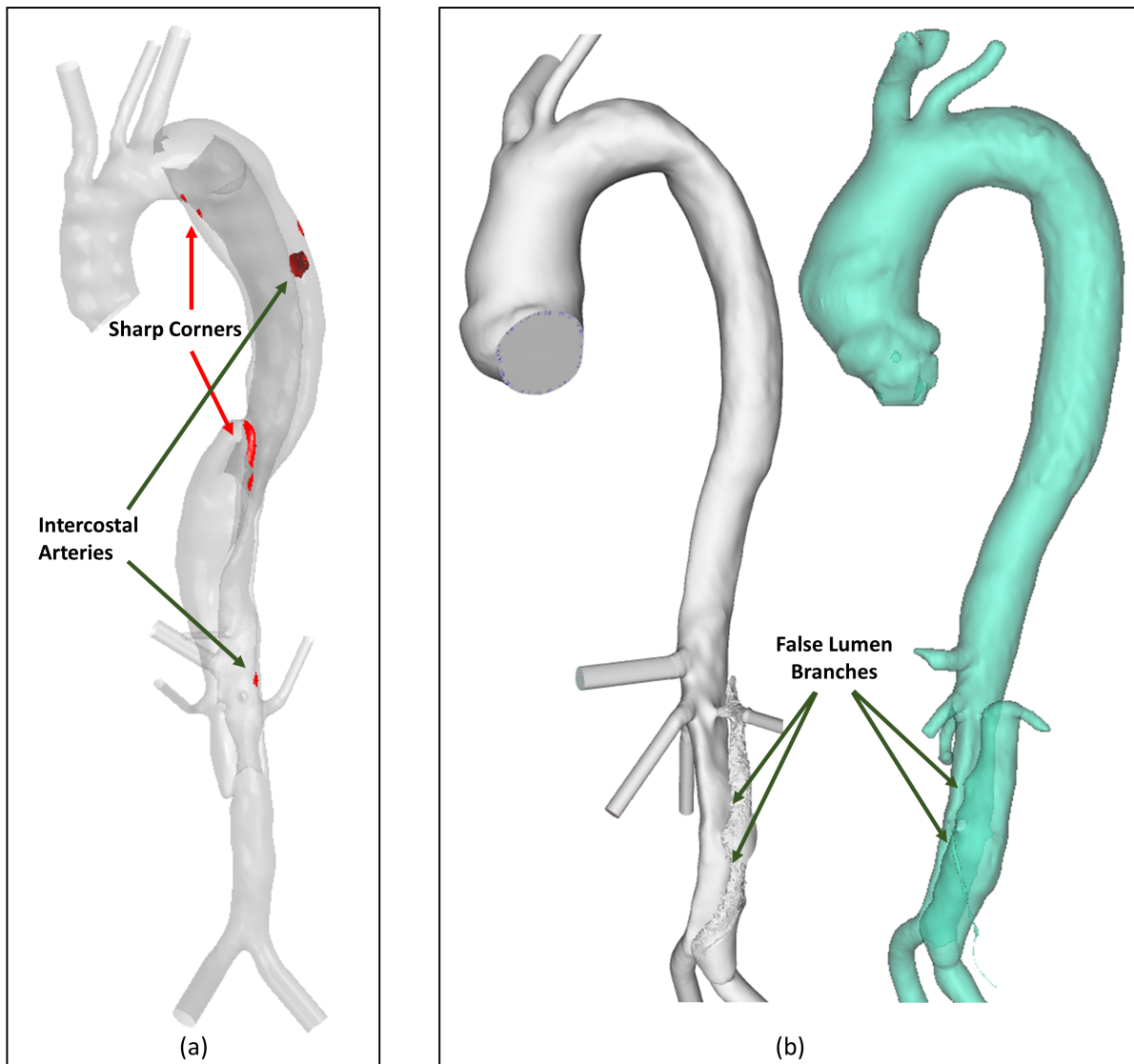


Figure 9.1: (a) In red, predicted thrombus after 20 cardiac cycles in patient BMT-P1. (b) Predicted FL surface following thrombus growth after 20 cardiac cycles and reconstructed lumen surface in patient TEVAR-P1 based on follow-up scans acquired 3 years after TEVAR.

as non-thrombogenic. In practical terms, this could be done by manually selecting the surface mesh elements on the wall in these regions, and setting the coagulant flux on these elements to zero. For both solutions, very high image resolution is needed in order to identify all the minor branches.

Geometric assumptions have also been made in the development of idealised models used in Chapter 7 to assess the individual impact of geometric parameters on FL hemodynamics and the chances for FL thrombosis and aortic growth. At the current stage, these phantom models are not suitable for assessing the impact of variables such as stent length and the presence of branches. In

order to continue this morphological study and evaluate the impact of other geometric parameters on FL hemodynamics, the phantom models should be extended up to the aortic bifurcation and should include all major branches. Separate phantom models should also be designed to study the impact of geometric parameters on post-TEVAR hemodynamics.

9.2.2 Wall Reactivity and Existence of Other Shear-Related Processes

In this thesis, the entire arterial wall has been assumed to have equal reactivity, implying that when the wall shear is below a certain threshold, accumulation near the walls could potentially occur in any region of the geometry. This choice was made as it is generally not expected that within the TL the local shear would fall below physiological values.

In reality, as explained in Chapter 2, tissue factor exposure plays an important role in initiating thrombus formation and thrombin production. The FL wall is inherently thrombogenic, as it originates from tearing of the aortic wall. On the other hand, healthy walls are generally not subject to tissue factor exposure unless a specific event triggers an inflammatory response. For most of the patients analysed in this thesis, this lack of distinction between thrombogenic surfaces and healthy walls has not affected predictions, as physiological shear values were found in the TL. However, complex geometries as the one shown in Figure 9.2 could potentially lead to the formation of recirculation zones and low shear within the TL. In these regions, other reactants transported by the blood and not necessarily related to thrombus formation such as low-density lipoprotein (LDL) or calcium could potentially accumulate near the walls, leading to atherogenesis or calcifications. As the model currently does not make distinction between thrombosis and other shear-induced accumulation processes, these conditions can potentially lead to treating other processes as thrombosis. An example of this limitation is shown in Fig. 9.2, where thrombosis was predicted in the TL above the aortic bifurcation while calcification was observed in this region during follow-up.

To overcome this limitation, it will be important to accurately select potentially thrombogenic surfaces and distinguish them from healthy walls. In order to build a unified model including phenomena such as calcification and atherogenesis, the transport of additional species could be included, with their respective diffusive fluxes being specified on the walls.

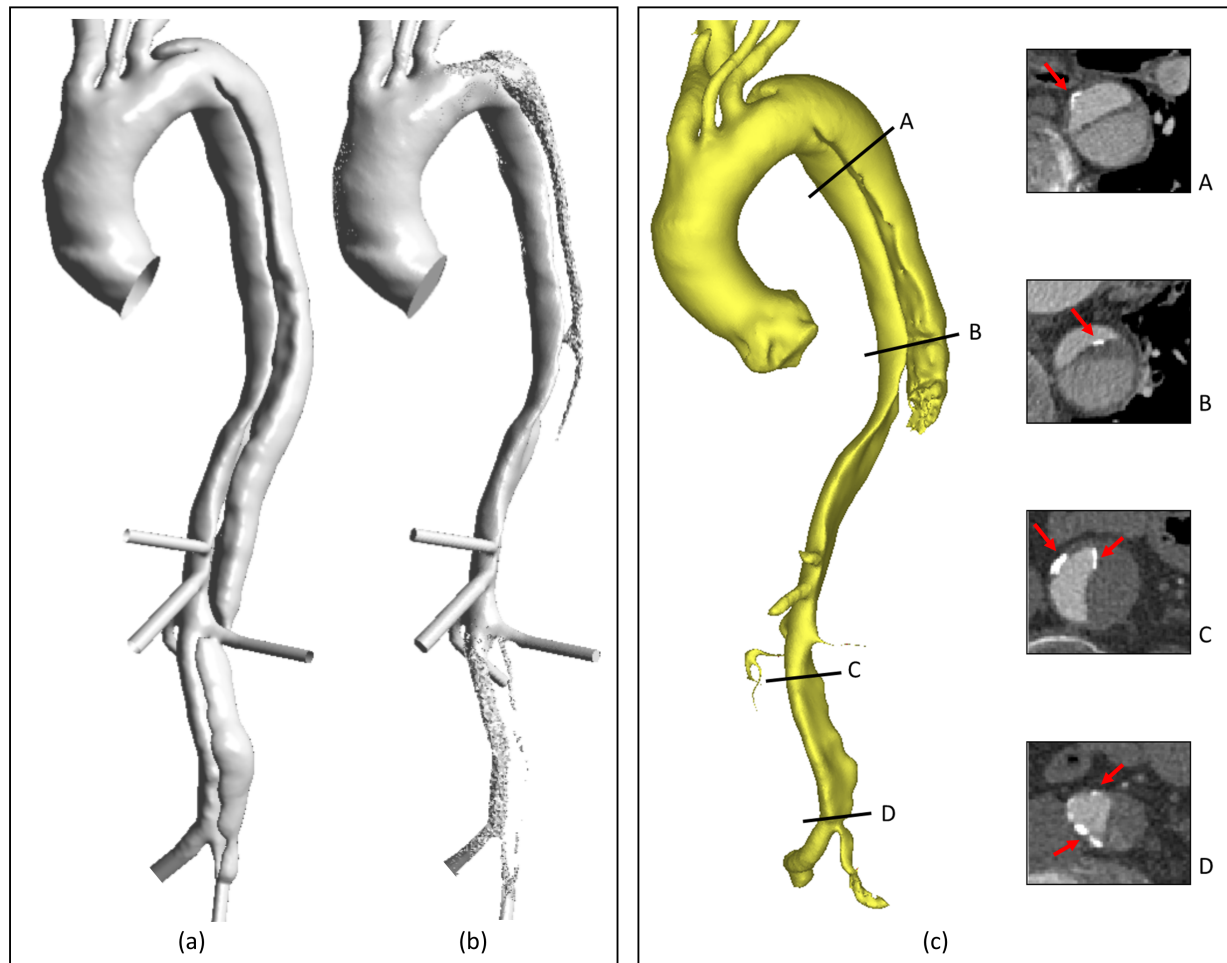


Figure 9.2: (a) Initial geometry, (b) predicted FL surface following thrombus growth after 40 cardiac cycles in patient BMT-P2 and (c) reconstructed lumen surface based on follow-up scans acquired 2 years after TEVAR. The planes A, B, C, D have been extracted from the CT data and show some of the locations where calcifications formed in the true lumen, indicated by the red arrows.

9.2.3 Rigid Wall Assumption

An important limitation of this study is the rigid wall assumption. The compliant nature of arterial walls has a damping effect on pressure waveforms, and affects the distribution of hemodynamic parameters [37, 44]. For aortic dissection, the compliance of the intimal flap varies over time. Chronic dissection are reportedly characterised by thicker and stiffer flaps, with reduced mobility as compared to acute cases [104]. For chronic cases, it is therefore expected that this assumption will not have major implications on thrombus predictions. Nonetheless, comparison between rigid walls studies and fluid structure interaction (FSI) simulations is recommended as future work in order to assess how the rigid wall assumption affects predictions of thrombus formation.

9.2.4 Cohort Size

The study presented in Chapter 7 has revealed several correlations between morphological parameters and changes in true and false lumen volume for both stented and medically treated patients. Currently, each parameter has been studied individually and only a univariate analysis could be carried out, given the small sample size. In order to perform a multivariate analysis aimed at evaluating the simultaneous effect of multiple parameters, a much larger cohort size would be needed.

Limitations regarding the cohort size used for analysis also affect the pilot study presented in Chapter 8. Preliminary results reveal a potential correlation between patient morphology and SINE formation. However, this study is limited to the analysis of two cases and a much larger cohort of patients should be analysed in order to validate these findings. The application of a similar methodology to a large number of patients with and without SINE during follow-up would allow an in-depth anatomical data analysis on the patients which could help clinicians elucidate which are the key factors associated with SINE formation.

9.2.5 Model Assumptions for FE Analysis of SINE Formation

The results shown in Chapter 8 demonstrate that the formation of SINE could potentially be predicted through a methodology based on a combination of computational fluid dynamics and finite element modelling. Our preliminary findings reveal that morphological parameters such as thoracic aortic length, curvature and tortuosity may be associated with the formation of new tears as these affect the distribution of wall stress. Although the results presented in the chapter show promise, the approach used for FE analysis is very simple and could be refined from different perspectives. Firstly, the geometries analysed in this study present several simplifications. Due to the lack of information regarding wall properties, uniform wall thickness was assumed and a simple linear elastic model was used for the wall. The availability of black-blood MR scans would allow the measurement of wall thickness [150], which could be used to build more realistic models with variable and patient-specific wall thickness, needed to accurately predict stress and strain distributions [151]. Also, due to image resolution limitations, the stent-graft is currently modelled as a composite material with uniform thickness and mechanical properties, and does not include the tapered bare stent at the proximal end of the stent-graft, which is known to affect stress distribution in this region. In the absence of high resolution CT data, this limitation could be overcome by artificially deploying the stent-graft within the dissected geometry. A more complete and reliable

analysis should also be performed by adopting more sophisticated wall models, such as hyperelastic or viscoelastic, and incorporating thrombus.

Another important limitation of this work is the use of static structural simulations. A uniform pressure load equal to the pulse pressure measured in the two patients was prescribed on the inner wall. Although Borghi et al. [152] found very small differences (0.1-3.4%) in terms of peak stress between transient and static simulations, the use of a spatially- and time-varying pressure load would allow us to refine the results obtained and improve the model accuracy.

Finally, even though from our analysis the formation of SINE appears to be driven by mechanical and geometrical factors, structural deformations and flow are not independent from one another. The use of fluid-structure interaction (FSI) simulations is recommended as future work to study their combined effects and to build a more complete model.

9.2.6 Development of a Hybrid Model

As shown in Chapter 4, the hemodynamics-based approach proposed in this thesis presents a significant advantage as compared to biochemical approaches in terms of computational costs. As biochemical reactions are not included in the model, computational costs are significantly lower than kinetics-based models. On the other hand, the kinetic processes included in the model are based on empirical correlations. Also, predictions are affected by the shear threshold value chosen and are therefore parameter-dependent. The choice of the parameters used in this thesis was justified by an in-depth flow analysis on aortic dissection cases, which showed that most cases modelled were well represented by the chosen threshold values. While these seem to be well suited for the study of thrombosis in aortic dissection, in order to extend the model to new applications such as aneurysms or aortic valves several parametric studies should be conducted to test the applicability of the chosen parameters. The use of measurable kinetics could speed up this process and ease the calibration of the model for different applications.

The comparative study presented in Section 4.2 demonstrated that similar predictions in terms of thrombus formation could be obtained with the hemodynamics-based model presented in this thesis and a biochemical model, although the former was much more computationally efficient. On the other hand, the study also highlighted as a limitation the parameter-dependent character of the hemodynamics-based model. The shear rate threshold used in this thesis to initiate coagulant production for pulsatile simulations was deemed inappropriate for static flow simulations, and had

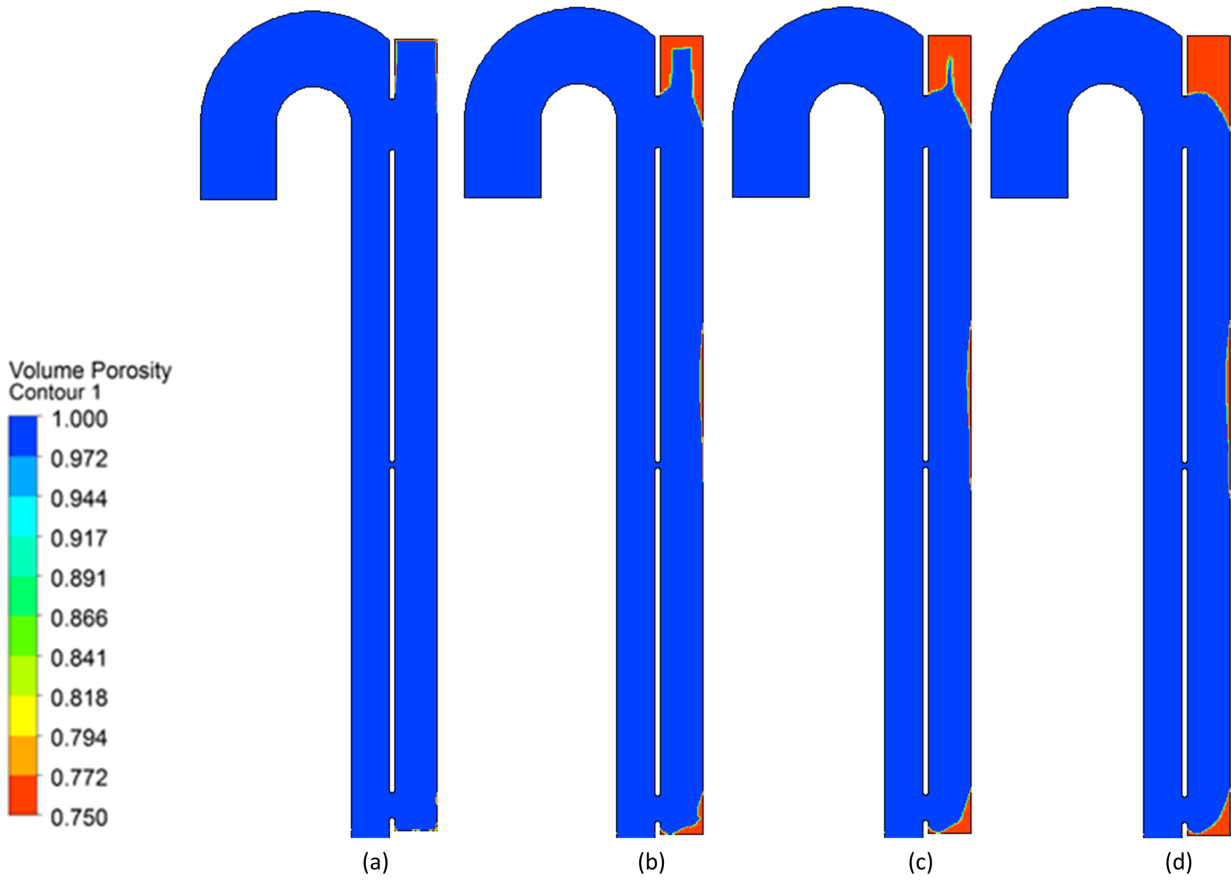


Figure 9.3: Clot porosity at different time points obtained with the hybrid model with kinetics increased by 100x. (a) $t = 10$ s; (b) $t = 25$ s; (c) $t = 35$ s; (d) $t = 50$ s.

to be reduced to 1 s^{-1} for both the study in 2D phantom geometries and the BFS case study. This is due to the fact that while a time-averaged value is used for pulsatile simulations, predictions are based on instantaneous shear stress for steady flow simulations.

In order to exploit the advantages of both approaches, i.e. reduced computational costs and at the same time the use of measurable kinetics constants that are independent of the flow regime, a hybrid modelling approach is proposed as future work. This hybrid approach consists of simplifying the biochemical model by introducing the same assumptions used in building the hemodynamics-based model, hence:

- Thrombus formation only occurs in regions of low Peclet numbers, hence diffusive transport. Transport of the main reactants can be therefore assumed to be exclusively diffusive. As diffusion is limiting, as soon as reactants are formed they will react. Hence, there will not be propagation in the convection-dominated region due to convective clearance.

- Controlled reaction enhancement. In regions where biochemical reactions are deemed “highly likely to occur”, kinetics would be artificially augmented. In order to account for both diffusion and reaction, both kinetic constants and diffusivities should be enhanced by the same factor (for example, 10x or 100x, the same results could be obtained in proportional times). This enhancement can be controlled through switching coefficients similar to the ones proposed in Chapter 3 and defined as:

$$\phi = 1 - \frac{\dot{\gamma}^2}{\dot{\gamma}^2 + \dot{\gamma}_t^2} \quad (9.1)$$

In regions of particularly low shear rates (e.g. very high viscosity, high resistance to flow and enhanced cell-cell interactions), kinetics and diffusivities will be higher. When shear rates are in the normal range ($\sim 300 \text{ s}^{-1}$ in large vessels) these will go back to normal values.

Preliminary results obtained by using this approach show promise (Fig 9.3), although more tests are needed to thoroughly evaluate the applicability of this approach.

9.2.7 Patient-Specific Modelling of Thrombus Formation in Other Arterial Diseases

The mathematical model developed and validated in this thesis has demonstrated to be a valuable tool for thrombus prediction in aortic dissection. Results reported in this thesis show good agreement between predicted thrombus growth patterns and *in vivo* observations. Preliminary tests have also been performed to evaluate the applicability of the model for thrombus prediction in different applications, such as saccular aneurysm (Fig. 9.4) and device-induced thrombosis following endovascular repair (EVAR) for abdominal aortic aneurysm (Fig. 9.5). These preliminary results

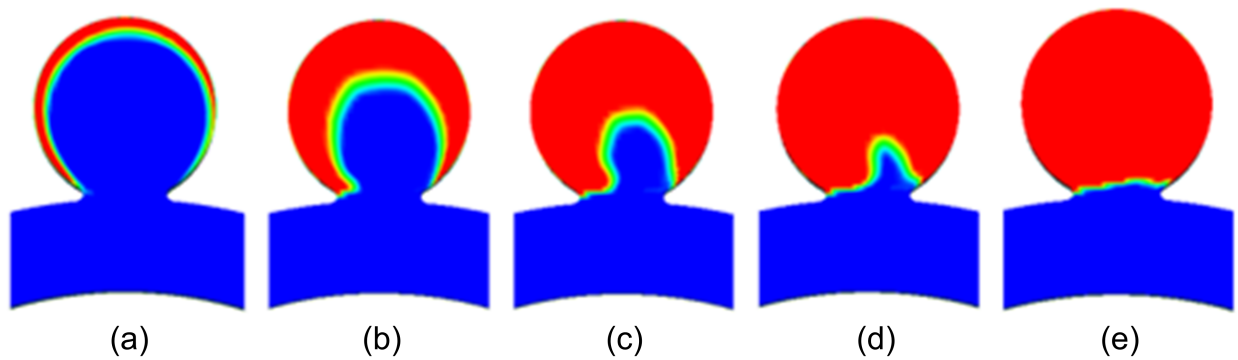


Figure 9.4: In red, thrombus growth over time in saccular aneurysm at (a) $T = 1.5 \text{ s}$, (b) $T = 4 \text{ s}$; (c) $T = 6 \text{ s}$; (d) $T = 8 \text{ s}$; and (e) $T = 15 \text{ s}$.

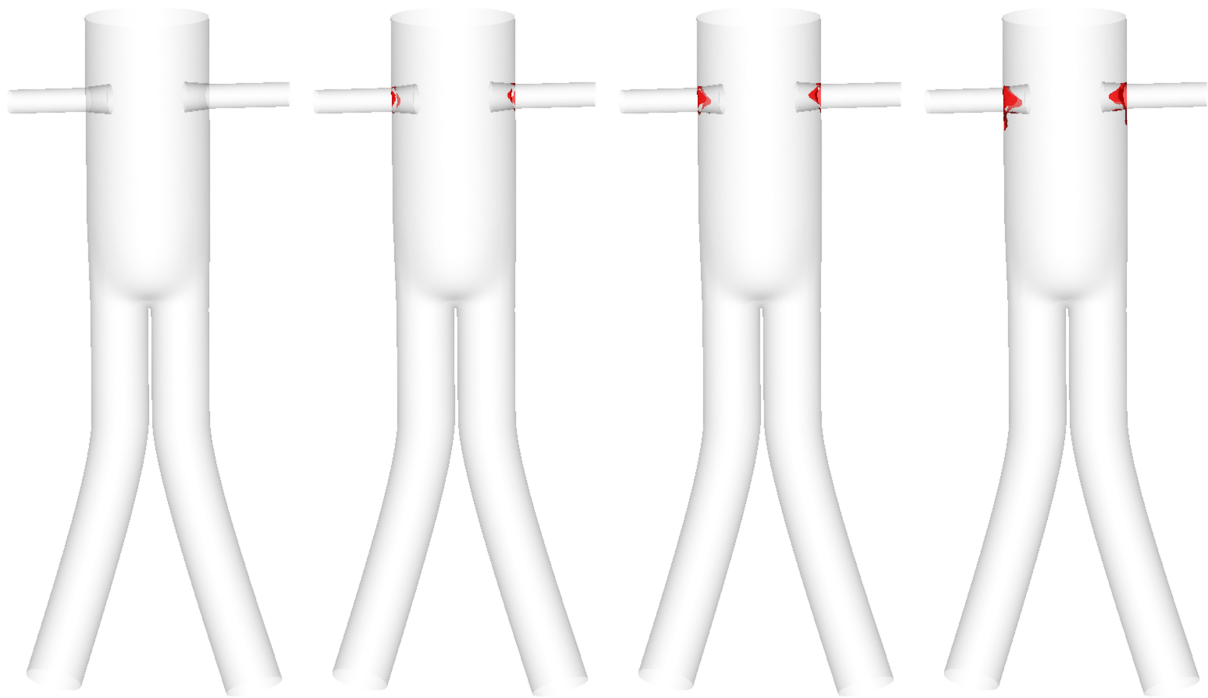


Figure 9.5: In red, thrombus predicted over time in an idealised 3D flared stent-graft for abdominal aneurysm, developed by Dr. H. Kandail.

demonstrate that the model could potentially be applied to predict thrombosis in other arterial diseases. Nonetheless, careful calibration and validation are needed to ensure the suitability of the model for these new applications.

Bibliography

- [1] Criado, J. *On the death of King George II in 1760: Aortic dissection in perspective*. 2016.
- [2] Walpole, H. *Memoires of the last ten years of the reign of George the Second*. 1822.
- [3] Thrumurthy, S. G., Karthikesalingam, A., Patterson, B. O., Holt, P. J. E., and Thompson, M. M. *The diagnosis and management of aortic dissection*. Tech. rep. Department of Outcomes Research, St Georges Vascular Institute, London SW17 0QT, UK, 2012.
- [4] Elefteriades, J. A., Hartleroad, J., Gusberg, R., Salazar, A., Black, H., Kopf, G., Baldwin, J. C., and Hammond, G. L. “Long-term experience with descending aortic dissection: The complication-specific approach.” In: *The Annals of Thoracic Surgery* 53.1 (1992), pp. 11–21.
- [5] Trimarchi, S., Tolenaar, J. L., Jonker, F. H., Murray, B., Tsai, T. T., Eagle, K. A., Rampoldi, V., Verhagen, H. J., Herwaarden, J. A. van, Moll, F. L., Muhs, B. E., and Elefteriades, J. A. “Importance of false lumen thrombosis in type B aortic dissection prognosis.” In: *The Journal of Thoracic and Cardiovascular Surgery* 145.3, Supplement (2013). Proceedings of the Aortic Symposium 2012, S208–S212.
- [6] Trimarchi, S., Eagle, K. A., Nienaber, C. A., Rampoldi, V., Jonker, F. H., Vincentiis, C. D., Frigiola, A., Menicanti, L., Tsai, T., Froehlich, J., Evangelista, A., Montgomery, D., Bossone, E., Cooper, J. V., Li, J., Deeb, M. G., Meinhardt, G., Sundt, T. M., and Isselbacher, E. M. “Role of age in acute type A aortic dissection outcome: Report from the International Registry of Acute Aortic Dissection (IRAD).” In: *The Journal of Thoracic and Cardiovascular Surgery* 140.4 (2010), pp. 784–789.
- [7] The International Registry of Aortic Dissection (IRAD). *Aortic Dissection*. URL: <http://www.iradonline.org/about.html>.
- [8] Alimohammadi, M., Agu, O., Balabani, S., and Daz-Zuccarini, V. “Development of a patient-specific simulation tool to analyse aortic dissections: Assessment of mixed patient-specific flow and pressure boundary conditions.” In: *Medical Engineering Physics* 36.3 (2014), pp. 275–284.
- [9] Cheng, Z., Tan, F., Riga, C., Bicknell, C., Hamady, M., Gibbs, R., Wood, N., and Xu, X. “Analysis of flow patterns in a patient-specific aortic dissection model.” In: *Journal of Biomechanical Engineering* 132.5 (2010).

- [10] Cheng, Z., Wood, N. B., Gibbs, R. G., and Xu, X. Y. "Geometric and flow features of type B aortic dissection: Initial findings and comparison of medically treated and stented cases." In: *Annals of Biomedical Engineering* 43.1 (2015), pp. 177–189.
- [11] Rudenick, P. A., Bijmens, B. H., Garca-Dorado, D., and Evangelista, A. "An in vitro phantom study on the influence of tear size and configuration on the hemodynamics of the lumina in chronic type B aortic dissections." In: *Journal of Vascular Surgery* 57.2 (2013), 464–474.e5.
- [12] Tsai, T. T., Schlicht, M. S., Khanafer, K., Bull, J. L., Valassis, D. T., Williams, D. M., Berguer, R., and Eagle, K. A. "Tear size and location impacts false lumen pressure in an ex vivo model of chronic type B aortic dissection." In: *Journal of Vascular Surgery* 47.4 (2008), pp. 844–851.
- [13] Bernard, Y., Zimmermann, H., Chocron, S., Litzler, J.-F., Kastler, B., Etievent, J.-P., Meneveau, N., Schiele, F., and Bassand, J.-P. "False lumen patency as a predictor of late outcome in aortic dissection." In: *The American Journal of Cardiology* 87.12 (2001), pp. 1378–1382.
- [14] CircsystemsUNSIG09R3a. *Comparing the human circulatory system with that of other species*. URL: <https://circsystemsunsig09r3b.wikispaces.com/%28e%29%09+Comparing+human+circulation+system+with+other+species>.
- [15] AorticDissection.com. *Aortic Dissection*. URL: <http://aorticdissection.com>.
- [16] Hagan, P., C.A.Nienaber, Isselbacher, E., and al, et. "The international registry of acute aortic dissection (IRAD): New insights into an old disease." In: *JAMA* 283.7 (2000), pp. 897–903.
- [17] Roberts, C. S. and Roberts, W. C. "Aortic dissection with the entrance tear in the descending thoracic aorta. Analysis of 40 necropsy patients." In: *Annals of Surgery* 213.4 (1991), pp. 356–368.
- [18] Nienaber, C. A. and Eagle, K. A. "Aortic dissection: new frontiers in diagnosis and management." In: *Circulation* 108.5 (2003), pp. 628–635.
- [19] Criado, F. "Aortic dissection - A 250-year perspective." In: *Texas Heart Institute Journal* 38.6 (2011), pp. 694–700.
- [20] Erbel, R., Alfonso, F., Boileau, C., Dirsch, O., Eber, B., Haverich, A., Rakowski, H., Struyven, J., Radegran, K., Sechtem, U., Taylor, J., Zollikofer, C., Klein, W., Mulder, B., and Providencia, L. "Diagnosis and management of aortic dissection: Task Force on Aortic Dissection, European Society of Cardiology." In: *European Heart Journal* 22.18 (2001), pp. 1642–1681.
- [21] Fann, J. I. and Miller, D. C. "Aortic dissection." In: *Annals of Vascular Surgery* 9.3 (1995), pp. 311–323.

- [22] Shiga, T, Wajima, Z, Apfel, C., Inoue, T, and Ohe, Y. “Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis.” In: *Archives of Internal Medicine* 166.13 (2006), pp. 1350–1356.
- [23] Chen, D., Müller-Eschner, M., Tengg-Kobligk, H. von, Barber, D., Böckler, D., Hose, R., and Ventikos, Y. “A patient-specific study of type B aortic dissection: evaluation of true-false lumen blood exchange.” In: *Biomedical Engineering Online* 12.1 (2013), p. 65.
- [24] Estrera, A. L., Miller, C. C., Safi, H. J., Goodrick, J. S., Keyhani, A., Porat, E. E., Achouh, P. E., Meada, R., Azizzadeh, A., Dhareshwar, J., and Allaham, A. “Outcomes of medical management of acute type B aortic dissection.” In: *Circulation* 114.1 suppl (2006), pp. I–384–I–389.
- [25] Golledge, J. and Eagle, K. A. “Acute aortic dissection.” In: *The Lancet* 372.9632 (2008), pp. 55–66.
- [26] Tolenaar, J. L., van Bogerijen, G. H., Eagle, K. A., and Trimarchi, S. “Update in the management of aortic dissection.” In: *Current treatment options in cardiovascular medicine* 15.2 (2013), pp. 200–213.
- [27] Nienaber, C. A., Kische, S., Skriabina, V., and Ince, H. “Noninvasive imaging approaches to evaluate the patient with known or suspected aortic disease.” In: *Circulation: Cardiovascular Imaging* 2.6 (2009), pp. 499–506.
- [28] Nienaber, C. A., Divchev, D., Palisch, H., Clough, R. E., and Richartz, B. “Early and late management of type B aortic dissection.” In: *Heart* (2014).
- [29] Dake, M. D., Kato, N., Mitchell, R. S., Semba, C. P., Razavi, M. K., Shimono, T., Hirano, T., Takeda, K., Yada, I., and Miller, D. C. “Endovascular stent-graft placement for the treatment of acute aortic dissection.” In: *New England Journal of Medicine* 340.20 (1999), pp. 1546–1552.
- [30] Nienaber, C. A., Fattori, R., Lund, G., Dieckmann, C., Wolf, W., Kodolitsch, Y. von, Nicolas, V., and Pierangeli, A. “Nonsurgical reconstruction of thoracic aortic dissection by stent-graft placement.” In: *New England Journal of Medicine* 340.20 (1999), pp. 1539–1545.
- [31] Brunkwall, J., Kasprzak, P., Verhoeven, E., Heijmen, R., Taylor, P., and ADSORB Trialists. “Endovascular repair of acute uncomplicated aortic type B dissection promotes aortic remodelling: 1 year results of the ADSORB trial.” In: *European Journal of Vascular and Endovascular Surgery* 48.3 (2014), pp. 285–291.

- [32] Karmonik, C., Bismuth, J., Shah, D., Davies, M., Purdy, D., and Lumsden, A. “Computational study of haemodynamic effects of entry- and exit-tear coverage in a DeBakey type III aortic dissection: Technical report.” In: *European Journal of Vascular and Endovascular Surgery* 42.2 (2011), pp. 172–177.
- [33] Qiao, A., Yin, W., and Chu, B. “Numerical simulation of fluid-structure interaction in bypassed DeBakey III aortic dissection.” In: *Computer Methods in Biomechanics and Biomedical Engineering* 18.11 (2015), pp. 1173–1180.
- [34] Tang, A., Fan, Y., Cheng, S., and Chow, K. “Biomechanical factors influencing type B thoracic aortic dissection: computational fluid dynamics study.” In: *Engineering Applications of Computational Fluid Mechanics* 6 (2012), 622632.
- [35] Chung, J. W., Elkins, C., Sakai, T., Kato, N., Vestring, T., Semba, C. P., Slonim, S. M., and Dake, M. D. “True-Lumen Collapse in Aortic Dissection.” In: *Radiology* 214.1 (2000), pp. 87–98.
- [36] Fan, Y., Cheng, S., Qing, K., and Chow, K. “Endovascular repair of type B aortic dissection: a study by computational fluid dynamics.” In: *Journal of Biomedical Science and Engineering* 3 (2010), 900907.
- [37] Soudah, E., Rudenick, P., Bordone, M., Bijmens, B., Garca-Dorado, D., Evangelista, A., and Oate, E. “Validation of numerical flow simulations against in vitro phantom measurements in different type B aortic dissection scenarios.” In: *Computer Methods in Biomechanics and Biomedical Engineering* 18.8 (2015), pp. 805–815.
- [38] Wan Ab Naim, N., Balan Ganesan, P., Sun, Z., Chee, K., Hashim, S., and Lim, E. “A perspective review on numerical simulations of hemodynamics in aortic dissection.” In: *The Scientific World Journal* (2014).
- [39] Chen, D., Mller-Eschner, M., Kotelis, D., Bekler, D., Ventikos, Y., and Tengg-Kobligk, H. von. “A longitudinal study of Type-B aortic dissection and endovascular repair scenarios: Computational analyses.” In: *Medical Engineering Physics* 35.9 (2013), pp. 1321–1330.
- [40] Cheng, Z., Riga, C., Chan, J., Hamady, M., Wood, N. B., Cheshire, N. J., Xu, X. Y., and Gibbs, R. G. “Initial findings and potential applicability of computational simulation of the aorta in acute type B dissection.” In: *Journal of Vascular Surgery* 57.2, Supplement (2013), 35S–43S.
- [41] Dillon-Murphy, D., Noorani, A., Nordsletten, D., and Figueroa, C. A. “Multi-modality image-based computational analysis of haemodynamics in aortic dissection.” In: *Biomechanics and Modeling in Mechanobiology* 15.4 (2016), pp. 857–876.

- [42] Tse, K. M., Chiu, P., Lee, H. P., and Ho, P. “Investigation of hemodynamics in the development of dissecting aneurysm within patient-specific dissecting aneurismal aortas using computational fluid dynamics (CFD) simulations.” In: *Journal of Biomechanics* 44.5 (2011), pp. 827–836.
- [43] Frazin, L. J., Lanza, G., Vonesh, M., Khasho, F., Spitzzeri, C., McGee, S., Mehlman, D., Chandran, K. B., Talano, J., and McPherson, D. “Functional chiral asymmetry in descending thoracic aorta.” In: *Circulation* 82.6 (1990), pp. 1985–94.
- [44] Rudenick, P. A., Bijmens, B. H., Segers, P., García-Dorado, D., and Evangelista, A. “Assessment of wall elasticity variations on intraluminal haemodynamics in descending aortic dissections using a lumped-parameter model.” In: *PloS One* 10.4 (2015), e0124011.
- [45] Alimohammadi, M., Sherwood, J. M., Karimpour, M., Agu, O., Balabani, S., and Díaz-Zuccarini, V. “Aortic dissection simulation models for clinical support: fluid-structure interaction vs. rigid wall models.” In: *Biomedical Engineering Online* 14.1 (2015), p. 34.
- [46] Tsai, T. T., Evangelista, A., Nienaber, C. A., Myrmel, T., Meinhardt, G., Cooper, J. V., Smith, D. E., Suzuki, T., Fattori, R., Llovet, A., Froehlich, J., Hutchison, S., Distant, A., Sundt, T., Beckman, J., Januzzi, J. L., Isselbacher, E. M., and Eagle, K. A. “Partial thrombosis of the false lumen in patients with acute type B aortic dissection.” In: *New England Journal of Medicine* 357.4 (2007), pp. 349–359.
- [47] BioNinja. *Clotting*. URL: <http://ib.bioninja.com.au/standard-level/topic-6-human-physiology/63-defence-against-infectio/clotting.html>.
- [48] Malek, A., Alper, S., and Izumo, S. “Hemodynamic shear stress and its role in atherosclerosis.” In: *JAMA* 282.21 (1999), pp. 2035–2042.
- [49] Tomaszewski, K. A., Radomski, M. W., and Santos-Martinez, M. J. “Nanodiagnos-tics, nanopharmacology and nanotoxicology of platelet–vessel wall interactions.” In: *Nanomedicine* 10.9 (2015), pp. 1451–1475.
- [50] Leiderman, K. and Fogelson, A. L. “Grow with the flow: a spatial–temporal model of platelet deposition and blood coagulation under flow.” In: *Mathematical Medicine and Biology* 28.1 (2011), pp. 47–84.
- [51] Virchow, R. L. *Thrombosis and Emboli*. Canton, Massachusetts: Science History Publications, 1998.
- [52] Woolf, N. *Pathology: Basic and Systemic*. Saunders, 1998.
- [53] Colman, R. W., Hirsh, J., Marder, V. J., Colman, Hirsh, Marder, Clowes, and George. *Hemostasis and thrombosis: Basic principles and clinical practice*. Lippincott Williams & Wilkins, 2001.

- [54] Folie, B. and McIntire, L. "Mathematical analysis of mural thrombogenesis. Concentration profiles of platelet-activating agents and effects of viscous shear flow." In: *Biophysical Journal* 56.6 (1989), pp. 1121–1141.
- [55] Bluestein, D., Niu, L., Schoepfoerster, R., and Dewanjee, M. "Fluid mechanics of arterial stenosis: Relationship to the development of mural thrombus." In: *Annals of Biomedical Engineering* 25.2 (1997), pp. 344–356.
- [56] Helms, C. C., Marvel, M., Zhao, W., Stahle, M., Vest, R., Kato, G. J., Lee, J. S., Christ, G., Gladwin, M. T., Hantgan, R. R., and Kim-Shapiro, D. B. "Mechanisms of hemolysis-associated platelet activation." In: *Journal of Thrombosis and Haemostasis* 11.12 (2013), pp. 2148–2154.
- [57] Hellums, J. "1993 Whitaker lecture: Biorheology in thrombosis research." In: *Annals of Biomedical Engineering* 22.5 (1994), pp. 445–455.
- [58] Suter, S. P., Nowak, M. D., Joist, J. H., Zeffren, D. J., and Bauman, J. E. "A programmable, computer-controlled cone-plate viscometer for the application of pulsatile shear stress to platelet suspensions." In: *Biorheology (Oxford)* 25.3 (1988). Ed. by IOS Press, pp. 449–459.
- [59] Yin, W., Shanmugavelayudam, S. K., and Rubenstein, D. A. "The effect of physiologically relevant dynamic shear stress on platelet and endothelial cell activation." In: *Thrombosis Research* 127.3 (2011), pp. 235–241.
- [60] Sheriff, J., Bluestein, D., Girdhar, G., and Jesty, J. "High-shear stress sensitizes platelets to subsequent low-shear conditions." In: *Annals of Biomedical Engineering* 38.4 (2010), pp. 1442–1450.
- [61] Nesbitt, W., Westein, E., Tovar-Lopez, F., Tolouei, E., Mitchell, A., Fu, J., Carberry, J., Fouras, A., and Jackson, S. "A shear gradient-dependent platelet aggregation mechanism drives thrombus formation." In: *Nature Medicine* 15.6 (2009), pp. 665–673.
- [62] Stein, P., Sabbah, H., and Pitha, J. "Continuing disease process of calcific aortic stenosis. Role of microthrombi and turbulent flow." In: *The American Journal of Cardiology* 39.2 (1977), pp. 159–163.
- [63] Goel, M. S. and Diamond, S. L. "Adhesion of normal erythrocytes at depressed venous shear rates to activated neutrophils, activated platelets, and fibrin polymerized from plasma." In: *Blood* 100.10 (2002), pp. 3797–3803.
- [64] Hathcock, J. J. "Flow effects on coagulation and thrombosis." In: *Arteriosclerosis, Thrombosis, and Vascular Biology* 26.8 (2006), pp. 1729–1737.
- [65] Cito, S., Mazzeo, M. D., and Badimon, L. "A review of macroscopic thrombus modeling methods." In: *Thrombosis Research* 131.2 (2013), pp. 116–124.

- [66] Pivkin, I. V., Richardson, P. D., and Karniadakis, G. “Blood flow velocity effects and role of activation delay time on growth and form of platelet thrombi.” In: *Proceedings of the National Academy of Sciences* 103.46 (2006), pp. 17164–17169.
- [67] Karino, T. and Goldsmith, H. “Adhesion of human platelets to collagen on the walls distal to a tubular expansion.” In: *Microvascular Research* 17.3 (1979), pp. 238–262.
- [68] Schoephoerster, R. T., Oynes, F., Nunez, G., Kapadvanjwala, M., and Dewanjee, M. K. “Effects of local geometry and fluid dynamics on regional platelet deposition on artificial surfaces.” In: *Arteriosclerosis, Thrombosis, and Vascular Biology* 13.12 (1993), pp. 1806–1813.
- [69] Raz, S., Einav, S., Alemu, Y., and Bluestein, D. “DPIV Prediction of Flow Induced Platelet Activation-Comparison to Numerical Predictions.” In: *Annals of Biomedical Engineering* 35.4 (2007), pp. 493–504.
- [70] Bark, D. L. and Ku, D. N. “Wall shear over high degree stenoses pertinent to atherothrombosis.” In: *Journal of Biomechanics* 43.15 (2010), pp. 2970–2977.
- [71] Goodman, P., Barlow, E., Crapo, P., Mohammad, S., and Solen, K. “Computational model of device-induced thrombosis and thromboembolism.” In: *Annals of Biomedical Engineering* 33.6 (2005), pp. 780–797.
- [72] Bark, D. L., Para, A. N., and Ku, D. N. “Correlation of thrombosis growth rate to pathological wall shear rate during platelet accumulation.” In: *Biotechnology and Bioengineering* 109.10 (2012), pp. 2642–2650.
- [73] Biasetti, J., Hussain, F., and Gasser, T. C. “Blood flow and coherent vortices in the normal and aneurysmatic aortas: a fluid dynamical approach to intra-luminal thrombus formation.” In: *Journal of The Royal Society Interface* 8.63 (2011), pp. 1449–1461.
- [74] Jeong, J. and Hussain, F. “On the identification of a vortex.” In: *Journal of fluid mechanics* 285 (1995), pp. 69–94.
- [75] Biasetti, J., Spazzini, P. G., Swedenborg, J., and Gasser, T. C. “An integrated fluid-chemical model towards modeling the formation of intra-luminal thrombus in abdominal aortic aneurysms.” In: *Frontiers in Physiology* 3.266 (2012).
- [76] Di Achille, P., Tellides, G., and Humphrey, J. D. “Hemodynamics-driven deposition of intra-luminal thrombus in abdominal aortic aneurysms.” In: *International Journal for Numerical Methods in Biomedical Engineering* 33.5 (2017), e2828.
- [77] Nauta, F. J., Lau, K. D., Arthurs, C. J., Eagle, K. A., Williams, D. M., Trimarchi, S., Patel, H. J., and Figueroa, C. A. “Computational fluid dynamics and aortic thrombus formation following thoracic endovascular aortic repair.” In: *The Annals of Thoracic Surgery* 103.6 (2017), pp. 1914–1921.

- [78] Sorensen, E. N., Burgreen, G. W., Wagner, W. R., and Antaki, J. F. "Computational simulation of platelet deposition and activation: I. Model development and properties." In: *Annals of Biomedical Engineering* 27.4 (1999), pp. 449–458.
- [79] Fogelson, A. L. "A mathematical model and numerical method for studying platelet adhesion and aggregation during blood clotting." In: *Journal of Computational Physics* 56.1 (1984), pp. 111–134.
- [80] Fogelson, A. L. "Continuum models of platelet aggregation: Formulation and mechanical properties." In: *SIAM Journal on Applied Mathematics* 52.4 (1992), pp. 1089–1110.
- [81] Fogelson, A. L. and Guy, R. D. "Immersed-boundary-type models of intravascular platelet aggregation." In: *Computer Methods in Applied Mechanics and Engineering* 197.2528 (2008), pp. 2087–2104.
- [82] Worth Longest, P. and Kleinstreuer, C. "Comparison of blood particle deposition models for non-parallel flow domains." In: *Journal of Biomechanics* 36.3 (2003), pp. 421–430.
- [83] Xu, Z., Chen, N., Kamocka, M. M., Rosen, E. D., and Alber, M. "A multiscale model of thrombus development." In: *Journal of the Royal Society Interface* 5.24 (2008), pp. 705–722.
- [84] Xu, Z., Lioi, J., Mu, J., Kamocka, M. M., Liu, X., Chen, D. Z., Rosen, E. D., and Alber, M. "A multiscale model of venous thrombus formation with surface-mediated control of blood coagulation cascade." In: *Biophysical Journal* 98.9 (2010), pp. 1723–1732.
- [85] Wootton, D. M., Markou, C. P., Hanson, S. R., and Ku, D. N. "A mechanistic model of acute platelet accumulation in thrombogenic stenoses." In: *Annals of Biomedical Engineering* 29.4 (2001), pp. 321–329.
- [86] David, T., Thomas, S., and Walker, P. G. "Platelet deposition in stagnation point flow: an analytical and computational simulation." In: *Medical Engineering & Physics* 23.5 (2001), pp. 299–312.
- [87] Kuharsky, A. L. and Fogelson, A. L. "Surface-mediated control of blood coagulation: The role of binding site densities and platelet deposition." In: *Biophysical Journal* 80.3 (2001), pp. 1050–1074.
- [88] Anand, M., Rajagopal, K., and Rajagopal, K. R. "A model incorporating some of the mechanical and biochemical factors underlying clot formation and dissolution in flowing blood." In: *Journal of Theoretical Medicine* 5.3-4 (2003), pp. 183–218.
- [89] Bedekar, A., Pant, K., Ventikos, Y., and Sundaram, S. "A computational model combining vascular biology and haemodynamics for thrombosis prediction in anatomically accurate cerebral aneurysms." In: *Food and Bioprocess Processing* 83.2 (2005), pp. 118–126.

- [90] Jenkins, J, Prabhakarpanthian, B, Lenghaus, K, Hickman, J, and Sundaram, S. “Fluidics-resolved estimation of protein adsorption kinetics in a biomicrofluidic system.” In: *Analytical Biochemistry* 331.2 (2004), pp. 207–215.
- [91] Menichini, C. and Xu, X. Y. “Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications.” In: *Journal of Mathematical Biology* 73.5 (2016), pp. 1205–1226.
- [92] Ferziger, J. and Peri, M. *Computational methods for fluid dynamics*. Springer, 2002.
- [93] Fung, Y. C. *Biomechanics: Circulation*. 2nd edition. New York: Springer-Verlag, 1997.
- [94] Quemada, D. “Rheology of concentrated disperse systems II. A model for non-newtonian shear viscosity in steady flows.” In: *Rheologica Acta* 17.6 (1978), pp. 632–642.
- [95] Truskey, G., Yuan, F., and Katz, D. *Transport Phenomena in Biological Systems*. Pearson Prentice Hall bioengineering. Pearson Prentice Hall, 2009.
- [96] Ghirelli, F. and Leckner, B. “Transport equation for the local residence time of a fluid.” In: *Chemical Engineering Science* 59.3 (2004), pp. 513–523.
- [97] Harrison, S., Smith, S., Bernsdorf, J., Hose, D., and Lawford, P. “Application and validation of the lattice Boltzmann method for modelling flow-related clotting.” In: *Journal of Biomechanics* 40.13 (2007), pp. 3023–3028.
- [98] Papadopoulos, K. P., Gavaises, M., and Atkin, C. “A simplified mathematical model for thrombin generation.” In: *Medical Engineering & Physics* 36.2 (2014), pp. 196–204.
- [99] Holme, P. A., Ørvim, U., Hamers, M. J., Solum, N. O., Brosstad, F. R., Barstad, R. M., and Sakariassen, K. S. “Shear-induced platelet activation and platelet microparticle formation at blood flow conditions as in arteries with a severe stenosis.” In: *Arteriosclerosis, Thrombosis, and Vascular Biology* 17.4 (1997), pp. 646–653.
- [100] Savage, B., Saldívar, E., and Ruggeri, Z. M. “Initiation of platelet adhesion by arrest onto fibrinogen or translocation on von Willebrand factor.” In: *Cell* 84.2 (1996), pp. 289–297.
- [101] Versteeg, H. K. and Malalasekera, W. *An introduction to computational fluid dynamics: The finite volume method*. Pearson Education, 2007.
- [102] Morbiducci, U., Ponzini, R., Gallo, D., Bignardi, C., and Rizzo, G. “Inflow boundary conditions for image-based computational hemodynamics: impact of idealized versus measured velocity profiles in the human aorta.” In: *Journal of Biomechanics* 46.1 (2013), pp. 102–109.

- [103] Ganten, M.-K., Weber, T. F., Tengg-Kobligk, H. von, Böckler, D., Stiller, W., Geisbüsch, P., Kauffmann, G. W., Delorme, S., Bock, M., and Kauczor, H.-U. “Motion characterization of aortic wall and intimal flap by ECG-gated CT in patients with chronic B-dissection.” In: *European Journal of Radiology* 72.1 (2009), pp. 146–153.
- [104] Peterss, S., Mansour, A. M., Ross, J. A., Vaitkeviciute, I., Charilaou, P., Dumfarth, J., Fang, H., Ziganshin, B. A., Rizzo, J. A., Adeniran, A. J., et al. “Changing pathology of the thoracic aorta from acute to chronic dissection: Literature review and insights.” In: *Journal of the American College of Cardiology* 68.10 (2016), pp. 1054–1065.
- [105] Ruel, J. and Lachance, G. “Mathematical modeling and experimental testing of three bioreactor configurations based on windkessel models.” In: *Heart International* 5.1 (2010).
- [106] Taylor, J. O., Witmer, K. P., Neuberger, T., Craven, B. A., Meyer, R. S., Deutsch, S., and Manning, K. B. “In vitro quantification of time dependent thrombus size using magnetic resonance imaging and computational simulations of thrombus surface shear stresses.” In: *Journal of Biomechanical Engineering* 136.7 (2014), p. 071012.
- [107] Marcinkowska-Gapiska, A., Gapinski, J., Elikowski, W., Jaroszyk, F., and Kubisz, L. “Comparison of three rheological models of shear flow behavior studied on blood samples from post-infarction patients.” English. In: *Medical & Biological Engineering & Computing* 45.9 (2007), pp. 837–844.
- [108] Polanczyk, A., Podyma, M., Stefanczyk, L., Szubert, W., and Zbicinski, I. “A 3D model of thrombus formation in a stent-graft after implantation in the abdominal aorta.” In: *Journal of Biomechanics* 48.3 (2015), pp. 425–431.
- [109] Ngoepe, M. and Ventikos, Y. “Computational modelling of clot development in patient-specific cerebral aneurysm cases.” In: *Journal of Thrombosis and Haemostasis* 14.2 (2016), pp. 262–272.
- [110] Hemker, H., Giesen, P., AlDieri, R., Regnault, V., De Smed, E., Wagenvoort, R., Lecompte, T., and Beguin, S. “The calibrated automated thrombogram (CAT): a universal routine test for hyper- and hypocoagulability.” In: *Pathophysiology of Haemostasis and Thrombosis* 32.5-6 (2002), pp. 249–253.
- [111] Wagenvoort, R., Hemker, P., and Hemker, H. “The limits of simulation of the clotting system.” In: *Journal of Thrombosis and Haemostasis* 4.6 (2006), pp. 1331–1338.
- [112] Cheng, Z. “Analysis of blood flow in patient-specific models of type B aortic dissection.” Doctoral dissertation. Imperial College London, 2012.

- [113] Cheng, Z., Juli, C., Wood, N., Gibbs, R., and Xu, X. "Predicting flow in aortic dissection: Comparison of computational model with PC-MRI velocity measurements." In: *Medical Engineering & Physics* 36.9 (2014), pp. 1176–1184.
- [114] Replogle, R. L., Meiselman, H. J., and Merrill, E. W. "SPECIAL ARTICLE Clinical Implications of Blood Rheology Studies." In: *Circulation* 36.1 (1967), pp. 148–160.
- [115] Nobili, M., Sheriff, J., Morbiducci, U., Redaelli, A., and Bluestein, D. "Platelet activation due to hemodynamic shear stresses: damage accumulation model and comparison to in vitro measurements." In: *ASAIO Journal (American Society for Artificial Internal Organs: 1992)* 54.1 (2008), pp. 64–72.
- [116] Ruggeri, Z. and Jackson, S. "Platelet thrombus formation in flowing blood." In: *Platelets*. Ed. by Michelson, A. D. Academic Press, 2013. Chap. 20, pp. 399–423.
- [117] Casa, L. D. and Ku, D. N. "High Shear Thrombus Formation under Pulsatile and Steady Flow." In: *Cardiovascular Engineering and Technology* 5.2 (2014), pp. 154–163.
- [118] Menichini, C., Cheng, Z., Gibbs, R. G., and Xu, X. Y. "Predicting false lumen thrombosis in patient-specific models of aortic dissection." In: *Journal of The Royal Society Interface* 13.124 (2016), p. 20160759.
- [119] Diamond, S. L. "Engineering design of optimal strategies for blood clot dissolution." In: *Annual Review of Biomedical Engineering* 1.1 (1999), pp. 427–461.
- [120] Taylor, J. O., Meyer, R. S., Deutsch, S., and Manning, K. B. "Development of a computational model for macroscopic predictions of device-induced thrombosis." In: *Biomechanics and modeling in mechanobiology* 15.6 (2016), pp. 1713–1731.
- [121] Grigioni, M., Morbiducci, U., D'Avenio, G., Di Benedetto, G., and Del Gaudio, C. "A novel formulation for blood trauma prediction by a modified power-law mathematical model." In: *Biomechanics and Modeling in Mechanobiology* 4.4 (2005), pp. 249–260.
- [122] Massai, D., Soloperto, G., Gallo, D., Xu, X. Y., and Morbiducci, U. "Shear-induced platelet activation and its relationship with blood flow topology in a numerical model of stenosed carotid bifurcation." In: *European Journal of Mechanics-B/Fluids* 35 (2012), pp. 92–101.
- [123] de Sousa, D. R., Vallecilla, C., Chodzynski, K., Jerez, R. C., Malaspinas, O., Eker, O. F., Ouared, R., Vanhamme, L., Legrand, A., Chopard, B., et al. "Determination of a shear rate threshold for thrombus formation in intracranial aneurysms." In: *Journal of Neurointerventional Surgery* 8.8 (2016), pp. 853–858.
- [124] Zimny, S., Chopard, B., Malaspinas, O., Lorenz, E., Jain, K., Roller, S., and Bernsdorf, J. "A multiscale approach for the coupled simulation of blood flow and thrombus formation in intracranial aneurysms." In: *Procedia Computer Science* 18 (2013), pp. 1006–1015.

- [125] Malaspinas, O., Turjman, A., de Sousa, D. R., Garcia-Cardena, G., Raes, M., Nguyen, P.-T., Zhang, Y., Courbebaisse, G., Lelubre, C., Boudjeltia, K. Z., et al. “A spatio-temporal model for spontaneous thrombus formation in cerebral aneurysms.” In: *Journal of Theoretical Biology* 394 (2016), pp. 68–76.
- [126] Bark, D. L. and Ku, D. N. “Platelet transport rates and binding kinetics at high shear over a thrombus.” In: *Biophysical Journal* 105.2 (2013), pp. 502–511.
- [127] Peach, T., Ngoepe, M., Spranger, K., Zajarias-Fainsod, D., and Ventikos, Y. “Personalizing flow-diverter intervention for cerebral aneurysms: from computational hemodynamics to biochemical modeling.” In: *International Journal for Numerical Methods in Biomedical Engineering* 30.11 (2014), pp. 1387–1407.
- [128] Menichini, C., Cheng, Z., Gibbs, R. G., and Xu, X. Y. “A computational model for false lumen thrombosis in type B aortic dissection following thoracic endovascular repair.” In: *Journal of Biomechanics* 66 (2018), pp. 36–43.
- [129] Hanna, J. M., Andersen, N. D., Ganapathi, A. M., McCann, R. L., and Hughes, G. C. “Five-year results for endovascular repair of acute complicated type B aortic dissection.” In: *Journal of Vascular Surgery* 59.1 (2014), pp. 96–106.
- [130] Qin, Y.-L., Deng, G., Li, T.-X., Jing, R.-W., and Teng, G.-J. “Risk factors of incomplete thrombosis in the false lumen after endovascular treatment of extensive acute type B aortic dissection.” In: *Journal of Vascular Surgery* 56.5 (2012), pp. 1232–1238.
- [131] Dong, Z., Fu, W., Wang, Y., Wang, C., Yan, Z., Guo, D., Xu, X., and Chen, B. “Stent graft-induced new entry after endovascular repair for Stanford type B aortic dissection.” In: *Journal of Vascular Surgery* 52.6 (2010), pp. 1450–1457.
- [132] Xiao, N., Alastruey, J., and Alberto Figueroa, C. “A systematic comparison between 1-D and 3-D hemodynamics in compliant arterial models.” In: *International Journal for Numerical Methods in Biomedical Engineering* 30.2 (2014), pp. 204–231.
- [133] Clough, R. E. and Nienaber, C. A. “Management of acute aortic syndrome.” In: *Nature Reviews Cardiology* 12.2 (2015), pp. 103–114.
- [134] Kamman, A. V., Brunkwall, J., Verhoeven, E. L., Heijmen, R. H., Trimarchi, S., Kasprzak, P., Heijmen, R., Alric, P., Verhoeven, E., Schumacher, H., et al. “Predictors of aortic growth in uncomplicated type B aortic dissection from the Acute Dissection Stent Grafting or Best Medical Treatment (ADSORB) database.” In: *Journal of Vascular Surgery* 65.4 (2017), pp. 964–971.
- [135] Nichols, W., O’Rourke, M., and Vlachopoulos, C. *McDonald’s blood flow in arteries: theoretical, experimental and clinical principles*. CRC press, 2011.

- [136] Rudenick, P. A., Segers, P., Pineda, V., Cuellar, H., García-Dorado, D., Evangelista, A., and Bijnens, B. H. “False lumen flow patterns and their relation with morphological and biomechanical characteristics of chronic aortic dissections. Computational model compared with magnetic resonance imaging measurements.” In: *PloS One* 12.1 (2017), e0170888.
- [137] Ge, Y. Y., Guo, W., Cheshire, N., Liu, X. P., Jia, X., Xiong, J., Ma, X. H., and Zhang, H. P. “Preoperative thoracic false lumen branches relate to aortic remodeling after thoracic endovascular aortic repair for DeBakey IIIb aortic dissection.” In: *Journal of Vascular Surgery* 65.3 (2017), pp. 659–668.
- [138] Van Puyvelde, J., Verbeken, E., Verbrugghe, P., Herijgers, P., and Meuris, B. “Aortic wall thickness in patients with ascending aortic aneurysm versus acute aortic dissection.” In: *European Journal of Cardio-Thoracic Surgery* 49.3 (2015), pp. 756–762.
- [139] Pasta, S., Cho, J.-S., Dur, O., Pekkan, K., and Vorp, D. A. “Computer modeling for the prediction of thoracic aortic stent graft collapse.” In: *Journal of Vascular Surgery* 57.5 (2013), pp. 1353–1361.
- [140] Chen, H., Peelukhana, S., Berwick, Z., Kratzberg, J., Krieger, J., Roeder, B., Chambers, S., and Kassab, G. “Editor’s choice – Fluid-structure interaction simulations of aortic dissection with bench validation.” In: *European Journal of Vascular and Endovascular Surgery* 52.5 (2016), pp. 589–595.
- [141] Reymond, P., Merenda, F., Perren, F., Rüfenacht, D., and Stergiopulos, N. “Validation of a one-dimensional model of the systemic arterial tree.” In: *American Journal of Physiology-Heart and Circulatory Physiology* 297.1 (2009), H208–H222.
- [142] Jánosi, R. A., Tsagakis, K., Bettin, M., Kahlert, P., Horacek, M., Al-Rashid, F., Schlosser, T., Jakob, H., Eggebrecht, H., and Erbel, R. “Thoracic aortic aneurysm expansion due to late distal stent graft-induced new entry.” In: *Catheterization and Cardiovascular Interventions* 85.2 (2015), E43–53.
- [143] Nauta, F. J., Conti, M., Marconi, S., Kamman, A. V., Alaimo, G., Morganti, S., Ferrara, A., Herwaarden, J. A. van, Moll, F. L., Auricchio, F., et al. “An experimental investigation of the impact of thoracic endovascular aortic repair on longitudinal strain.” In: *European Journal of Cardio-Thoracic Surgery* 50.5 (2016), pp. 955–961.
- [144] Nauta, F. J., de Beaufort, H. W., Conti, M., Marconi, S., Kamman, A. V., Ferrara, A., Herwaarden, J. A. van, Moll, F. L., Auricchio, F., and Trimarchi, S. “Impact of thoracic endovascular aortic repair on radial strain in an ex vivo porcine model.” In: *European Journal of Cardio-Thoracic Surgery* 51.4 (2016), pp. 783–789.

- [145] Poullis, M. P., Warwick, R., Oo, A., and Poole, R. J. "Ascending aortic curvature as an independent risk factor for type A dissection, and ascending aortic aneurysm formation: a mathematical model." In: *European Journal of Cardio-Thoracic Surgery* 33.6 (2008), pp. 995–1001.
- [146] Shirali, A. S., Bischoff, M. S., Lin, H.-M., Oyfe, I., Lookstein, R., Grieppe, R. B., and Luozzo, G. D. "Predicting the risk for acute type B aortic dissection in hypertensive patients using anatomic variables." In: *JACC: Cardiovascular Imaging* 6.3 (2013), pp. 349–357.
- [147] Chen, S., Larion, S., Ahanchi, S. S., Ammar, C. P., Brandt, C. T., and Panneton, J. M. "A novel anatomic severity grading score for acute Type B aortic dissections and correlation to aortic reinterventions after thoracic endovascular aortic repair." In: *Journal of Cardiothoracic Surgery* 12.1 (2017), p. 39.
- [148] Craiem, D., Batti, S. E., Casciaro, M. E., Mousseaux, E., Sirieix, M.-E., Simon, A., and Alsac, J.-M. "Age-related changes of thoracic aorta geometry used to predict the risk for acute type B dissection." In: *International Journal of Cardiology* 228 (2017), pp. 654–660.
- [149] Vorp, D. A. and Geest, J. P. V. "Biomechanical determinants of abdominal aortic aneurysm rupture." In: *Arteriosclerosis, Thrombosis, and Vascular Biology* 25.8 (2005), pp. 1558–1566.
- [150] Steinman, D. A., Thomas, J. B., Ladak, H. M., Milner, J. S., Rutt, B. K., and Spence, J. D. "Reconstruction of carotid bifurcation hemodynamics and wall thickness using computational fluid dynamics and MRI." In: *Magnetic Resonance in Medicine* 47.1 (2002), pp. 149–159.
- [151] Ferraro, M., Trachet, B., Aslanidou, L., Fehervary, H., Segers, P., and Stergiopulos, N. "Should we ignore what we cannot measure? How non-uniform stretch, non-uniform wall thickness and minor side branches affect computational aortic biomechanics in mice." In: *Annals of Biomedical Engineering* 46.1 (2018), pp. 159–170.
- [152] Borghi, A., Wood, N. B., Mohiaddin, R. H., and Xu, X. Y. "Fluid–solid interaction simulation of flow and stress pattern in thoracoabdominal aneurysms: a patient-specific study." In: *Journal of Fluids and Structures* 24.2 (2008), pp. 270–280.

Appendices

Calibration of Windkessel Models for Patient-Specific Dissections

A realistic set of boundary conditions was developed for the study carried out in Chapter 7 in order to include the major aortic branches in the computational models. This allows a more detailed and realistic assessment of flow and pressure distributions and hence more reliable thrombus prediction. Several parametric studies were carried out on one of the reconstructed geometries extracted from a BMT patient, including 9 major branches (brachiocephalic, left common carotid, left subclavian, celiac, superior mesenteric, renals and iliacs). Using a 3-element Windkessel model, a total of 27 parameters are needed to incorporate realistic outlet boundary conditions in a patient-specific model. In order to make these parameters patient-specific, a simple algorithm was developed which can adjust the values according to the patient geometry.

As no patient-specific flow and pressure data were available for the patient taken under analysis, the study by Dillon-Murphy et al. [41] was taken as a reference. Dillon-Murphy et al. [41] reported a complete case study on a single aortic dissection case including all major outlets, with flow data measured by PC-MRI. All their Windkessel outlets were calibrated based on acquired PC-MRI data and literature data. The total resistance (R_t) of each branch j in Dillon-Murphy et al. [41]’s model was calculated as follows [132]:

$$R_{t_j} = R_{c_j} + R_{p_j} \tag{A.1}$$

where R_c is the characteristic impedance (or proximal resistance) and R_p is the peripheral (or distal) resistance. As the number of branches used by Dillon-Murphy et al. [41] is different from the ones used in Chapter 7, the total resistance and compliance of each branch i used in our model

was calculated by assuming that two minor arteries branching off one major artery will behave as a parallel circuit, and hence:

$$\frac{1}{R_{t_i}} = \sum_j \frac{1}{R_{t_j}} \quad (\text{A.2})$$

$$C_{t_i} = \sum_j C_{t_j} \quad (\text{A.3})$$

Proximal and distal resistances of each branch i were then calculated as follows [132]:

$$R_{c_i} = \frac{\rho c_i}{A_{D_i}} \quad (\text{A.4})$$

$$R_{p_i} = R_{t_i} - R_{c_i} \quad (\text{A.5})$$

where ρ is blood density, c_i is the pulse-wave velocity at each of the outflow branches and A_{D_i} is the diastolic area of each branch. Assuming that the reconstructed geometry represents the one at diastole, A_{D_i} corresponds to the area of each branch outlet.

Presentations and Publications

B.1 Journal Publications

- **Menichini, C.** and Xu, X.Y. “Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications.” *Journal of mathematical biology*, 73.5 (2016), pp. 1205-1226. <https://doi.org/10.1007/s00285-016-0986-4>
- **Menichini, C.**, Cheng, Z., Gibbs, R.G.J., Xu, X.Y. “Predicting false lumen thrombosis in patient-specific models of aortic dissection.” *Journal of The Royal Society Interface*, 13.124 (2016), 20160759. <https://doi.org/10.1098/rsif.2016.0759>
- **Menichini, C.**, Cheng, Z., Gibbs, R.G.J., Xu, X.Y. “A computational model for false lumen thrombosis in type B aortic dissection following thoracic endovascular repair.” *Journal of Biomechanics*, (2017). <https://doi.org/10.1016/j.jbiomech.2017.10.029>
- **Menichini, C.**, Milinis, K., Gibbs, R.G.J., Xu, X.Y. “The effect of FL perfusion on aortic remodelling in Type B aortic dissection.” (Manuscript in preparation)
- **Menichini, C.**, Pirola, S., Guo, B., Dong, Z., Fu, W., Xu, X.Y. “Stent graft-induced new entry formation is associated with high wall stress.” (Manuscript in preparation)
- Pirola, S., **Menichini, C.**, Guo, B., Dong, Z., Fu, W., Xu, X.Y. “Deriving patient-specific boundary conditions for aortic flow simulation based on 4D-MRI.” (Manuscript in preparation)
- Johari, N., **Menichini, C.**, Hamadi, M., Xu, X.Y. “Effects of the carotid stents design on the hemodynamic features and LDL accumulation of carotid artery bifurcation.” (Manuscript in preparation)

B.2 Presentations

- **Menichini, C.** “Patient-specific prediction of false lumen thrombosis in Type B aortic dissection.” PhD Symposium, Department of Chemical Engineering, Imperial College London, 2017.
- **Menichini, C.**, Cheng, Z., Gibbs, R.G.J., and Xu, X.Y. “Mathematical modeling of thrombus formation in aortic dissection. Zhongshan Hospital Fudan University - Imperial College London Symposium, Shanghai, China, 12 April 2017. (*Invited*)
- **Menichini, C.**, Cheng, Z., Gibbs, R.G.J., and Xu, X.Y. “Patient-specific prediction of false lumen thrombosis in type B aortic dissection.” The 16th International Conference on Biomedical Engineering (ICBME 2016), Singapore, 7 - 10 December 2016. (*Invited*)
- **Menichini, C.**, Cheng, Z., Gibbs, R.G.J., and Xu, X.Y. “Predicting false lumen thrombosis in 3D patient-specific models of type B aortic dissection.” Summer Biomechanics, Bioengineering and Biotransport Conference (SB3C 2016), National Harbor, MD, USA, June 29 - July 2 2016.
- **Menichini, C.**, “Mathematical modeling of thrombus formation in idealized models of aortic dissection.” PhD Symposium, Department of Chemical Engineering, Imperial College London, 2015.
- **Menichini, C.**, Xu, X.Y. “Mathematical Modeling of Thrombus Formation in Idealized Models of Aortic Dissection. Summer Biomechanics, Bioengineering and Biotransport Conference (SB3C 2015), Snowbird resort, Utah, USA, 17-20 June 2015.

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2.1a	6	CircsystemsUNSIG09R3a [14]	CircsystemsUNSIG09R3a [14]	N/A
2.1b	6	The International Registry of Aortic Dissection (IRAD) [7]	The International Registry of Aortic Dissection (IRAD) [7]	N/A
2.2a	8	The International Registry of Aortic Dissection (IRAD) [7]	The International Registry of Aortic Dissection (IRAD) [7]	N/A
2.2b	8	AorticDissection.com [15]	AorticDissection.com [15]	N/A
2.3	10	Nienaber and Eagle [18]	Wolters Kluwer Health, Inc.	4218860989857
2.4	12	Chen et al. [23]	Chen et al. [23]	N/A
2.5	13	The International Registry of Aortic Dissection (IRAD) [7]	The International Registry of Aortic Dissection (IRAD) [7]	N/A
2.6a	14	Nienaber et al. [27]	Wolters Kluwer Health, Inc.	4218880113948
2.6b	14	Nienaber et al. [28]	BMJ Publishing Group Ltd.	4218871373741
2.7	16	Chen et al. [23]	Chen et al. [23]	N/A
2.8	19	Tsai et al. [46]	Massachusetts Medical Society	N/A
2.9	20	BioNinja [47]	BioNinja [47]	N/A
2.10	22	Tomaszewski et al. [49]	Future Medicine Ltd.	42370900046416
2.11	23	Leiderman and Fogelson [50]	Oxford University Press	4218880257211
2.12	25	Hellums [57]	Springer	4218880386559
3.5	47	Ruel and Lachance [105]	Ruel and Lachance [105]	N/A