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Ph.D. dissertation in Bioengineering



**Personalized computational study of
hemodynamics in Transcatheter
Aortic Valve Implantation:
assessment of long-term degeneration**

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Abstract

Transcatheter Aortic Valve Implantation (TAVI) is a minimally invasive technique for the treatment of severe aortic valve disease which consists in the deployment via catheter of a bio-prosthetic valve in place of the native aortic valve. Introduced twenty years ago as an alternative to surgery for elderly patients at high-risk for open-heart surgery, TAVI has been recently extended to lower-risk, younger patients thanks to comparable performances with the surgical gold-standard. In this context, it is particularly relevant to assess the long-term durability of the TAVI bio-prosthetic valves which is limited by Structural Valve Deterioration (SVD). SVD is an inevitable process manifested as intrinsic permanent changes in the prosthesis (calcification, wear and tear) which ultimately leads to the hemodynamic failure of the implanted valve, but its pathogenesis is still not completely understood. In particular, SVD has been associated with an increased infiltration of host immune cells in the bio-prosthetic leaflets and clinical risk factors for SVD suggest a possible influence of aortic hemodynamics on its development.

Accordingly, in this thesis we aim to propose computational-based hemodynamic indices able to identify a premature onset of SVD. To this aim, we develop a highly personalized Computational Fluid Dynamics (CFD) model to efficiently simulate realistic early post-TAVI hemodynamics, i.e. when the implanted valve is still fully functioning, in order to study its relationship with SVD. Specifically, we consider a cohort of fourteen patients with and without SVD at long-term follow-up exam and, starting from pre-operative clinical images, we build post-TAVI virtual geometries, providing a realistic representation of the implanted TAVI valve. Personalized flow rate conditions, derived from Echo Doppler data, are used to perform CFD simulations exploiting an ad-hoc algebraic preconditioner proposed in this thesis. From a post-processing of the CFD results we propose novel computational hemodynamic indices and scores that show statistically significant differences between patients with and without SVD, proving a correlation between aortic hemodynamics features and SVD. Furthermore, based on the hemodynamic scores, we propose a synthetic scoring system that clearly separates the SVD from the non-SVD sub-group of patients, suggesting the our model captures some key biomechanical drivers of SVD. This study represents a preliminary proof of the influence of aortic hemodynamics on a

premature onset of SVD, which has been poorly investigated by clinicians and researchers, showcasing the power of computational modeling in providing a detailed description of complex features that would be impossible to capture otherwise. Finally, the synthetic score could assist clinicians in a patient-specific planning of follow-up exams in order to closely monitor those patients at high-risk of prematurely developing SVD.

Keywords: Transcatheter Aortic Valve Implantation (TAVI), Long-term durability, Structural Valve Deterioration (SVD), Patient-specific clinical data, Personalized Computational Fluid Dynamics (CFD) model, Inexact block preconditioners, Computational hemodynamic indices

Abstract in lingua italiana

L'impianto valvolare aortico transcateretere (TAVI; dall'inglese) è una tecnica minimamente invasiva per il trattamento di una patologia severa della valvola aortica che consiste nel rilascio tramite catetere di una valvola bio-prostetica al posto della valvola aortica nativa. Introdotta venti anni fa come alternativa all'intervento chirurgico per pazienti anziani ad alto rischio per una chirurgia a cuore aperto, la TAVI è stata recentemente estesa a pazienti a minor rischio e più giovani grazie a prestazioni comparabili al gold-standard chirurgico. In questo contesto è particolarmente importante valutare la durabilità a lungo termine delle valvole bio-prostetiche TAVI che è limitata dal deterioramento strutturale della valvola (SVD; dall'inglese). SVD è un processo inevitabile che si manifesta con modifiche intrinseche e permanenti nella protesi (calcificazione, usura) risultanti nel fallimento emodinamico della valvola impiantata, ma la sua patogenesi non è stata ancora completamente capita. In particolare, SVD è stata associata con un'elevata infiltrazione di cellule immunitarie nei lembi bio-prostetici e i fattori clinici di rischio per SVD suggeriscono una possibile influenza dell'emodinamica aortica sul suo sviluppo.

Di conseguenza in questa tesi miriamo a proporre indici emodinamici computazionali capaci di identificare una manifestazione prematura di SVD. A questo scopo sviluppiamo un modello di fluido-dinamica computazionale (CFD; dall'inglese) altamente personalizzato per simulare efficientemente un'emodinamica realistica immediatamente dopo la TAVI, i.e. quando la valvola impiantata è ancora pienamente funzionante, al fine di studiare la sua relazione con la SVD. Specificatamente, consideriamo un campione di quattordici pazienti con e senza SVD all'esame follow-up a lungo termine e, partendo da immagini cliniche pre-operative, costruiamo geometrie virtuali post-TAVI, fornendo una rappresentazione realistica della valvola TAVI impiantata. Condizioni di flusso personalizzate, derivate da dati Eco Doppler, sono utilizzate per eseguire simulazioni CFD sfruttando un preconditionatore algebrico ad-hoc proposto in questa tesi. Da un'analisi dei risultati CFD proponiamo nuovi indici e score emodinamici computazionali che mostrano differenze statisticamente rilevanti tra pazienti con e senza SVD, provando una correlazione tra le caratteristiche dell'emodinamica aortica e la SVD. Inoltre, basandoci sugli score emodinamici, proponiamo un sistema di score sintetico che separa chiaramente i sot-

togruppi di pazienti con e senza SVD, suggerendo che il nostro modello catturi alcuni fattori biomeccanici chiave della SVD. Questo studio rappresenta una prova preliminare dell'influenza dell'emodinamica aortica su una manifestazione prematura di SVD, che non è stata propriamente investigata da clinici e ricercatori, mettendo in luce l'abilità dei modelli computazionali nel fornire una descrizione dettagliata di fenomeni complessi che sarebbe impossibile catturare altrimenti. Infine, lo score sintetico potrebbe assistere i medici in una pianificazione paziente specifica degli esami follow-up al fine di monitorare strettamente quei pazienti che si trovano ad alto rischio di sviluppare prematuramente la SVD.

Parole chiave: Impianto valvolare aortico transcateretere, Durabilità a lungo termine, Deterioramento strutturale della valvola, Dati clinici paziente-specifici, Modello personalizzato di Fluidodinamica computazionale, Precondizionatori inesatti a blocchi, Indici emodinamici computazionali

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General overview of the contents of the thesis

Transcatheter Aortic Valve Implantation (TAVI) is becoming an increasingly popular treatment for severe aortic valve disease [149, 184]. Nonetheless, the long-term durability of the bio-prosthetic valves used for TAVI is still an open clinical question due to a lack of follow-up data [229]. In particular, the durability of these valves is limited by Structural Valve Deterioration (SVD) which leads to their hemodynamic failure through irreversible changes in the prosthesis [128]. However, the drivers of the SVD process have not been clearly identified and clinical risk factors for SVD suggest a possible influence of aortic hemodynamics on a premature onset of this pathology [175].

In this context, computational modeling represents a powerful tool able to provide a detailed description of aortic hemodynamics in presence of the TAVI valve in order to investigate the features that may influence the development of SVD. Indeed, computational models have been extensively applied in the literature to gain insights on blood-dynamic features that would be very difficult to capture with standard clinical tools [48, 64, 174, 208, 219]. Accordingly, in this thesis we aim to develop personalized Computational Fluid Dynamics (CFD) models for the efficient and realistic numerical simulation of early post-TAVI hemodynamics, i.e. when the implanted valve is yet to be degenerated. Additionally, our goal is to analyze the CFD results in order to propose computational hemodynamic indices and scores in early post-TAVI scenarios that correlate with a premature onset of SVD in a cohort of patients with and without SVD at long-term follow-up exam.

To these aims we develop a pipeline to build virtual post-TAVI geometries starting from pre-operative clinical images and providing a realistic representation of the TAVI bio-prosthetic valve (stent and leaflets). Furthermore, we derive a personalized flow rate profile from Echo Doppler data and we impose it as a boundary condition in the numerical simulations exploiting an ad-hoc formulation of the mathematical problem of interest. The algebraic Finite Elements problem associated with our problem of interest is iteratively

solved using an ad-hoc preconditioner proposed in this thesis. Finally, from the CFD results we identify some hemodynamic indices and we build scores based on these indices in order to assess their correlation with a premature onset of SVD using statistical tools.

In particular, this thesis is organized as follows:

- **Chapter 1:** We introduce the anatomy and physiology of the aortic valve, and the aortic valve disease. We describe the diagnosis and treatment of this valvular pathology, specially the aortic valve replacement treatment. We provide a detailed discussion on TAVI, which is the valve replacement technique on which we are interested in this thesis. We present SVD, which is the post-TAVI complication that we aim to investigate, focusing on its underlying mechanisms and clinical risk factors. We conclude by listing some highlights of the chapter that are essential to understand the models and analyses presented in this thesis;
- **Chapter 2:** We present the state of the art in computational modeling relevant to the thesis. In particular, we focus on computational models for clinical applications in general, computational models applied in the TAVI context, and computational models studying SVD specifically. We conclude by discussing the objectives of the thesis, detailing the methodologies used and the novelties introduced by this thesis;
- **Chapter 3:** We deal with the pre-processing of the available data, i.e. the techniques used to generate the inputs of the numerical simulations. Specifically, we present: the available clinical data; the creation of the bio-prosthetic valve model; the building of the post-TAVI virtual geometries, together with a qualitative validation against post-TAVI CT scans; the generation of the associated computational mesh, focusing on the mesh sensitivity analysis employed to fix the mesh details; the derivation, from Echo Doppler data, of the personalized flow rate profile prescribed in the numerical simulations;
- **Chapter 4:** We discuss the mathematical model and numerical methods used in this thesis to numerically simulate post-TAVI hemodynamics. In particular, we present the Navier-Stokes problem considered to model hemodynamics with a moving immersed surface, and the strategy to model leaflets dynamics. Additionally, we deal with the temporal and spatial discretization of the problem, presenting an ad-hoc weak formulation used to impose an average flow rate boundary condition;
- **Chapter 5:** We propose and analyze two block preconditioners, derived from a standard Navier-Stokes preconditioner, for the numerical solution of the algebraic problem of interest. In the numerical results section we highlight the advantages of

prescribing an average flow rate condition instead of a Dirichlet (velocity) condition, and we extensively test the performance of the two proposed preconditioner in both idealized and real life scenarios;

- **Chapter 6:** We present a general analysis of the post-TAVI hemodynamics obtained with two different CFD models, which are detailed in the chapter. We validate the numerical results against Echo Doppler data, showing that both CFD models are associated with a good quantitative agreement with the clinical data. We analyze the obtained hemodynamic patterns in presence of a small size TAVI valves which show the formation of a high-velocity jet and vortical structures in the aorta leading to disturbed hemodynamics possibly influencing the development of SVD. Lastly, we compare the numerical results obtained with the two CFD models;
- **Chapter 7:** We analyze the numerical results with the aim of identifying a premature onset of SVD. In particular, we discuss the definition of SVD adopted in this thesis, we propose some computational hemodynamic indices and associated scores that show statistically significant differences between patients with and without SVD, and we define a synthetic scoring system able to clearly separate between the two sub-populations of patients;
- **Chapter 8:** We provide some final remarks on the analysis presented in the thesis and we list the main limitations of this work.

1 | The pathophysiology of the aortic valve: treatments and open questions

This chapter provides the medical background needed to contextualize the thesis. In particular, we introduce the anatomy and physiology of the aortic valve (Section 1.1), and its pathology (Section 1.2); we provide an overview on the clinical routines regarding the diagnosis and treatment of the aortic valve disease (Section 1.3); we go into detail on Transcatheter Aortic Valve Implantation, a minimally-invasive treatment of severe aortic valve disease (Section 1.4), and on Structural Valve Deterioration, a pathology affecting the bio-prosthetic valves used in this intervention (Section 1.5).

1.1. Aortic valve: anatomy and physiology

The aortic valve is located between the Left Ventricle (LV) and the aorta, at the end of the *Left Ventricular Outflow Tract* (LVOT). It usually has three semilunar cusps, or leaflets, with 1-2% of the population congenitally having a bicuspid (two leaflets) aortic valve [213]. The cusps are made of *ExtraCellular Matrix* (ECM), *Valve Interstitial Cells* (VICs), and *Valve Endothelial Cells* (VECs). Specifically, the highly organized ECM is stratified into three distinct layers: a collagen-rich layer on the aortic side providing tensile stiffness (fibrosa), an elastin-rich layer on the ventricular side facilitating tissue motion (ventricularis), and a proteoglycan-rich layer connecting the collagen and elastin fibers (spongiosa) [115]. VICs reside within the cusp core and can be activated to produce and remodel the ECM, contributing to maintain its integrity. VECs form a single protective layer between VICs and the hemodynamic environment able to sense and respond to mechanical stimuli [124, 263] (see Figure 1.1). Additionally, the aortic valve comprises also the aortic annulus, a crown-shaped fibrous support apparatus at the site of cusps insertion in the aortic wall.

The aortic valve is part of the aortic root, together with the *sinuses of Valsalva* and the

6 1| The pathophysiology of the aortic valve: treatments and open questions

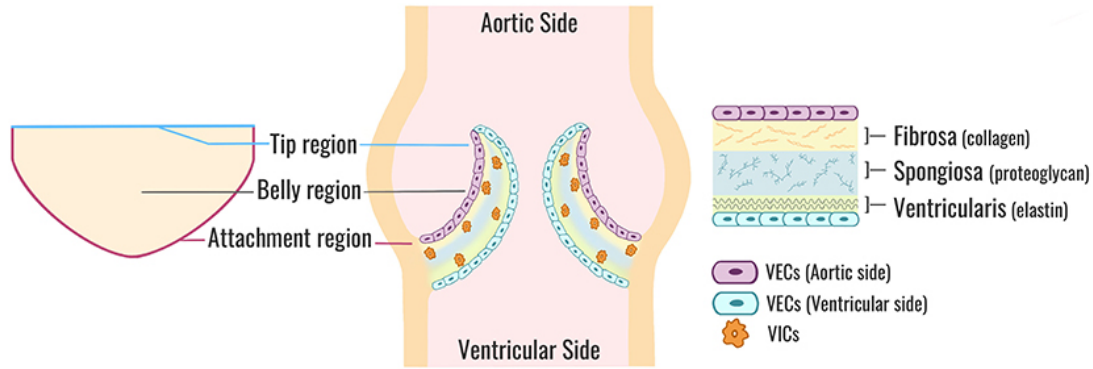


Figure 1.1: Structure of the aortic valve cusps. The ECM is made of three layers: fibrosa (aortic side), ventricularis (ventricular side), spongiosa (in-between). VICs live in the cusp core whereas VECs act as a protective layer surrounding the cusp. ECM: extracellular matrix; VICs: valve interstitial cells; VECs: valve endothelial cells. Image taken from Kazik, Kandail, LaDisa and Lincoln [124] under CC BY license.

SinoTubular Junction (STJ). The former are outward pouches of the aortic root, located behind each aortic valve cusp, from where the coronary branches originate. Accordingly, the cusps are often named left-coronary cusp, right-coronary cusp, and non-coronary cusp. Finally, the STJ represents the intersection between the sinuses of Valsalva and the ascending aorta.

The role of the aortic valve is to act as a one-way door regulating the blood flow from the LV to the coronary and systemic circulations, that provide oxygenated blood to each muscle of the human body. Ventricular contraction (systole) generates a positive pressure gradient between the LV and the aorta which opens the valve, allowing blood to flow into the aortic root (see Figure 1.2). The presence of the sinuses of Valsalva gives rise to the formation of vortices behind the open cusps preventing the leaflets from touching the aortic root wall, which would possibly diminish the coronary flow [163]. On the other hand, ventricular relaxation (diastole) results in a pressure drop in the ventricle that leads to a reverse flow which closes the valve (see Figure 1.2). The closure is facilitated by the vortices in the sinuses and the detachment of the leaflets from the wall, requiring only very little reversed flow to seal the valve [21, 22].

In physiological conditions the aortic valve is fully open during systole, allowing blood to effectively reach the periphery, and fully closed during diastole, preventing blood from returning into the LV. However, the human heart performs approximately 100,000 cycles per day [209] and the aortic valve is subject to alternate and severe pressure gradients during each cycle, making it prone to deterioration over time.

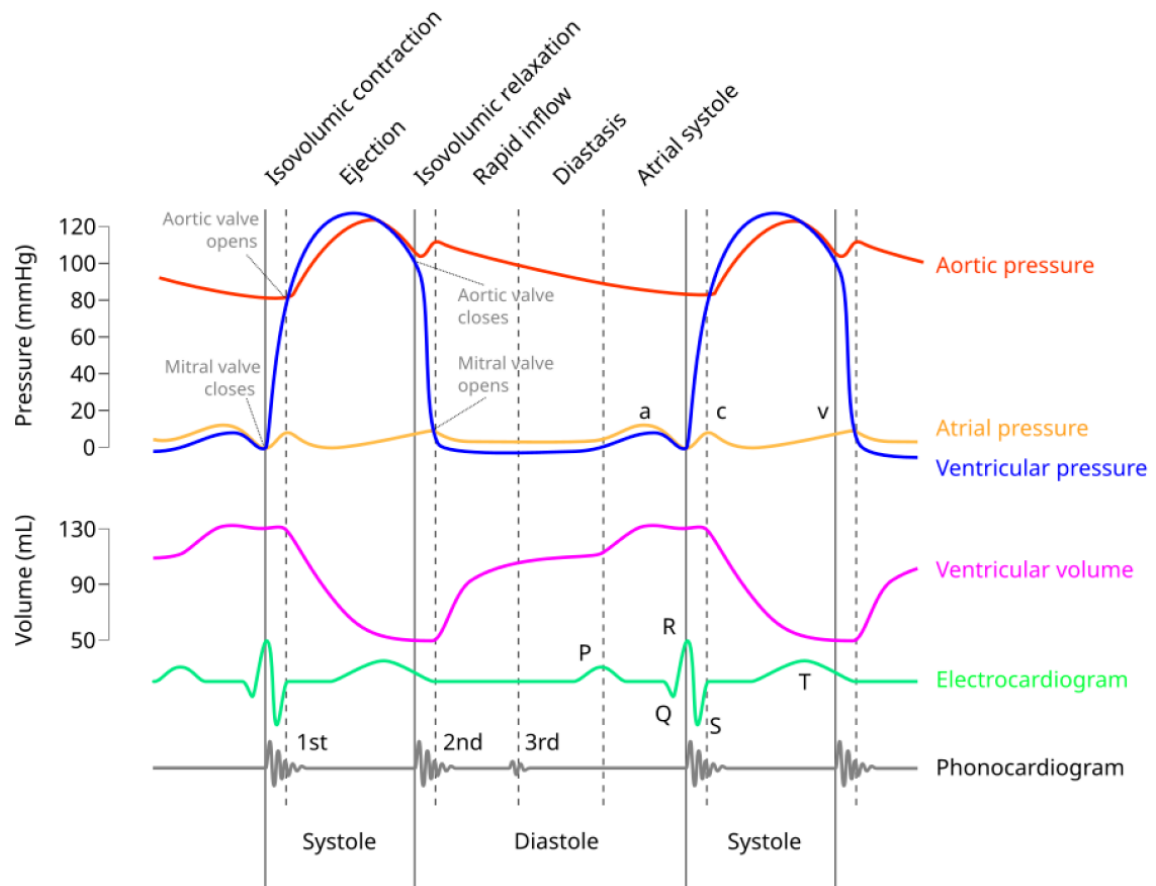


Figure 1.2: A Wiggers diagram, showing the cardiac cycle events occurring in the left ventricle. Specifically, the instants of aortic valve opening and closure. Image taken from [257] under CC BY-SA 4.0 license.

1.2. Aortic valve disease

The aortic valve disease manifests itself as *aortic stenosis*, i.e. an obstruction to flow, and/or as *aortic regurgitation*, i.e. a backward leakage. This pathology can ultimately lead to heart failure or even sudden death [172]. In particular, if not treated, the 5-year mortality of aortic valve disease is estimated from 50% to 80% [235].

Aortic stenosis is a pathological narrowing of the aortic valve opening area that can lead to a significant pressure loss across the valve, requiring additional work for the heart to effectively pump blood into the circulation. This results in a thickening and stiffening of the cardiac muscle (hypertrophy) associated to a high pressure in the LV that can cause symptoms such as shortness of breath, chest pain, and dizziness. Aortic stenosis is the most common valvular pathology in developed countries, with around 9 million cases worldwide, and its prevalence is increasing [7]. It can be caused by congenital

abnormalities of the valve, such as the presence of two cusps, or by calcium and scar tissue buildup.

Aortic regurgitation is a diastolic leakage into the LV due to a non-complete closure of the aortic valve. The cardiac muscle is able to adjust to the volume of blood re-entering the LV through remodeling, however long-standing regurgitation can result in an irreversible damage to the muscle. Aortic regurgitation can remain asymptomatic for many years before leading to symptoms such as shortness of breath or chest discomfort. It can be due to abnormalities of the aortic valve and root or to an atherosclerotic degeneration of the valve.

Due to the aging populations, the most common cause of aortic stenosis and regurgitation is *Calcific Aortic Valve Disease* (CAVD), i.e. the progressive formation of calcium deposits in the aortic valve cusps [84, 172]. The prevalence of CAVD has increased by 150% in the last thirty years and is now more than 1.000 per 100.000 beyond the age of 75 years [205].

CAVD is thought to be an active process characterized by lipoprotein deposition, chronic inflammation, and active leaflet calcification which ultimately leads to an impaired leaflet motion (see Figure 1.3). An endothelial disruption due to high mechanical and low shear stresses acting on the aortic valve leaflets is thought to have a crucial role in initiating the calcification process [93]. Specifically, the hemodynamic environment can cause an increased endothelial permeability which results in the diffusion of cells into the valve leaflets that subsequently initiate a phenotypic switch of quiescent VICs to a myofibroblast-phenotype, promoting aortic valve sclerosis. Aortic valve sclerosis is the thickening and stiffening of the leaflets and can lead to stenosis through active processes of biomineralization and ossification of cells derived from modified VECs and activated VICs [263].

According to the mechanisms underlying CAVD, we conclude this section by stating that aortic root hemodynamics have an influence on the calcification process.

1.3. Diagnosis and treatment of aortic valve disease

In absence of specific citations, all the information reported in this section are extracted from the latest European guidelines for the management of valvular heart disease [185].

In the following we introduce *echocardiography*, a common diagnostic tool for aortic valve disease (Section 1.3.1); we discuss the diagnosis and suggested treatments for aortic stenosis (Section 1.3.2) and for aortic regurgitation (Section 1.3.3); finally, we present aortic valve replacement techniques, the most common treatment choices in case of severe aortic valve disease (Section 1.3.4).

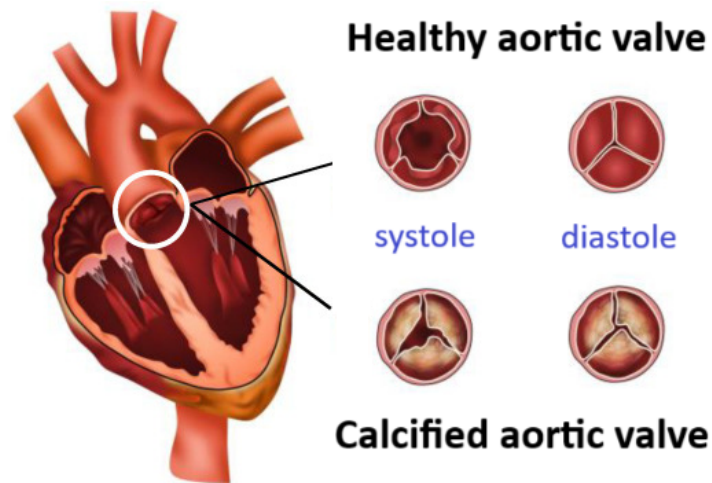


Figure 1.3: Open and closed aortic valve configurations both in physiological condition and in presence of calcific aortic valve disease. Image taken from Hanna, Armour, Yun Xu, and Gibbs [110] under CC BY license and modified

1.3.1. Echocardiography

The key diagnostic examination for aortic valve disease is echocardiography. This technique is based on ultrasound waves that are sent into the patient's chest by a transducer and received back by the same transducer after reflecting off the encountered tissue. A computer processes the reflected waves based on their intensity to generate dynamic pictures of the heart's chambers and valves. This allows for an assessment of the LV function, and of the aortic valve leaflets thickness and motion.

Echocardiography can be used in combination with Doppler techniques to measure the blood velocity by detecting the oscillation in frequency between emitted and reflected ultrasound signals. In particular, in this thesis we exploit data obtained with two Doppler echocardiographic modalities: *Continuous Wave* (CW) Doppler and *Pulsed Wave* (PW) Doppler.

In CW Doppler, within the same transducer two separate crystals are used to continuously emit and receive ultrasound waves in order to measure blood velocities along the entire length of the ultrasound beam. This technique does not have any limitation on recordable velocities, allowing for accurate measurements of high velocities. However, the signal is not gated, i.e. it receives all underlying velocities, thus it cannot provide information on the specific location where the velocity was measured [194].

In PW Doppler, a single crystal sends short pulses of ultrasound and then waits to receive the returning echos in order to measure the blood velocity in a small area at a specified

depth from the transducer. Thus, this technique provides information on the specific location where the velocity was measured. However, due to the intermittency of the ultrasounds, the signal is subject to aliasing, not allowing for accurate measurements of high velocities [194].

Depending on where the transducer is placed to emit and receive the ultrasound waves, echocardiographic techniques can be divided into: *Transthoracic Echocardiography* (TTE), *Transesophageal Echocardiography* (TEE), and *Intracardiac Echocardiography* (ICE).

TTE consists in the placement of the transducer on the patient's skin and it is often the first-choice thanks to its non-invasive nature. However, it could result in a poor image quality due to an inadequate patient's acoustic window.

In case of poor TTE image quality, the minimally-invasive TEE is usually employed. In this technique the transducer is inserted into the esophagus by means of an endoscope, allowing for better quality images.

Finally, in ICE the transducer is mounted on a catheter that is then guided inside the patient's heart following a venous access. This results in high-quality images of the cardiac structures and it is often used during catheter-based procedures. ICE is the most invasive technique between the ones presented, hence TTE and TEE are usually preferred for diagnostic purposes.

Let us highlight already at this stage that in this thesis we leverage data coming from Doppler TTE. Accordingly, we report in Figure 1.4 an example of a Doppler TTE assessment of aortic stenosis. In particular, PW Doppler TTE is used to measure the blood velocity at the center of the LVOT, which is not particularly high, thus avoiding aliasing effects. Additionally, CW Doppler TTE is used to measure the blood velocity along a beam passing through the center of the aortic valve, since high velocity magnitude values are expected in this region.

1.3.2. Aortic stenosis: diagnosis and treatment

In case of suspected aortic stenosis, echocardiography is exploited to assess valve calcification and LV function. Additionally, a Doppler echocardiographic evaluation of aortic stenosis is performed based on the peak transvalvular blood velocity, the mean pressure gradient across the valve, and the valve area. Specifically, the maximum transvalvular blood velocity in different instants of the cardiac cycle can be directly measured with CW Doppler ultrasounds (see Figure 1.4-Top right). These measurements are then used to compute the mean pressure gradient across the valve using a simplified Bernoulli equa-

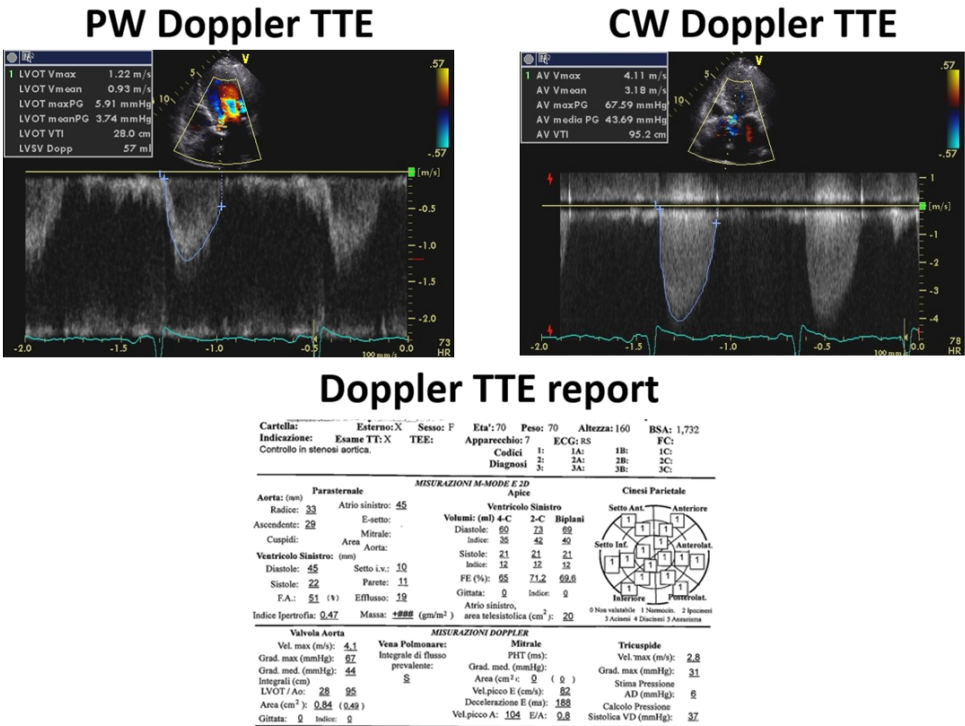


Figure 1.4: Doppler Transthoracic Echocardiographic assessment of aortic stenosis. Top left: PW Doppler TTE image with measurement of the blood velocity at the center of the LVOT for multiple heartbeats. Top right: CW Doppler TTE image with measurement of the blood velocity through the aortic valve for multiple heartbeats. Bottom: complete Doppler TTE report.

tion and the valve area using the continuity equation [20]. For the latter computation the blood velocity inside the LVOT and the diameter of the LVOT are needed and measured from PW Doppler echocardiography (see Figure 1.4-Top left). Severe aortic stenosis is unequivocally identified by a peak transvalvular velocity higher than 4 m/s , a mean pressure gradient higher than 40 mmHg , and a valve area smaller than 1 cm^2 , which is the case in the example shown in Figure 1.4.

In the clinical practice, aortic stenosis can be defined as *severe* even if the latter conditions are not satisfied. In this case several additional parameters should be taken into account for a proper assessment of aortic stenosis, such as the LV function, the Doppler velocity index, the degree of valve calcification, and the presence of LV hypertrophy. Specifically, clinicians often rely on Computed Tomography (CT) for a description of the anatomy and calcification of the aortic root and ascending aorta. Furthermore, in case of percutaneous interventions CT is crucial for the pre-operative planning.

A valve replacement intervention is recommended for all patients with symptomatic severe

aortic stenosis who would likely benefit from the procedure. Additionally, an intervention is also advised in the asymptomatic case under certain conditions: severe aortic stenosis with a LV ejection fraction smaller than 50%; severe aortic stenosis, LV ejection fraction greater than 50%, low procedural risk and stenosis is very severe, or valve calcification is severe, or LV ejection fraction smaller than 55%; severe aortic stenosis and a blood pressure fall greater than 20 *mmHg* during exercise [185].

1.3.3. Aortic regurgitation: diagnosis and treatment

For the identification of aortic regurgitation, echocardiography is used to have a description of the aortic valve anatomy and the morphology of the aorta. Specifically, the three main mechanisms of aortic regurgitation are: normal cusps but insufficient coaptation due to dilatation of the aortic root, cusp prolapse, and retraction with poor cusp tissue quality. An integrated approach exploiting qualitative and quantitative parameters is followed to quantify aortic regurgitation. Echocardiography is also useful to assess the patient's suitability for valve repair.

In case of equivocal echocardiographic measurements, Magnetic Resonance Imaging (MRI) is advised to quantify the regurgitant fraction. This technique can be also used for a follow-up exam, whereas for surgical planning CT should be preferred.

An intervention is recommended for symptomatic patients with severe aortic regurgitation at a non-prohibitive surgical risk. In the other cases indications for surgery depend on symptoms, status of the LV, and dilatation of the aorta. There exist different procedures to treat aortic regurgitation, such as aortic valve replacement, aortic valve-sparing root replacement, and valve repair. A choice between such possible interventions should be made according to the presence of an aortic root aneurysm, the characteristics of the cusps, and the patient's life expectancy. For patients who are deemed unsuitable for an intervention, a medical therapy is advised.

Finally, an intervention is also recommended in case of mixed moderate aortic stenosis and moderate aortic regurgitation in symptomatic patients with a mean pressure gradient greater than 40 *mmHg* or a peak transvalvular blood velocity greater than 4 *m/s*, and in asymptomatic patients with a peak transvalvular blood velocity greater than 4 *m/s* and a LV ejection fraction smaller than 50% [185].

1.3.4. Aortic valve replacement

We focus here on *aortic valve replacement*, which is the most used intervention in case of severe aortic stenosis or regurgitation.

This procedure consists in the replacement of the native aortic valve with a prosthetic valve, aiming to restore the valve's functionality. Specifically, prosthetic valves can be either *Mechanical Heart Valves* (MHV) or *Biological Heart Valves* (BHV).

MHV can only be surgically implanted and are made of pyrolytic carbon, various polymers, and metal alloys. Different MHV types have been produced over the years, such as caged ball valves, tilting disk valves, and bileaflet valves [102] (see Figure 1.5). These valves lead to non-physiological hemodynamics in the valve region due to a design that does not mimic the real native valve. Moreover, they are associated to a high risk of thrombosis, so that lifelong anticoagulation medications need to be prescribed to their recipients. On the other hand, being made of resistant materials, MHV show excellent durability properties [128]. Current guidelines suggest the use of MHV for patients at risk of accelerated BHV deterioration and accept it for young patients (less than 60 years old) or in patients already on anticoagulation because of other implanted MHV [185].



Figure 1.5: Types of mechanical heart valves. Left: caged ball valve (Starr Edwards); Center: tilting disk valve (Medtronic Hall); Right: bileaflet valve (St. Jude Medical). Images taken from Leviner, Abraham, Ronai and Sharoni [137] under CC BY license and modified.

BHV are prosthetic valves whose leaflets are derived from animal or human tissue. In particular, xenografts are made of chemically stabilized tissues of animal origin, homografts are made of human tissue taken from donors and autografts are made of the patient's own tissue. BHV can be implanted both surgically and via minimally-invasive transcatheter techniques. The surgical valves can be either stented, i.e. mounted on an external rigid/flexible stent, or stentless (see Figure 1.6). Whereas transcatheter valves

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are always stented (see Section 1.4). BHV do not require anticoagulation medications and are characterized by excellent hemodynamic properties, however their durability is undermined by *Structural Valve Deterioration* (SVD) (see Section 1.5), which eventually leads to the failure of the implanted valves and requires to redo the intervention [128]. The use of BHV is suggested for those patients unsuitable for anticoagulation and it is accepted for elderly patients (more than 65 years old) [185].

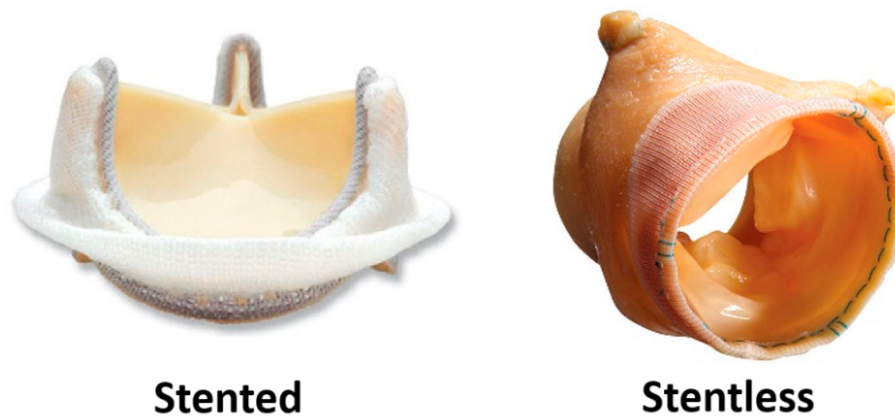


Figure 1.6: Types of surgically implantable biological heart valves. Left: stented valve (Edwards PERIMOUNT); Right: stentless valve (Medtronic Freestyle). Images taken from Tabssum, Phillips, Hage and Hage [224] under CC BY license and modified.

There are two alternative techniques for the implantation of BHV: *Surgical Aortic Valve Replacement* (SAVR) and *Transcatheter Aortic Valve Implantation* (TAVI).

SAVR represents the gold standard of aortic valve replacement, with the first successful intervention being performed by Dr. Dwight Harken in 1960 [112] revolutionizing the treatment of severe aortic disease. Prior to the SAVR procedure the patient has to be sedated through general anesthesia. Then, a surgeon replace the native aortic valve with a prosthesis after performing an incision in the middle of the chest and accessing the heart by separating the breastbone. Furthermore, during the procedure the patient is connected to a heart-lung machine which takes over the cardiac pumping and pulmonary oxygenation activities. Being a highly invasive technique, SAVR is characterized by an increased surgical risk, thus it is not suitable for patients with significant comorbidities.

TAVI has been introduced with the purpose of treating patients unsuitable for SAVR and is recently becoming more and more appealing in the clinical world thanks to improved performances and its minimally-invasive nature. Since this thesis is completely devoted to TAVI, we dedicate a separate section to discuss in depth this technique (see Section 1.4).

1.4. Transcatheter Aortic Valve Implantation

In the following we give a general description of the TAVI procedure (Section 1.4.1); we discuss the adoption of this technique in the clinical practice during the years (Section 1.4.2); finally, we present the main complications associated to this intervention (Section 1.4.3).

1.4.1. General description of TAVI

TAVI is a minimally-invasive technique for the treatment of severe aortic valve disease. It consists in the deployment via catheter of a BHV in place of the native aortic valve without its removal (see Figure 1.7), as opposed to SAVR. Indeed, the native valve's leaflets are only pushed aside by the inserted prosthesis which is anchored to the native annulus.

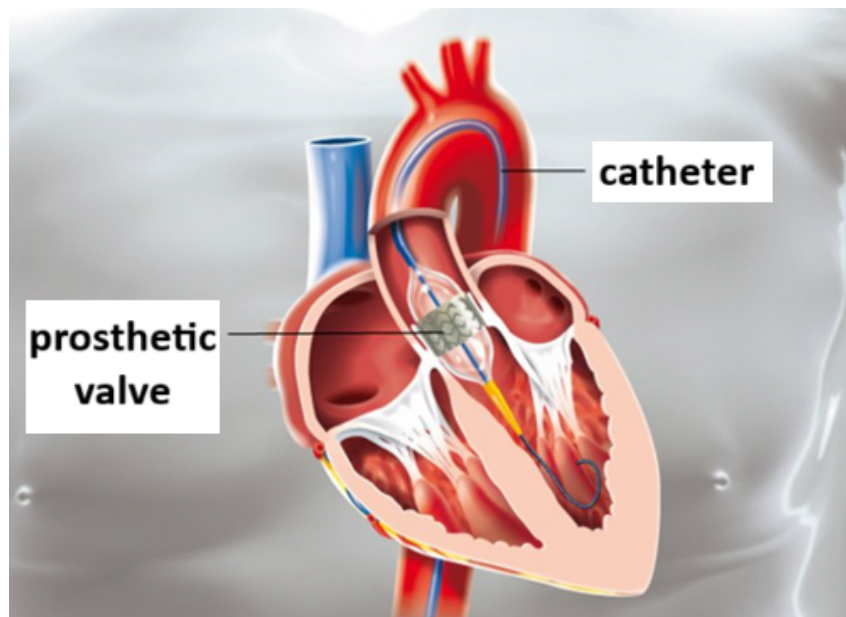


Figure 1.7: TAVI procedure: deployment via catheter of a bio-prosthetic valve in place of the native one. Images taken <https://ccibelledonne.com/en/patient-guide/transcatheter-aortic-valve-implantation-tavi/> and modified.

The BHV is first crimped into a delivery system within a catheter which is then guided in the aortic annulus following a wire. In severely calcified cases, a balloon valvuloplasty can be performed before delivering the prosthesis. A trans-femoral access for the catheter is recommended as first-choice by all guidelines thanks to its minimal invasiveness. Nonetheless, in up to 15–20% of TAVI candidates this is not possible due to existing pathologies or vessels anatomy, thus alternative access routes are considered, e.g. trans-aortic, trans-

apical, trans-carotid, and trans-septal [30].

The prosthetic valves used for TAVI are referred to as *Transcatheter Heart Valves* (THV). These are stented BHV that can be divided into balloon-expandable valves and self-expandable valves (see Figure 1.8). Specifically, balloon-expandable valves are mounted on an elasto-plastic stent (stainless steel, chromium-cobalt) and need to be deployed with the inflation of a balloon in order to obtain their expected shape. On the other hand, this is not the case for self-expandable valves thanks to the shape-memory properties of their super-elastic stent (nitinol).

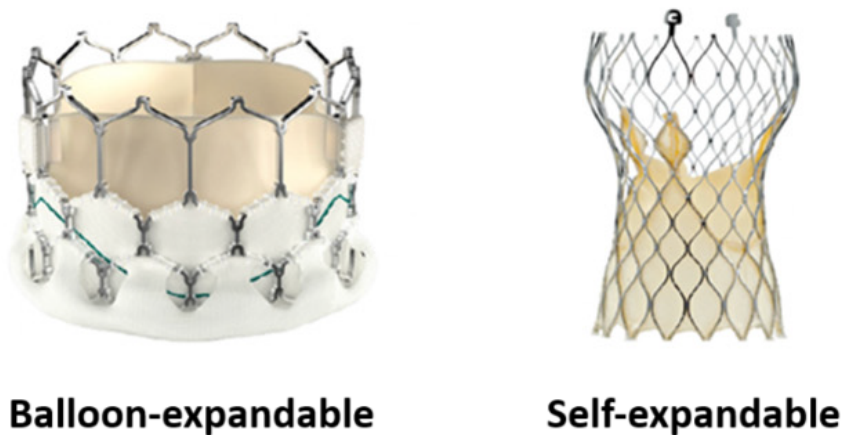


Figure 1.8: Types of transcatheter heart valves. Left: balloon-expandable valve (Meril Life Sciences Myval THV); Right: self-expanding valve (Medtronic Evolut R). Images taken from Barki, Ielasi, Buono, et al [18] under CC BY license and modified.

1.4.2. History of TAVI

Clinical outcomes TAVI was first performed in human by Dr. Cribier in 2002 and was initially only used in compassionate cases, having a 30 days mortality rate of 20% [82]. Moving forward, the outcomes of this procedure drastically improved due to the experience gained by clinicians and the technological advancements of the prostheses.

Specifically, firstly the feasibility of the TAVI procedure was demonstrated in patients unsuitable for surgery with both balloon expandable [56] and self-expandable [104] valves considering a trans-femoral access, and with balloon-expandable valves considering a trans-apical access [250]. Then, TAVI with both type of valves was shown to represent a valid alternative to open heart surgery in high-surgical-risk patients [105, 254]. Following this series of clinical trials, the first TAVI devices, Edwards SAPIEN and Medtronic CoreValve, were approved in the European market in 2007 [82].

In the early 2010s, the PARTNER 1B [134] clinical trial showed that TAVI with balloon-expandable valves (Edwards SAPIEN) outperformed standard medical therapy in patients who were not suitable for surgery. Additionally, the PARTNER 1A [214] and CoreValve HR [2] clinical trials showed that TAVI was not inferior to SAVR in patients at high-risk for surgery with balloon-expandable (Edwards SAPIEN) and self-expandable (Medtronic CoreValve) valves, respectively. This led to the approval of these TAVI devices in the American market from 2012 [82].

In the late 2010s, the PARTNER 2A [135] and SURTAVI [193] clinical trials showed that TAVI had similar outcomes with respect to SAVR in patients at intermediate-risk for surgery with balloon-expandable (Edwards SAPIEN XT) and self-expandable (Medtronic CoreValve, Evolut R) valves, respectively. More recently, the PARTNER 3 [148] and the Evolut LR [184] clinical trials showed the TAVI was not inferior to SAVR in patients at low-risk for surgery with balloon-expandable (Edwards SAPIEN 3) and self-expandable (Medtronic CoreValve, Evolut R, Evolut PRO) valves, respectively. Moreover, an update after 5 years of the PARTNER 3 clinical trial [149] and an update after 4 years of the Evolut LR clinical trial [91] confirmed the non inferiority of TAVI with respect to SAVR in low-surgical-risk patients.

Devices development A significant development of the TAVI devices is the main driver for the improved clinical outcomes of this procedure through the years. In this paragraph we focus on the balloon-expandable valves manufactured by Edwards Lifesciences and the self-expandable valves manufactured by Medtronic, as these valves have been subject to several improvements in the last twenty years. Nonetheless, valves manufactured by different companies have nowadays been employed for TAVI.

As for the balloon-expandable valves, the first TAVI devices consisted of three bovine pericardial leaflets mounted on a stainless steel balloon-expandable stent and were implanted with a trans-femoral access using a 24 *Fr* sheath. These devices showed a high incidence of paravalvular regurgitation, thus the Edwards SAPIEN valve was developed, including a sewn polyethylene terephthalate (PET) fabric on the internal face of the stent in its ventricular side. The Edwards SAPIEN was extensively tested in the PARTNER 1 clinical trials revealing the occurrence of cerebrovascular events and vascular complications. In order to address these issues, a further refinement of this technology led to the introduction of the Edwards SAPIEN XT valve. This valve is made of a cobalt-chromium frame with an open-cell design facilitating coronary access and can be implanted using a 18 – 19 *Fr* sheath, thus decreasing the risk of vascular complications. The Edwards SAPIEN 3 represents a further refinement of this technology characterized by a smaller

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crimping profile, a longer cobalt-chromium open-cell stent frame, and an additional external PET skirt to reduce the incidence of paravalvular regurgitation. Lastly, Edwards introduced the SAPIEN 3 Ultra with a taller external PET skirt and the SAPIEN 3 Ultra RESILIA with an anti-calcification tissue technology [37].

Regarding the self-expandable valves, the CoreValve, incorporating porcine pericardial leaflets mounted on a nitinol frame and a pericardial skirt, was the first device developed by Medtronic and can be implanted using a 18 *Fr* delivery system. The first refinement of this technology is the Medtronic CoreValve Evolut R, showing a shorter nitinol frame to better fit in tortuous anatomies and increased radial force to optimize annular sealing. Other improvements are related to the chemical treatment of the porcine pericardium to reduce leaflet calcification, and a lower delivery profile (14 – 16 *Fr*). In an effort to decrease the incidence of paravalvular regurgitation, the CoreValve Evolut Pro valve has been introduced with an additional external porcine pericardial tissue wrap [37]. Finally, the CoreValve Evolut PRO+, Evolut FX, and Evolut FX+ have been recently developed to obtain an advanced sealing, to improve control during the TAVI procedure, and to enhance coronary access, respectively.

Clinical guidelines Thanks to the continuous technological and clinical improvements and the minimally-invasive nature of this technique, TAVI is now often the preferred option for the treatment of severe aortic valve disease across the whole spectrum of surgical risk [229]. Specifically, European guidelines recommend TAVI for all patients older than 70 years with a tricuspid valve and a suitable anatomy; recommend SAVR for patients younger than 70 years at low-risk for surgery; and accept both techniques in all the other cases [185]. Furthermore, American guidelines recommend TAVI for all patients older than 80 years, with a life expectancy shorter than 10 years, or unsuitable/at high-risk for surgery; recommend SAVR for patients younger than 65 years, with a life expectancy longer than 20 years or unsuitable for TAVI; and accept both techniques in all the other cases [157].

1.4.3. Complications after TAVI

Due to the relative young age of TAVI and the limited life expectancy of its original recipients, there is a reduced availability of long-term follow-up data regarding this intervention. This makes it difficult to properly assess the long-term durability of TAVI valves. In particular, the durability of TAVI valves is limited by both short-term and long-term complications, and in this thesis we are interested in their long-term degeneration.

Short-term complications The short-term procedural complications comprise stroke, conduction abnormalities, vascular complications, paravalvular leakage, and coronary obstruction [17].

Post-procedural stroke often occurs within 72 hours after the intervention and is mainly due to procedural embolization [123].

Conduction abnormalities requiring a permanent pacemaker implant, mainly result from the mechanical stresses exerted from the conduction system during TAVI; newer generation prostheses together with an higher implantation site reduced the incidence of these abnormalities, which are still the most common complication after TAVI [14].

Vascular complications resulting from the percutaneous insertion of the catheter were frequent events with first-generation delivery systems [98], but their occurrence was significantly reduced thanks to the use of smaller systems allowed by newer valve designs [210].

Paravalvular leakage or regurgitation is due to a suboptimal sealing of the BHV in the native aortic annulus and it used to develop after 10-25% of TAVI procedures; however refinements in valve sizing, procedural planning and prosthesis design, such as the introduction of external skirts, reduced the incidence of this complication [17].

Coronary obstruction after TAVI is an infrequent but life-threatening complication [198] and can be caused by the native valve leaflets being pushed against the coronary ostia or by the bio-prosthetic leaflets preventing blood to flow from the ascending aorta to the coronary sinuses [17].

More specifically, conduction abnormalities and paravalvular leakage are more frequent with self-expandable valves than with balloon-expandable valves [60, 240], whereas the vice-versa holds true for coronary obstruction [197]. Nonetheless, clinical studies showed equivalent performance in terms of mortality between self-expandable and balloon-expandable valves [233, 241, 256].

Long-term complications The main long-term complication related to TAVI is the degeneration or failure of THV that can be caused by leaflet thrombosis or *Structural Valve Deterioration* (SVD). In particular, in case of a failed prosthesis re-intervention is needed and the gold standard is redo-SAVR, but the valve-in-valve TAVI procedure has been recently introduced showing promising results [165]. This technique consists in the transcatheter implantation of a THV inside an existing prosthesis [247].

Leaflet thrombosis is defined as the formation of blood clots on the THV biological leaflets

and its incidence is reported as 13% after TAVI. However, the incidence of clinically relevant thrombosis, i.e. leading to symptoms related to valve stenosis, is around 2.8% after TAVI and 7.6% after valve-in-valve TAVI. Moreover, leaflet thrombosis may be treated with anticoagulation [158].

SVD is a gradual degenerative process which is intrinsic to all BHV, also the surgically implanted ones, and eventually leads to the failure of the bio-prosthetic valves [128]. Being an inevitable complication, the incidence of SVD has not been particularly reduced by the technological and procedural developments obtained in the TAVI framework. However, it is important to study its pathogenesis to explain and possibly predict the onset of this pathology, allowing for a timely diagnosis and treatment. In this thesis we focus on SVD, thus its definition, underlying mechanisms, and associated risk factors are detailed in Section 1.5.

1.5. Structural Valve Deterioration

SVD is the main limiting factor to the long-term durability of BHV (10 to 15 years) [55]. This is an intrinsic degenerative process characterized by irreversible modifications in the bio-prosthetic valve, such as connective tissue delamination, pannus growth, fibrosis and calcification of the leaflets, and leaflet perforation and tear (see Figure 1.9). This process eventually leads to the hemodynamic failure of the implanted valve due to stenosis or regurgitation [128]. SVD is particularly relevant in the TAVI context and may limit the use of this technique, because of the reduced durability of the implanted valves. For this reason, in this thesis we focus on SVD in TAVI valves to understand its underlying mechanisms and potentially predict its onset.

Definition and diagnosis of SVD The clinical definition of valve deterioration often differs between studies, preventing a fair comparison of the long-term durability of different bio-prosthetic valves. This becomes even more relevant when comparing surgical and transcatheter BHV, for which SVD is a shared pathology. In particular, many clinical studies have freedom from re-intervention as primary endpoint, which is an inaccurate indicator of SVD occurrence. Indeed, SVD is not the only possible cause for re-intervention and patients having many comorbidities with a failed BHV would likely not be re-operated or considered only for TAVI, potentially leading to an underestimation of the long-term durability of THV [72].

To overcome this issue, Dvir et al proposed a standardized definition of SVD [72], which does not depend on the patient's clinical status, but on the implanted valve's one. In

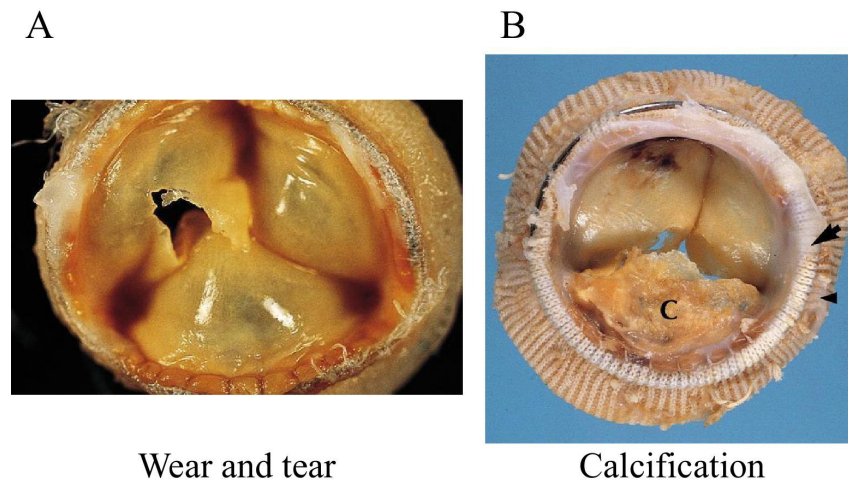


Figure 1.9: Different manifestations of structural valve deterioration in bio-prosthetic valves. (A) Leaflet wear and tear; (B) Calcific degeneration. Image taken from Piazza, Bleiziffer et al [181] with permission through Copyright Clearance Center. ©Elsevier.

particular, in order to characterize the time-dependent nature of the SVD process, which takes place over years, the authors defined different SVD stages. These stages span from a Stage 1 SVD defined as early morphological leaflet abnormalities without significant hemodynamic consequences to a Stage 3 SVD defined as the development of severe stenosis or regurgitation of the implanted valve.

According to these definitions, the key diagnostic tool for the identification of SVD in BHV is TTE. Specifically, a complete Doppler TTE analysis should be performed in each patient subject to SAVR or TAVI at discharge to have a baseline to compare with follow-up measurements. A comprehensive imaging of the bio-prosthetic valve components, transvalvular blood velocity, mean pressure gradient, valve orifice area and the presence of any prosthetic regurgitation are crucial for the assessment of BHV function. A TTE analysis is recommended yearly after TAVI [72], nonetheless patients often go for a follow-up only when symptoms occur. Furthermore, often the follow-up exam happens in a different center from where the TAVI intervention was performed, making it difficult to study the development of SVD and thus to understand its causes.

Underlying mechanisms of SVD The mechanisms underlying SVD pathogenesis are yet to be fully understood. This pathology was originally thought to be a passive degenerative process, but recent evidences suggest that the host immune response plays a crucial role in the development of SVD, characterized by active processes similar to transplant rejection, atherosclerosis, and calcification of native aortic valves [128].

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BHV are usually pre-treated with glutaraldehyde in order to fix the tissue, preventing its chemical and enzymatic degradation and decreasing the host immune response. However, this treatment causes cell death and the ECM provides calcium ions and a specific space structure allowing calcium to deposit in the cell debris. This makes bio-prosthetic leaflets highly susceptible to calcification [255].

Furthermore, implanted BHV are subject to sustained stresses, which may contribute to initiate the calcification process by damaging the bio-prosthetic leaflets structural integrity [229, 234]. A tissue damage is particularly dangerous in BHV, made of dead tissue, since they are lacking VICs that would be able to maintain leaflet integrity by producing and remodeling the ECM. Thus, BHV lifespan strictly depends on the durability of their chemically treated ECM [128].

A damage of the tissue increases its permeability, easing the infiltration of host-derived particles into the bio-prosthetic leaflets and promoting calcification. Specifically, an increase immune cell infiltration was found by comparing explanted BHV with and without SVD [38].

Clinical risk factors for SVD Several risk factors contributing to an early onset of SVD have been proposed in the literature, such as young age, patient-prosthesis mismatch, raised Body Surface Area (BSA), smoking, small prosthesis size, valve-in-valve procedure, female sex, small annulus size, hypertension, and abnormal calcium and lipid metabolism [72, 109, 196, 236].

Younger patients have a more vigorous immune system, further validating the hypothesis that immune response have a significant influence on the development of SVD [255].

Patient-prosthesis mismatch is defined as a valve opening area too small for the patient's size and depends on the effective opening area and the BSA. A severe patient-prosthesis mismatch often leads to increased pressure gradients across the prosthetic valve possibly accelerating the SVD rate [236].

The implantation of stented bio-prosthetic valves, such as THV, results in a narrowing of the lumen (stenosis up to 20%) with respect to the native case because of the space taken by the stent and the fabric sewing cuff [212]. Moreover, young age, raised (BSA), and smoking are all associated to a high cardiac output which, specially with a small valve opening area, leads to accelerated flow across the bio-prosthetic valve. Thus, this is thought to possibly be a common mechanism of bio-prosthetic valve degeneration [175].

The proposed mechanisms of SVD pathogenesis and its clinical risk factors suggest the influence of aortic hemodynamics on the development of SVD.

1.6. Highlights in view of TAVI modeling

In this thesis we develop a personalized computational model to numerically simulate post-TAVI blood-dynamics and we propose computational indices that correlate with a premature onset of SVD. In what follows we stress the main highlights reported in the previous sections with the aim of providing useful key points for the understanding of the subsequent model and analysis:

- CW and PW Doppler TTE, described in Section 1.3.1, are commonly used to assess post-TAVI hemodynamics;
- During TAVI a bio-prosthetic valve is deployed via catheter in place of the native aortic valve, without its removal (Section 1.4.1);
- TAVI has been nowadays extended to "young" patients (Section 1.4.2), thus it is crucial to assess the long-term durability of the bio-prosthetic valves used for TAVI;
- SVD is the main limiting factor to the durability of TAVI valves (Section 1.5);
- SVD has been associated with an increased infiltration of immune cells in the bio-prosthetic leaflets. In particular, the hemodynamic environment can facilitate leaflet infiltration by causing an endothelial disruption, analogously to what happens for the calcification of native aortic valves. Additionally, clinical risk factors for SVD further suggest a possible influence of hemodynamics on a premature onset of SVD (Section 1.5).

2 | State of the art and objectives

This chapter provides a detailed discussion on the state of the art in computational models relevant to the thesis. In particular, we give a general overview of computational modeling in clinical applications (Section 2.1); then we focus on computational models in the TAVI (Section 2.2) and in the SVD (Section 2.3) contexts; finally, we present the main objectives of the thesis (Section 2.4).

2.1. Computational modeling in clinical applications

Computational modeling is a technique where computers are used to simulate the behavior of a real-world system based on a mathematical model. This technique starts with an in-depth analysis of the physical system in order to identify the most important variables which influence its behavior. The system is then described using mathematical equations, regulating the relationship between the system's variables and possibly introducing simplifying assumptions. The resulting mathematical model is often characterized by a set of, possibly non-linear, partial differential equations for which an analytical solution is not available due to their complexity. For this reason, suitable numerical methods are introduced to approximate these equations and their solution. This allows for the implementation of an algorithm or code on a computer for the solution of the approximated equations and thus the simulation of the system's behavior. In particular, the accuracy of the computed system's behavior with respect to the real physical one depends both on the mathematical equations used to model the system and on the numerical methods used to approximate them [225].

There is currently a growing interest on computational modeling due to its ability to provide a detailed, quantitative description of complex physical phenomena that could be hardly investigated otherwise. Specifically, a system can be studied under different conditions just by changing the model parameters. This allows to easily investigate the impact of a certain condition on the overall behavior of the system or on some specific features. Additionally, computational modeling enables to predict the system's evolution, highlight the forecasting power of these models. Furthermore, in the industrial setting,

this approach often represents a quicker, cheaper and more sustainable alternative to experimental testing during the development of new products.

In this thesis we are particularly interested in computational models applied in the clinical setting. Clinical imaging techniques and measurements allow to assess the physiology and pathology of a patient, but often provide not very detailed information. On the other hand, computational modeling is able to investigate complex features that are impossible to be captured with standard clinical techniques and that can be relevant for a full assessment of the patient's present and future health. Moreover, in case of intervention, computational models can drive the development and the selection of different clinical devices based on their predicted performance or can be used to optimize the procedural settings [187].

Computational models are typically applied in the clinical setting to study one or multiple physical phenomena (blood-dynamics, electric signal propagation, mechanical deformation, etc) in a region of interest, which is a bounded region representing, e.g., a cardiovascular district, an organ, or a clinical device. The region of interest is usually referred to as computational domain and has to be discretized by generating a computational mesh in order to solve the approximated equations on the computer. Additionally, a set of *boundary conditions* have to be prescribed at the domain's boundary to surrogate the effect of the surrounding environment which is not part of the computational domain.

A biomedical computational study generally comprises the following steps:

- *Pre-processing*: deals with the inputs of the model, such as the computational domain, the computational mesh and the boundary conditions. In particular, a computational domain can be reconstructed from clinical images such as CT or MRI to provide a patient-specific description of the domain's geometry. A computational mesh can be subsequently obtained by discretizing the domain using, most commonly, triangular or quadrilateral elements in two dimensions and tetrahedral or hexahedral elements in three dimensions. Also boundary conditions can be obtained from clinical data to prescribe, e.g., a flow rate, a pressure, or a displacement, with the aim of further personalizing the numerical simulation;
- *Choice of the mathematical model and associated numerical methods*: A set of mathematical equations has to be chosen to represent the physics of interested, introducing simplifying assumptions and selecting the most suitable type of boundary conditions. Accordingly, the equations are then approximated using numerical methods based on the Finite Difference Method, the Finite Element Method (FEM), the Finite Volume Method, or the Spectral Element Method;

- *Numerical simulation*: resolution of the approximated equations using the computer;
- *Post-processing*: qualitative and quantitative analysis of the numerical results based on their visualization and on the derivation of significant features to gain a detailed understanding on the simulated scenario.

Several biomedical computational models can be found in the literature and their main applications are reported in the following. Computational models have been used to: study the deformation of bones [125, 176, 268] and the performance of bone-related devices [32, 227, 264]; investigate blood-dynamics in several arterial districts [48, 174, 219] and organs [64, 173, 208]; simulate the propagation of the electric signal in the heart muscle, focusing on the atria [69, 81, 258] on the ventricles [25, 228, 237], and on the whole heart [99, 101, 182]; describe the heart contraction [106, 155, 168].

2.2. Computational models for TAVI

In the following we focus on computational models for the implantation of the bio-prosthetic valve (Section 2.2.1) and for post-TAVI blood dynamics (Section 2.2.2); finally, we deal with models addressing different complications related to the TAVI procedure (see Section 2.2.3).

2.2.1. Implantation of the bio-prosthetic valve

In the TAVI context, computational modeling can be used to numerically simulate the implantation of the bio-prosthetic valve. In these simulations a bio-prosthetic valve model is initially crimped by reducing the stent size and subsequently expanded into a native valve model. According to the analyzed valve, the expansion can be achieved either by numerically simulating the inflation of a balloon placed coaxially to the valve (balloon-expandable valves) or by a gradual removal of the sleeve catheter (self-expandable valves) [46]. The numerical results provide the position and deformation of the prosthetic valve model after its expansion, and a description of the stress state of both the prosthetic and the native valve models [44]. Therefore, they can be used to investigate the outcomes of the TAVI procedure in order to possibly improve pre-procedural planning.

Bio-prosthetic valve implantation simulations can be performed considering a Finite Element Analysis (FEA) or a Fluid-Structure Interaction (FSI) framework. FEA refers to those computational approaches, based on FEM, performing structural numerical simulations by neglecting the presence of blood, which is surrogated using suitable pressure loadings. On the other hand, FSI accounts for the interaction between blood and the

implanted device, thus providing more accurate results at the price of a higher computational cost. The assumption of neglecting the presence of blood is widely accepted in the literature and justified by the high speed of deployment of balloon-expandable valves. Nonetheless, an FSI approach should be preferred in case of self-expandable valves due to their slower deployment and possible migration caused by blood pressure [248]. An example of the results of an implantation simulation is reported in Figure 2.1.

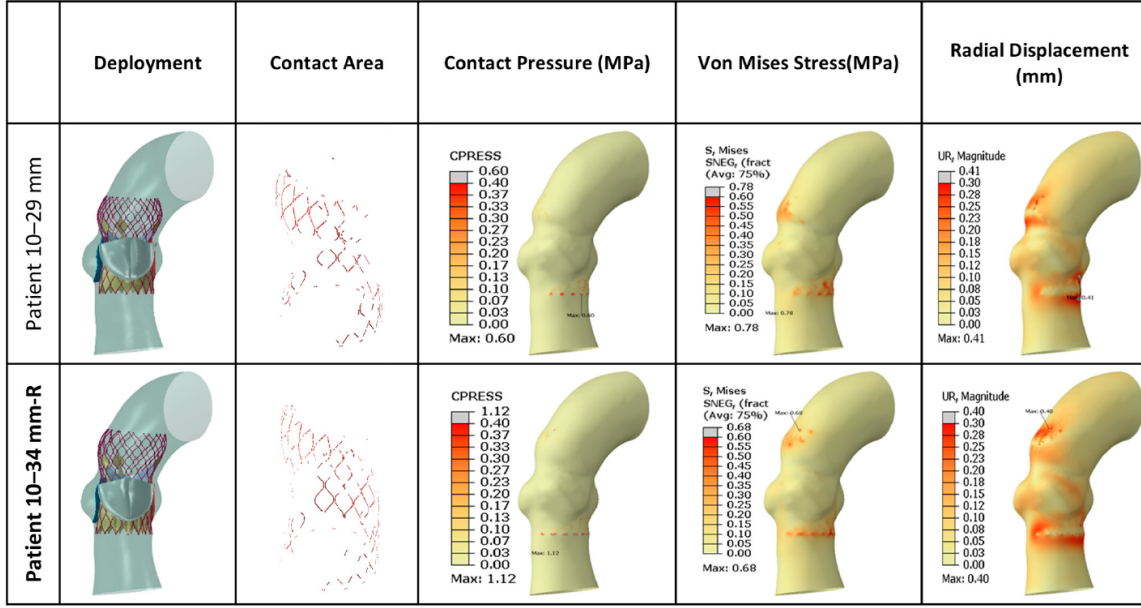


Figure 2.1: Example of bio-prosthetic valve implantation simulation results using FEA for two different valve sizes with associated post-processing. Image taken from Mutlu, Mazhar, Saribay et al [164] under CC BY license.

To achieve accurate numerical results, it is crucial to properly characterize the bio-prosthetic and the native valve models both from a geometrical and a mechanical point of view.

As for the bio-prosthetic valve model, its geometry can be either reconstructed from micro-CT images [83] or obtained from a CAD model [146]. In particular, the presence of the bio-prosthetic leaflets is sometimes neglected when simulating the implantation of TAVI valves due to their marginal impact on the final stent position [16]. However, some studies are interested in assessing the bio-prosthetic leaflets stresses in relation to valve durability, thus including them in the simulation [39]. On the other hand, the mechanical properties of the bio-prosthetic stent and leaflets depend on the analyzed valve. Specifically, balloon-expandable stents are usually characterized with an elastic-plastic constitutive model and self-expandable stents with hyperelastic material properties [139]. Moreover, a linear, elastic model is usually chosen for the bio-prosthetic leaflets, with

different specific properties between balloon-expandable valves leaflets, made of bovine pericardium [177], and self-expandable valves leaflets, made of porcine pericardium [147].

Regarding the native valve model, the aortic root geometry and the calcifications are reconstructed from CT images [161]. Furthermore, the native valve's leaflets can be either reconstructed from CT images [265] or a template geometry can be adapted to match the patient-specific sinuses of Valsalva [103]. Several constitutive models have been used to characterize the aortic tissue, going from a simplified St. Venant-Kirchhoff model [162], to an anisotropic hyperelastic model [253]. On the other hand, the calcific deposits can be characterized by an elasto-plastic model with perfect plasticity to simulate fracture [35].

Bio-prosthetic valve implantation numerical simulations have been used to assess how the outcomes of TAVI are affected by several factors, such as the aortic geometries and valve sizes [164], the calcification patterns [220], the material models and discretization procedures [83], the positioning of the prosthesis [15], and the use of balloon- or self-expandable valves [139, 166].

2.2.2. Post-TAVI hemodynamics

Another possible application of computational models in the TAVI context is the numerical simulation of post-TAVI hemodynamics. These simulations study the behavior of blood inside an aortic root model in presence of a virtually implanted bio-prosthetic valve model. Specifically, the computational domain is often obtained following a valve implantation simulation. The numerical results provide a detailed description of the blood velocity and pressure fields in presence of a TAVI valve, allowing to identify the presence of pathological hemodynamic patterns.

Post-TAVI hemodynamics can be simulated following a Computational Fluid Dynamics (CFD) or an FSI approach. In a purely CFD model only the fluid problem is resolved, thus neglecting the interaction between blood and the structural parts of the domain (aortic wall, bio-prosthetic valve). CFD models are usually characterized by a rigid structure assumption [131], alternatively, the movement of the structural parts can be prescribed a priori in order to obtain more accurate hemodynamic results [42]. On the other hand, an FSI framework allows to describe both the flow-driven movement and the stress state of the structural parts, modeling their interaction with blood. In the literature there are examples of full CFD models [202], hybrid models, where an FSI approach is considered only for some structural parts, e.g., the bio-prosthetic leaflets [139], or the aortic wall [119], and full FSI models [141]. In the FSI models, the bio-prosthetic leaflets are often

modeled following an immersed-boundary approach [19, 139]. However, this could lead to a non accurate computation of the fluid-exerted stresses on the leaflets, thus some studies considered a boundary-fitted method [121], which increases the computational complexity. An example of the results of a post-TAVI hemodynamics simulation is reported in Figure 2.2.

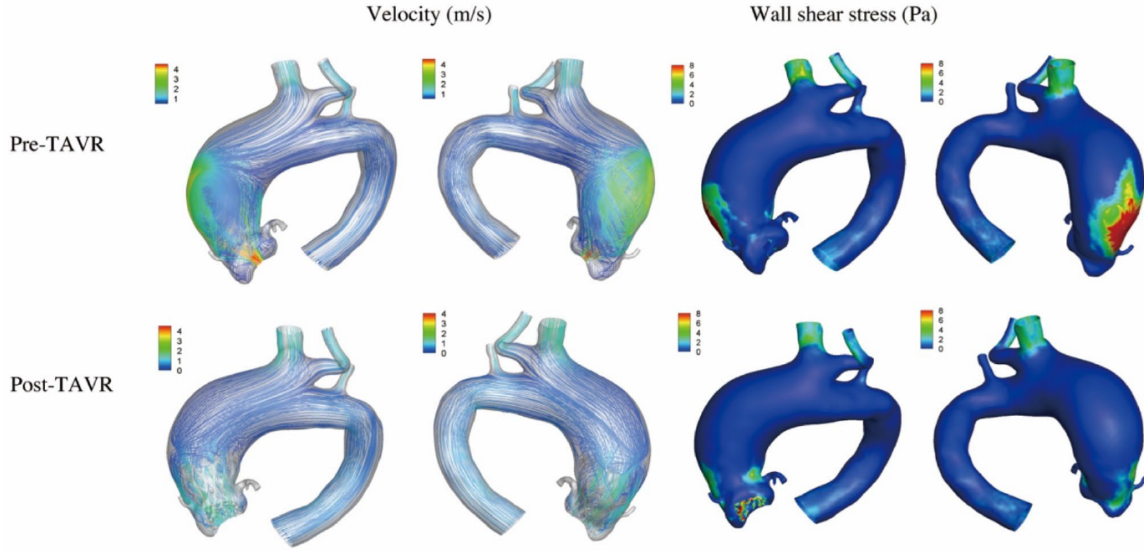


Figure 2.2: Comparison of CFD results before and after TAVI. Image taken from An, Zhang, Ouyang, and Pan [8] under CC BY-NC-ND 4.0 license.

Blood is generally modeled as an homogeneous Newtonian fluid using the incompressible Navier-Stokes equations. However, the presence of platelets has been considered using a two-phase fluid [29]. Additionally, the presence of turbulence in the aorta has been accounted for using suitable turbulence models [19, 119].

Post-TAVI hemodynamics simulations have been employed to: investigate the impact of the aortic arch morphology on post-TAVI blood-dynamics patterns in the aortic root [169]; to compare aortic hemodynamics before and after TAVI in patients with native tricuspid [226] and bicuspid [8] aortic valves; to assess the effect of TAVI implantation depth on the blood flow [142]; and to study how TAVI can influence coronary blood flow [249].

2.2.3. Post-procedural complications

Both bio-prosthetic valve implantation and post-TAVI hemodynamics simulations have been used to study the post-procedural complications of TAVI (see Section 1.4).

Conduction abnormalities, resulting from left bundle branch or atrioventricular blocks,

still represent an important drawback of the TAVI procedure often requiring the implantation of a permanent pacemaker [222]. The expansion of the bio-prosthetic valve is thought to cause an ischemic and inflammatory damage to the conduction system leading to the formation of electrical pathways blocks [152]. In this context, valve implantation numerical simulations have been employed to study the stresses and strains on the aortic annulus in relation to a possible damage [36, 70, 96, 156, 201, 252]. Specifically, the impact of the implantation depth on the stress distribution in proximity of the bundle of His has been investigated in a patient-specific anatomy and a supra-anular position showed the lowest stresses, possibly reducing the risk of conductance inference [156]. In a computational study performed on 112 patients the maximum contact pressure and the contact pressure index at the atrioventricular septum were identified as independent predictors for conduction abnormalities [201]. This was further validated from another FEM-based analysis which found significantly higher contact pressure and contact pressure index in patients with conduction abnormalities [96]. The strain in the implantation site were also found to be highest in patients requiring pacemaker implantation [36].

Paravalvular leakage is a common complication after TAVI and may even possibly neutralize the survival benefits of TAVI in patients with moderate or severe leakage [28]. It is identified as a diastolic leakage resulting from the presence of gaps between the bio-prosthetic valve and the native annulus due to a suboptimal anchoring. Paravalvular leakage has been extensively investigated with computational approaches [19, 29, 35, 36, 40, 100, 126, 129, 131, 147, 153, 161, 177, 178, 202] considering an implantation simulation followed by a hemodynamics simulation. Notably, an optimal implantation depth and balloon inflation volume lead to up to 47% in paravalvular leakage volume reduction in a computational study showing good agreement with echocardiography data in terms of the paravalvular jets locations and degree [29]. In another study performed on nine patients with bicuspid aortic valve the predicted paravalvular flows corresponded well with those determined by clinical data [177]. The effect of the native calcification pattern on paravalvular leakage has been assessed and calcium deposits along the cups coaptation resulted in mild leakage, while deposits along the attachment line in moderate leakage [147].

Bio-prosthetic valve thrombosis, i.e. the thickening of the leaflets due to the formation of a blood clot, and thrombogenic events, such as stroke, show a significant incidence after TAVI [111, 203]. Specifically, valve thrombosis is not included in the definition of Structural Valve Deterioratio (SVD), but it may lead to SVD [72]. Computational hemodynamic models focused on blood stagnation in the neosinuses (i.e. sinuses generated downstream the bio-prosthetic leaflets) in relation to a valve thrombosis risk [51, 127]. In

particular, different implantation depths have been analyzed using hemodynamic indices and an intra-annular valve position resulted in a higher blood stagnation [51]. Additionally, regional under expansion of the stent leading to impaired leaflet kinematics, possibly fostering valve thrombosis, has been analyzed with a structural model [186]. On the other hand, the risk of flow-induced thrombogenicity has been also investigated in computational studies [9, 29, 100, 129]. Specifically, the link between paravalvular leakage and an increased thrombogenic risk has been investigated with an FSI model demonstrating that platelets have the potential to enter the paravalvular gaps multiple times over successive cardiac cycles, increasing the thrombogenic risk [129].

The obstruction of the coronary arteries following the TAVI procedure is a rare, but potentially fatal complication [199]. Coronary blood flow in presence of a TAVI valve has been rarely investigated with computational models [113, 118, 249]. In particular, valve implantation FEA simulations were run in twenty eight TAVI patients at high-risk for coronary obstruction, identified using pre-operative clinical metrics, with only six patients actually developing an obstruction after TAVI. In this context, a new metric derived from the numerical results outperformed the clinical metrics in assessing the risk of coronary obstruction [113].

2.3. Computational models for SVD

There are several examples of structural computational models employed to study bio-prosthetic valve durability in a broader sense [39, 140, 223, 261], and SVD in particular [154, 167, 215–217, 260]. Specifically, these studies build on the assumption that increased stresses on the bio-prosthetic leaflets can lead to connective tissue damage and thus reduce valve durability. In the following we detail some notable examples of these models.

During the TAVI crimping phase the bio-prosthetic leaflets are subject to high stresses, possibly damaging the tissue even before the deployment of the valve, which was analyzed for different leaflets thicknesses showing that the stress increases with the thickness [39]. Bio-prosthetic leaflets made of both bovine and porcine pericardium were subject to physiological diastolic pressure loadings in a FEM setting and porcine pericardium resulted in higher peak stresses, potentially leading to a reduced durability [223]. Comparing the leaflet mechanical stresses in old and new generations of self- and balloon-expandable TAVI valves using an experimental/computational approach, the stresses were higher for the old generation devices and balloon-expandable valves, possibly leading to faster degeneration [217]. The effect of altered leaflet and stent elastic properties on non-calcific SVD was investigated using a computational leaflet fatigue model simulating cyclic load-

ings and the results showed that heterogeneity of the leaflet elastic properties, poor leaflet coaptation, and little stent-tip deflection may accelerate leaflet fatigue [154]. An example of the results of a computational study on leaflet mechanical stresses in relation to bio-prosthetic valve durability is reported in Figure 2.3.

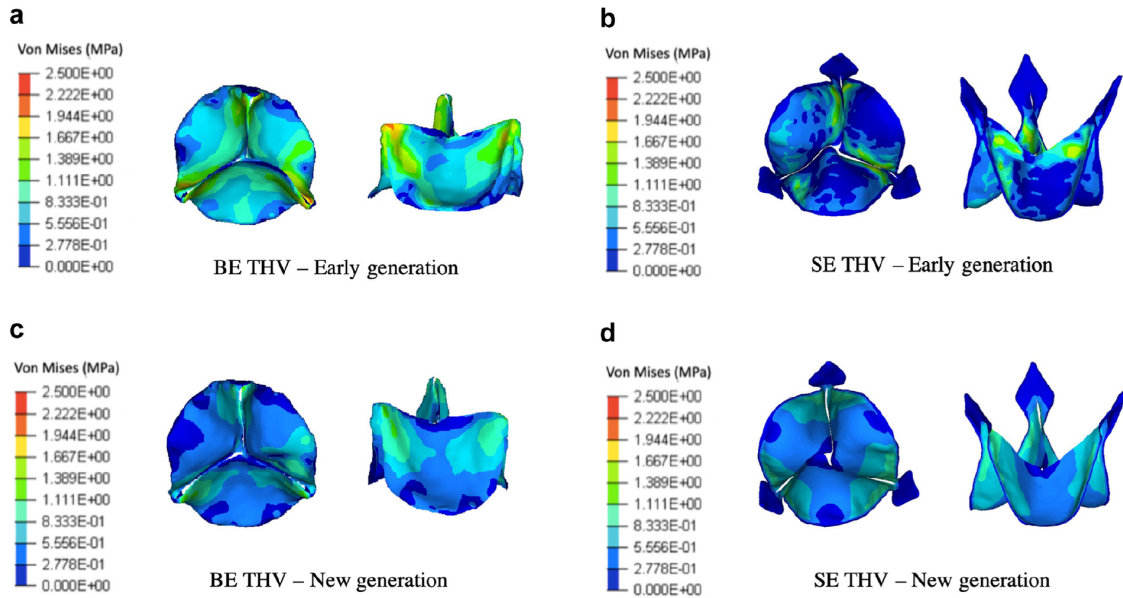


Figure 2.3: Comparison of leaflet stress magnitude and distribution obtained by FEA at leaflet closure according to type and generation of THV. BE: balloon-expandable; SE: self-expandable; THV: transcatheter heart valve. Image taken from Stanova, Rieu, Thollon et al [217] under CC BY-NC-ND 4.0 license.

On the other hand, the relationship between SVD and aortic hemodynamics has been rarely addressed with computational models. A fully coupled FSI model for a patient-specific analysis of hemodynamics in presence of a surgically implantable bio-prosthetic valve has been recently proposed and the authors suggest that it could be used to gain insight on the role of hemodynamics in SVD [262]. Nonetheless, this role was not investigated in their work. In another recent work [239], the calcific degeneration of bio-prosthetic heart valves has been investigated using a multiscale, multimodal analysis in failed bio-prosthetic valve explants with full histoanatomical context. In particular, they demonstrated that calcific degeneration is associated with mineral precipitation and cellular infiltration in the leaflets and, using high-fidelity numerical simulations, they proposed computational hemodynamic indices that qualitatively correlate with their findings in idealized geometries [239].

To the best of our knowledge, the only computational studies investigating the relationship between aortic hemodynamics and SVD using patient-specific geometries were carried out

in our research group [58, 59, 95]. These studies aimed to identify hemodynamic features that correlate with a premature onset of SVD, detected at follow-up exam after TAVI. Specifically, higher flow-induced stresses were found on the proximal aortic wall in patients with SVD using post-TAVI blood-dynamics simulations, neglecting the presence of the bio-prosthetic leaflets and considering an idealized model for the stent [95]. Additionally, this analysis was refined in [58] by including a representation of the bio-prosthetic leaflets, and extending the study population of [95]. A further refinement of the computational model was obtained in [59] by considering a more realistic geometry for the bio-prosthetic leaflets, accounting for the leaflets opening/closure dynamics, and prescribing an highly personalized flow rate condition based on Echo Doppler data. A detailed description of the methodologies employed in [58, 59] as well as a complete overview of the results obtained with the corresponding computational models are going to be presented in the next Chapters of the thesis.

2.4. Objectives of the thesis

This thesis project originates from the promising results of [95] and comprises the analysis carried out in [57–59].

The main objectives of the thesis are:

- 1) to build a CFD model to efficiently simulate highly personalized early post-TAVI hemodynamics, i.e. when the implanted valve is fully functioning;
- 2) to use the results obtained with the CFD model of point 1) to identify computational hemodynamic indices and scores in early post-TAVI scenarios able to discriminate between patients with and without SVD at long-term follow-up exam after TAVI.

In order to achieve these objectives we develop and/or apply several methodologies. In particular:

- starting from pre-TAVI CT scans, we create early post-TAVI virtual geometries providing a realistic representation of the TAVI bio-prosthetic valve (stent and leaflets). The procedure to build the post-TAVI geometries, which exploits the open-source software programs *Vascular Modeling Toolkit (VMTK)* and *Paraview*, is specifically developed for this thesis project building on a simplified procedure proposed in [95]. Specifically, the main advancements introduced in this thesis are: the representation of the bio-prosthetic leaflets in the valve model, which was not considered in [95]; the modeling of the opening/closure leaflets dynamics; the description of the wire-frame design of the valve's stent which was modeled as a hollow cylinder in

[95];

- we consider a novel approach to derive a personalized flow rate profile from Pulse Wave Echo Doppler data, which is commonly acquired in the clinical practice;
- we extend the in-house developed Finite Elements library `lifex` [3, 6] by implementing dedicated computational tools for the imposition of average flow rate conditions and for the efficient solution of the algebraic problem associated to these conditions. These utilities are exploited to numerically simulate post-TAVI hemodynamics using `lifex`;
- we perform a post-processing of the numerical results to identify computational hemodynamic indices that correlate with a premature onset of SVD and we apply statistical methods to assess the relevancy of these indices.

Finally, this thesis introduces the following main novelties with respect to the existing literature:

- the proposition of a personalized computational model to simulate post-TAVI hemodynamics based on patient-specific Echo Doppler data;
- the formulation of an ad-hoc preconditioner to efficiently solve the monolithic algebraic system arising from the Finite Element discretization of our problem of interest;
- the study of the relationship between post-TAVI hemodynamics and SVD using a computational model with patient-specific data;
- the definition of computational scores able to identify patients experiencing a premature onset of SVD.

3 | Data pre-processing

This chapter deals with the pre-processing of the available TAVI data, i.e. the techniques used to generate the inputs of the numerical simulations for post-TAVI hemodynamics. In particular, we introduce the available clinical data (Section 3.1); we deal with the geometrical modeling of the bio-prosthetic TAVI SAPIEN valves (Section 3.2); we present the steps to build the post-TAVI virtual geometries (Section 3.3); we go into details on the generation of the associated computational mesh (Section 3.4); finally we discuss the derivation of a personalized flow rate temporal profile based on Echo Doppler data (Section 3.5).

3.1. Available clinical data

In this thesis we leverage clinical data related to 14 patients who underwent TAVI in Centro Cardiologico Monzino between 2008 and 2012. An Edwards SAPIEN valve of either first or second generation with a nominal size of 23 mm in external diameter was implanted in all the patients. These are trileaflet bio-prosthetic valves made of bovine pericardium mounted on a balloon-expandable cylindrical stent with an inner fabric on its ventricular side [191] (see Figure 3.1-first row). In particular, the 23 mm size is the smallest available size for these valves and the most likely to develop SVD [109].

The clinicians in Centro Cardiologico Monzino identified 7 patients with SVD at long-term follow-up and 7 patients without SVD at same exam were randomly extracted from the same cohort and matched for baseline characteristics. We will refer to the former group as DEG patients and to the latter group as NODEG patients. Specifically, we name the patients as DEG1, DEG2, ..., and NODEG1, NODEG2, ..., respectively. In particular, the definition of SVD adopted in this paper is in agreement with both the "stage 3 SVD" definition proposed by Dvir et al in [72] and the definition of SVD with "Stage 3 Hemodynamic Valve Deterioration" proposed by the Valve Academic Research Consortium (VARC) 3 in [53]. This means that all DEG patients satisfy the corresponding criteria as highlighted in Section 7.1).

Let us notice that we consider relatively “old data” since Centro Cardiologico Monzino had at disposal data related to DEG patients only with older generation devices. This is due to the fact that SVD is a degenerative process which develops during several years and to the fact that often patients do not return to the same hospital for the follow-up exam, thus the information gets lost. Additionally, we consider also NODEG patients with older generation devices in order to have a fair comparison between the two sub-groups of patients.

We have at disposal the following data that we use as input in our computational model:

1. **Pre-TAVI Computed Tomography Angiography (CTA) scan.** Available for each patient in the study population. We exploit it in our model to reconstruct the patient-specific aortic geometry and calcific deposits used to build the post-TAVI virtual geometry (see Section 3.3.1). Specifically, it was taken at late diastole with a Discovery HD750 scanner (GE Healthcare) using the following configuration: $64 \times 0.625 \text{ mm}$; gantry rotation time 350 ms ; tube voltage, 120 kVp ; and effective tube current, 650 mA . Contrast enhancement was achieved with a triphasic injection of an 80 ml bolus of Iomeron 400 mg/ml (Bracco Imaging S.p.A.) through an antecubital vein at a 5 ml/s infusion rate, followed by 50 ml of saline solution, and a further 50 ml bolus of contrast at 3.5 ml/s [58, 109];
2. **Early post-TAVI Pulsed Wave (PW) Doppler Transthoracic Echocardiography (TTE).** Available for each patient except for DEG3 and NODEG3. This was obtained between two days and seven months after the implantation. We exploit this data to derive a personalized flow rate temporal profile that we impose as boundary condition in the numerical simulation (see Section 3.5). Since we use this data to have a description of the post-TAVI hemodynamic features when the implanted valve is not yet degenerated, which should be the case both a few days after TAVI and a few months after TAVI, then we accept the high variability in its time of acquisition. Specifically, it was obtained with commercially available equipment (iE33 or Epiq, Philips Medical System, or Vivid-9, GE Healthcare) [58, 109];
3. **Long-term follow-up Doppler TTE.** Available for each patient in the study population. This was obtained 5-10 years after TAVI and we report in Table 3.1 the specific time for each patient. We exploit this data to identify which patients developed SVD. The acquisition details are the same as in the previous point.

Additionally, we have at disposal also the following data that we use them for validation purposes:

Table 3.1: Long-term follow-up times for each patient in the study population.

ID	years	ID	years
DEG1	9.35	NODEG1	7.04
DEG2	7.83	NODEG2	4.96
DEG3	-	NODEG3	-
DEG4	7.21	NODEG4	10.40
DEG5	8.05	NODEG5	7.72
DEG6	7.58	NODEG6	5.05
DEG7	7.69	NODEG7	4.91

1. **Post-TAVI CTA scan.** This was taken some years after TAVI and is available only for patient DEG1 and NODEG1. We exploit this data to qualitative validate the virtual insertion of the bio-prosthetic valve model in the patient-specific aortic geometry;
2. **Early post-TAVI Continuous Wave (CW) Doppler TTE.** This is available for eleven out of fourteen patients (not for DEG2, DEG3 and NODEG3). We exploit this data to validate the numerical hemodynamic results based on the maximum blood velocity measurement through the bio-prosthetic aortic valve.

In this chapter we deal with the pre-TAVI CTA scan, the early post-TAVI PW Doppler TTE and post-TAVI CTA scan, whereas the remaining data are going to be exploited in the next chapters.

We report in Table 3.2 the patients' characteristic and the data availability in the whole study population. In particular, all the patients are females, with the only exception of patient DEG6. Additionally, on average, DEG patients are characterized by: age = 76.8, BSA = $1.783 m^2$, and CO = $5.60 L/min$. Whereas, on average, NODEG patients are characterized by: age = 80.0, BSA = $1.572 m^2$, and CO = $5.22 L/min$. This is in agreement with the fact that young age and a raised BSA have been identified as risk factors for SVD (see Section 1.5). Moreover, the higher cardiac output in the DEG further validates the hypothesis [175] that an accelerated flow across the bio-prosthetic valve can promote an early onset of SVD. However, the risk factors reported in Table 3.2 alone are not able to discriminate between DEG patients and NODEG patients.

The study was approved from the Institutional Review Board of Centro Cardiologico Monzino on August 3rd, 2020 and registered with number R.1262/20-CCM 1326. Informed

Table 3.2: Collection of data: type of valve, patients' characteristics, and data availability in the study population. SAPIEN: type of SAPIEN valve. age: age at the time of TAVI. BSA: Body surface area. CO: cardiac output (computed according to (3.2)). SD: standard deviation. Notice that, due to the unavailability of patient-specific data, the cardiac output of patients DEG3 and NODEG3 is computed as the average in the study population.

ID	SAPIEN	Characteristics			Data availability			
		age	BSA [m^2]	CO [L/min]	pre-TAVI CT	post-TAVI PW TTE	post-TAVI CT	post-TAVI CW TTE
DEG1	1 st gen.	70	1.712	5.94	✓	✓	✓	✓
DEG2	2 nd gen.	87	1.599	6.13	✓	✓	✗	✗
DEG3	NA	NA	NA	5.41	✓	✗	✗	✗
DEG4	2 nd gen.	86	1.761	4.84	✓	✓	✗	✓
DEG5	1 st gen.	75	2.062	5.45	✓	✓	✗	✓
DEG6	1 st gen.	66	1.885	5.95	✓	✓	✗	✓
DEG7	2 nd gen.	77	1.678	5.31	✓	✓	✗	✓
NODEG1	2 nd gen.	87	1.504	5.37	✓	✓	✓	✓
NODEG2	2 nd gen.	77	1.349	4.52	✓	✓	✗	✓
NODEG3	NA	NA	NA	5.41	✓	✗	✗	✗
NODEG4	1 st gen.	84	1.533	5.08	✓	✓	✗	✓
NODEG5	2 nd gen.	66	1.593	4.37	✓	✓	✗	✓
NODEG6	2 nd gen.	80	1.663	6.03	✓	✓	✗	✓
NODEG7	2 nd gen.	86	1.787	5.94	✓	✓	✗	✓
mean	-	78.42	1.677	5.41				
SD	-	7.93	0.187	0.61				

consent was obtained from all patients.

3.2. Modeling the bio-prosthetic valve

In this thesis we aim to perform a personalized computational analysis of post-TAVI hemodynamics, so that we create a digital model of the SAPIEN valves of first and

second generations considered in this study (see Section 3.1). In particular, we first deal with the stent model (Section 3.2.1) and then with the leaflets model (Section 3.2.2).

3.2.1. Geometrical model for the stent

The considered Edwards SAPIEN valves are characterized by a cylindrical stent (see Figure 3.1-first row). In particular, in this thesis we consider two strategies to geometrically model their stent, namely a *simplified* strategy and a *realistic* strategy.

Simplified strategy In the *simplified* strategy we model the stent as an hollow cylinder with the same nominal dimensions of the real SAPIEN valves. Specifically, the external diameter of the stent is set to 23 mm and its height to 14 mm [191].

Realistic strategy In the *realistic* strategy we provide a geometrical description of the wire-frame design of the SAPIEN valves, which differs between the first and the second generation valve. Notice that, since we did not know whether the SAPIEN valves implanted in patients DEG3 and NODEG3 were of first or second generation (see Table 3.2), then we could only employ the *simplified* strategy for these patients and not the *realistic* one.

The SAPIEN valves are characterized by an inner fabric, preventing blood flow, on their ventricular side (see Figure 3.1-first row). Accordingly, we consider a cylindrical model for the stent and we provide a wire-frame design only on its aortic side, due to the presence of the fabric on the ventricular one. In particular, since in our CFD study we consider only the blood domain, then we are only interested in representing the geometrical interface between the blood and the valve, neglecting the different mechanical properties of the stent and the fabric. The procedure to obtain the *realistic* stent model is detailed in what follows.

Based on publicly available data, realistic CAD models of the SAPIEN valves' stent (see Figure 3.1-third row) were generated in *SolidWorks* and *Autodesk Fusion* by students Elisa Fortini, Cristina Filorizzo, Ada Finetti, and Marika Fontanarosa under the supervision of Crugnola-Vergara. The external diameter of the stent was set to 23 mm and the stent's struct was assumed to have a thickness of 0.5 mm and a height of 14.4 mm [191]. A detailed description of the steps performed to generate these CAD models can be found in [92].

Furthermore, we create a hollow cylinder with the same dimensions (internal and external radius, height) and position of the CAD model and we compute the distance between the

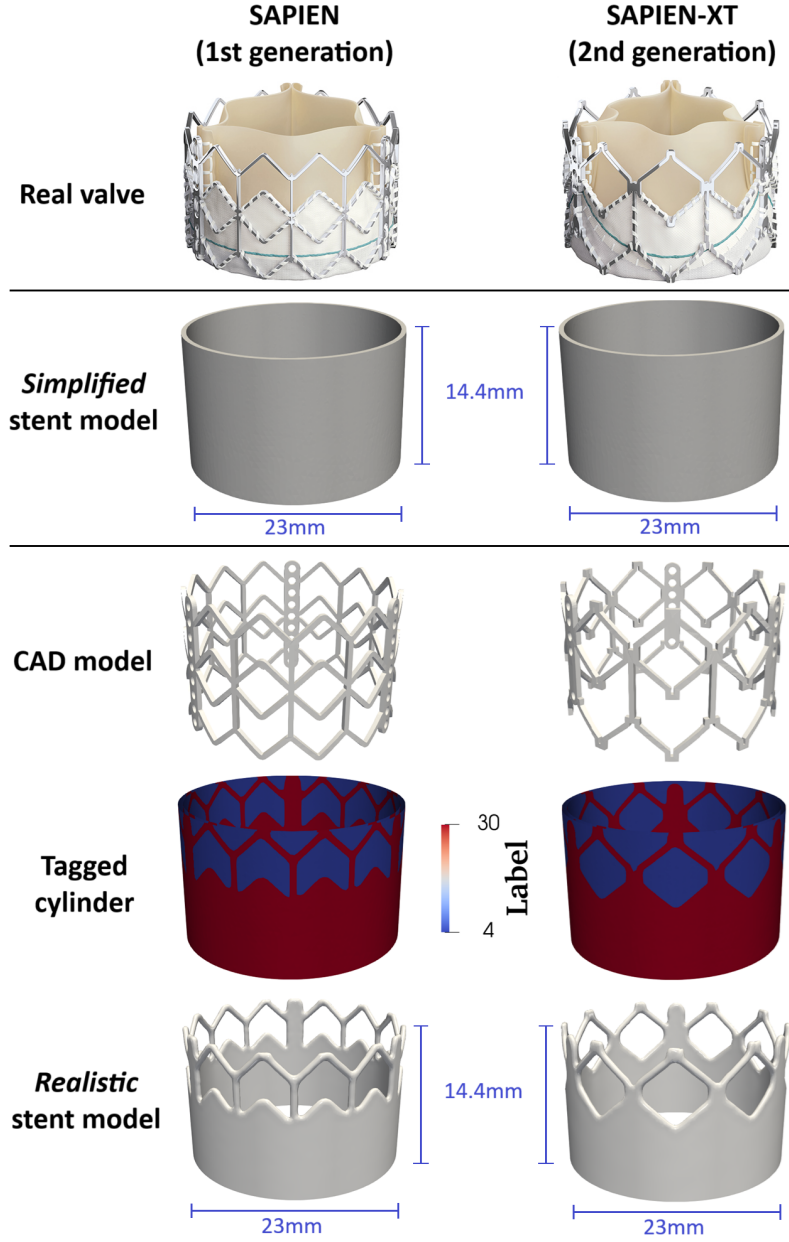


Figure 3.1: Geometrical model for the bio-prosthetic valve’s stent. For each SAPIEN valve, we report: the real valve (first block), the *simplified* stent model (second block), and the steps to obtain the *realistic* stent model (third block). In particular, to create the *realistic* stent model, we start from a CAD model and we tag a hollow cylinder to match the wire-frame design on the aortic side. The “Real valve” images are taken from Rheude, Blumenstein, Möllmann, Husser [195] under CC-BY-NC license, ©Edwards Lifesciences Corporation.

cylinder and the CAD model of the stent. Exploiting this distance, we tag the cylinder lateral surfaces assigning the label 30 to the interface between blood and the valve and

the label 4 to the void spaces between the stent's struts on the aortic side (see Figure 3.1-fourth row). Specifically, the fabric is manually tagged on the cylinder. The tagged cylinder is going to be virtually inserted in the reconstructed aortic geometries (see Section 3.3.2) and the label 30 is going to be extracted to create the stent model used in the CFD simulations (see Figure 3.1-fifth row).

3.2.2. Geometrical model for the leaflets

As for the bio-prosthetic leaflets, in the numerical simulations we provide an implicit representation as an immersed surface (see Section 4.1.4), so that we need a fully open and a fully closed configuration of the leaflets. In particular, in this thesis we consider two strategies also to geometrically model the bio-prosthetic leaflets, namely a *simplified* strategy and a *realistic* strategy.

Simplified strategy In the *simplified* strategy, we consider an idealized leaflets geometry, which mimics the native aortic valve morphology (see Figure 3.2-left), taken from another study [145]. In [145], the authors applied a physiological pressure gradient to obtain the open and closed configurations of the leaflets. In particular, the pressure gradient was directly applied on the aortic side of the leaflets in a structural Finite Element analysis.

Realistic strategy In the *realistic* strategy we consider a realistic geometry, which mimics the SAPIEN valves' leaflets [47] (Figure 3.2-right). An open and a closed configuration of the leaflets were obtained with a mechanical simulation in *Abaqus* by PhD. Chiara Catalano and Prof. Salvatore Pasta. Specifically, the leaflets were initially modeled in a stress-free configuration. A physiological pressure waveform was then applied to the leaflet surfaces, while the leaflet-to-stent attachment region was fully constrained, to obtain the fully open and closed configurations of the bioprosthetic valve leaflets.

In order to describe the leaflets opening/closure dynamics, a distance from the closed to the open configuration is computed. This distance is going to be used in the numerical simulations to interpolate between the two configurations. Finally, the leaflets geometry is inserted in the stent model so that it has the same orientation of the stent and it is consistent with its wire-frame design.



Figure 3.2: Geometrical model for the bio-prosthetic valve's leaflets in open configuration. Left: *simplified* leaflets model. Center: real valve's leaflets. Right: *realistic* leaflets model. The image of the real valve is taken from Holoshitz, Kavinsky, Hijazi [117] with written permission by Hijazi.

3.3. Post-TAVI virtual geometries

In this thesis we aim to perform a personalized computational analysis of post-TAVI hemodynamics, so that we build post-TAVI virtual geometries starting from the available pre-TAVI CTA scans (see Section 3.1). This procedure is extensively based on the use of the *Vascular Modeling Toolkit (VMTK)* (<http://www.vmtk.org/>) and *Paraview* (<https://www.paraview.org/>) open-source software programs. In particular, we reconstruct the patient-specific geometries of aortic root, ascending aorta and calcific deposits (Section 3.3.1); we virtually insert in the reconstructed aortic geometry the model of the SAPIEN valve (Section 3.3.2); finally, we qualitatively validate the obtained post-TAVI virtual geometry against the post-TAVI CTA scans available for patients DEG1 and NODEG1.

3.3.1. Reconstruction of the patient-specific geometries

Patient-specific geometries of the aortic root, the ascending aorta and the calcific deposits on the native aortic valve are reconstructed from pre-TAVI CT scans. This is done with the aim of virtually inserting the bio-prosthetic valve model inside the reconstructed aortic geometries by accounting for the native calcification patterns. The procedure to reconstruct the geometries is detailed in what follows.

Regarding the aortic geometries, a segmentation mask identifying the patient-specific lumen going from the left ventricle to the descending aorta is semi-automatically created with a level-set segmentation technique considering a colliding front initialization, as commonly done for vascular structures [10]. The geometry of the lumen external surface is then generated with a marching cubes algorithm [143] (see Figure 3.3a). A region of

interest going from the LVOT to the ascending aorta, neglecting the coronary branches, is then extracted and a morphing procedure is applied in order to smooth the geometry and to get rid of possible artifacts resulting from the presence of the calcified aortic valve leaflets in the CTA scan (see Figure 3.3b). In particular, morphing refers to a technique which starts with a template geometry (in our case a cylinder) and iteratively deforms it to match the reconstructed geometry.

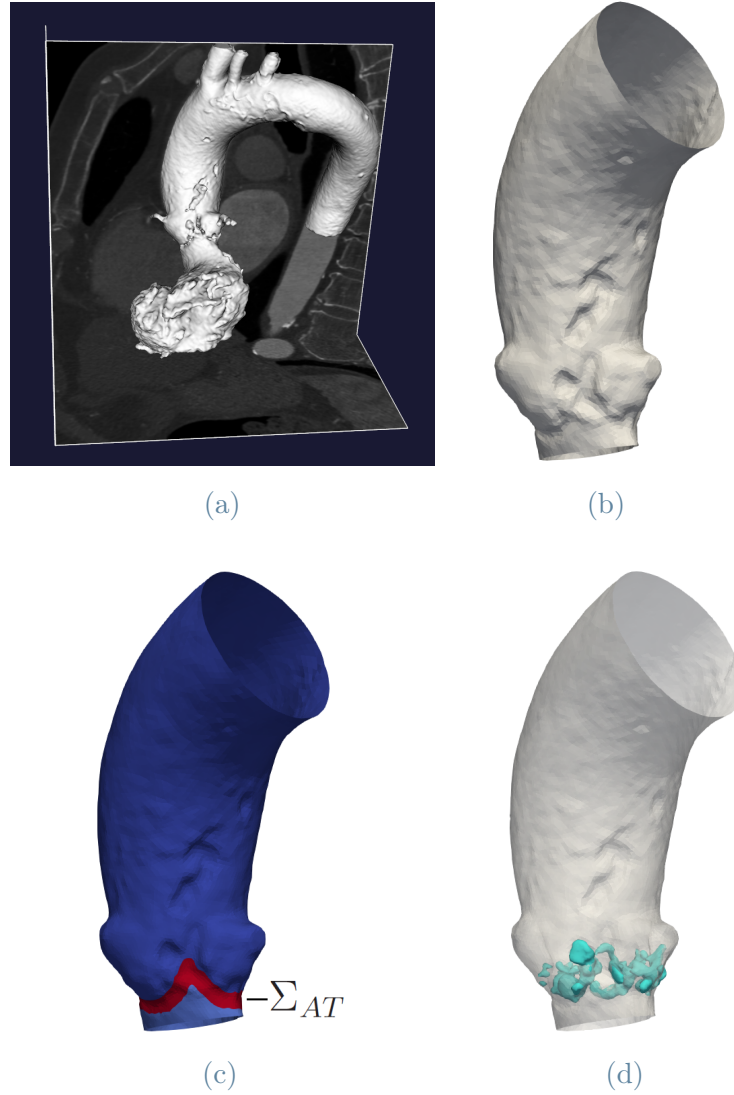


Figure 3.3: Reconstruction of the patient-specific geometries. (a) Lumen external surface going from left ventricle to descending aorta, reconstructed from CTA scan. (b) Reconstructed geometry of the aortic root and ascending aorta after morphing. (c) Identification of the annulus trace (Σ_{AT}), in red, on the reconstructed aortic wall. (d) Calcific deposits, in light blue, on the aortic annulus and the aortic valve leaflets.

Furthermore, the intersection between the native aortic valve leaflets and the aortic wall,

referred to as *annulus trace* (Σ_{AT}) in the following, is determined (see Figure 3.3c). Specifically, the aortic border of this intersection is manually identified on the reconstructed aortic wall and a 3 mm wide ring-shaped region extending toward the ventricle is generated. The annulus trace is going to be exploited to define the relative position of the bio-prosthetic valve inside the aortic geometry.

As for the calcific deposits, the segmentation mask is automatically created with a level-set segmentation technique considering a thresholding initialization by isolating the CTA scan voxels with associated Hounsfield unit greater than 900. A marching-cube algorithm is still used to generate the geometries starting from the segmentation mask. Lastly, only the calcific deposits on the aortic annulus and leaflets are extracted (see Figure 3.3d).

3.3.2. Virtual insertion of the bio-prosthetic valve model inside the patient-specific aortic geometry

In this thesis we perform a virtual insertion of the bio-prosthetic valve model inside the patient-specific aortic geometry, without numerically simulating the implantation of the valve. This procedure has been proposed and detailed in [95] and has been refined in [58, 59]. In particular, we perform a geometrical insertion of the bio-prosthetic valve model accounting for the native calcification pattern; we deform the aortic geometry to be able to host the valve model; finally, we build the virtual post-TAVI computational domain.

Geometrical insertion of the valve model

The bio-prosthetic valve model (stent and leaflets) is geometrically roto-translated in such a way that: it is placed in the barycenter $\mathbf{G}_0$ of the annulus trace Σ_{AT} with 70% of the stent inside the aorta, according to clinical practice; and it is oriented according to the centerline $\mathbf{e}_c$ of aortic root (see Figure 3.4-a). Additionally, the valve model is radially rotated so that the radial orientation of the bio-prosthetic leaflets matches the one of the native aortic valve leaflets, identified by the reconstructed sinuses of Valsalva, according to clinical practice.

Subsequently, the valve model is radially translated in order to account for the patient-specific calcification pattern. To this aim, we compute the thickness of the calcific deposits in the radial direction and we extrude the annulus trace toward the inner side of the lumen according to the calcium thickness. We refer to the deformed annulus trace as $\tilde{\Sigma}_{AT}$. Then, we compute the average radial distance of $\tilde{\Sigma}_{AT}$ from $\mathbf{G}_0$ on the plane orthogonal to the

centerline $\mathbf{e}_c$ as

$$\mathbf{d} = \frac{1}{|\tilde{\Sigma}_{AT}|} \int_{\tilde{\Sigma}_{AT}} [(\mathbf{x} - \mathbf{G}_0) - ((\mathbf{x} - \mathbf{G}_0) \cdot \mathbf{e}_c) \mathbf{e}_c] d\mathbf{x}.$$

Finally, we radially translate the valve model using $\mathbf{d}$ [95]. For simplicity, we report in Figure 3.4-b the result of this radial translation only for the stent model, but the same translation is applied also to the leaflets geometry.

Deformation of the aortic geometry

The SAPIEN valves considered in this study are balloon-expandable valves, thus, analogously to what happens during TAVI due to the inflation of the balloon, we circularize and expand the reconstructed aortic root in case of a dimensional mismatch with the bioprosthetic valve. In particular, we proceed as follows:

1. we identify on the aortic root wall Σ^{root} the area of active expansion Σ^{act} , i.e. the area that would be actively expanded by the inflation of the balloon, as:

$$\Sigma^{act} = \{\mathbf{x} \in \Sigma^{root} : d_{cent}(\mathbf{x}) \leq 13 \text{ mm}\},$$

where d_{cent} is the distance from the centerline (see Figure 3.4-c). This is done since the external radius of the valve is 11.5 mm and we assume that the thickness of the native calcified aortic annulus is 1.5 mm , thus the distance to the centerline has to be greater than 13 mm for the aortic geometry to be able to contain both the bio-prosthetic and native annulus;

2. we define on Σ^{act} the magnitude of active expansion $actExp$ as:

$$actExp(\mathbf{x}) = 13 - \alpha \|d_{cent}(\mathbf{x})\| - (1 - \alpha) \min_{\mathbf{x} \in \Sigma^{act}} \{\|d_{cent}(\mathbf{x})\|\}.$$

Notice that expanding Σ^{act} considering $\alpha = 1$ corresponds to a pure circularization of Σ^{act} , whereas considering $\alpha = 0$ corresponds to a rigid expansion of Σ^{act} . In this work we set $\alpha = 0.8$.

3. we define, on the whole aortic wall surface, a smooth scalar field $\varphi : \Sigma^{aorta} \rightarrow [0, 1]$ taking value 1 in Σ^{act} and 0 in the ascending aorta as the solution of a Laplace-Beltrami problem (see Figure 3.4-d). This field is going to be used to achieve a smooth deformation of the aortic root;

4. we define on Σ^{root} the magnitude of the global expansion $globExp$ as:

$$globExp = actExp * \frac{(1 - \cos(\pi\varphi))}{2},$$

and we deform the aortic geometry by extruding it according to $globExp$ in the radial direction (see Figure 3.4-e).

Building of the post-TAVI computational domain

To build the virtual post-TAVI computational domain we have to connect the geometrically inserted stent model and the deformed aortic geometry.

To this aim, we project the expanded annulus trace onto the external lateral surface of the cylinder representing the stent model, assigning to the projected trace the label 16 (see Figure 3.4-f). Notice that the *realistic* stent model already presents the tags related to the wire-frame design.

From the tagged cylinder we extract the label 30, neglecting, only on the external surface, the area on the ventricular side of the projected trace. Then, we create the stent model for the CFD simulations by connecting the internal and external lateral surfaces of the stent and smoothing. The resulting stent model comprises only the interface between the blood flowing into the aorta and the bio-prosthetic stent.

Additionally, we connect the expanded annulus trace and the projected annulus trace on the cylinder and we identify the resulting structure as the aortic annulus. In particular, only the interface between blood and the annulus, i.e. the downstream face of the annulus, is part of our computational domain.

The resulting computational domain comprises: the deformed aortic wall downstream the annulus trace, the interface between blood and the annulus, the interface between blood and the stent, and the bio-prosthetic leaflets (see Figure 3.4-g). We notice that the calcium deposits are not part of the computational domain, we reconstructed them from the pre-TAVI CTA scan only to account for a non-symmetric insertion of the bio-prosthetic valve model.

In Figure 3.5 we report the computational domains obtained following the procedure presented above in the whole study population.

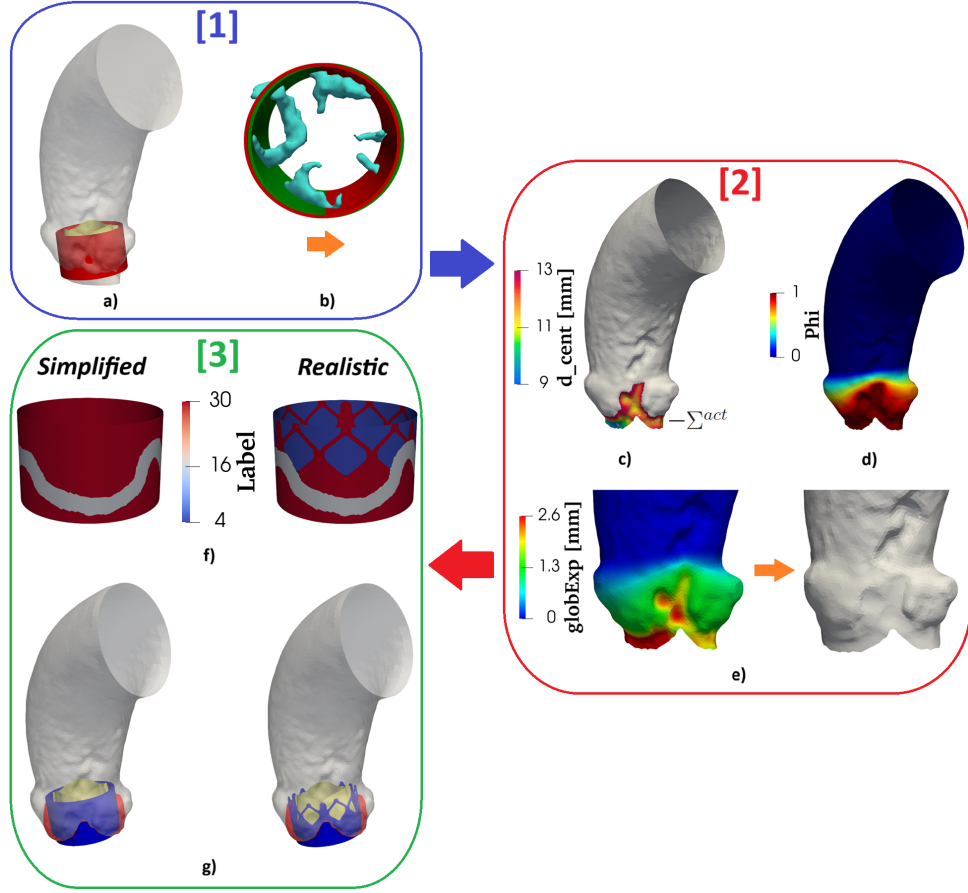


Figure 3.4: Virtual insertion of the valve model inside the reconstructed geometry. **1)** Geometrical insertion of the valve. a) Insertion of the valve. b) The originally inserted stent (red) is radially translated into its final position (green) to account for the native calcifications (light blue). The same translation is also applied to the leaflets geometry. **2)** Deformation of the aortic geometry. c) Active expansion area Σ^{act} defined by a distance from the centerline d_{cent} smaller than 13 mm. d) Scalar field φ used to smoothly deform the aortic root. e) Extrusion of the aortic root in radial direction according to global expansion magnitude $globExp$. **3)** Building of the post-TAVI computational domain for both the *simplified* and the *realistic* valve model. f) Projection of the expanded annulus trace onto the external surface of the cylinder representing the stent. The projected trace is identified by label 16 (grey). g) Computational domain comprising: the deformed aortic wall (grey), the interface between blood and the annulus (red), the interface between blood and the stent (blue), and the bio-prosthetic leaflets (yellow).

3.3.3. On the accuracy of the post-TAVI virtual geometries

Starting from the post-operative CT scans available for patients DEG1 and NODEG1, we reconstruct the post-operative aortic geometry and the implanted stent in order to assess

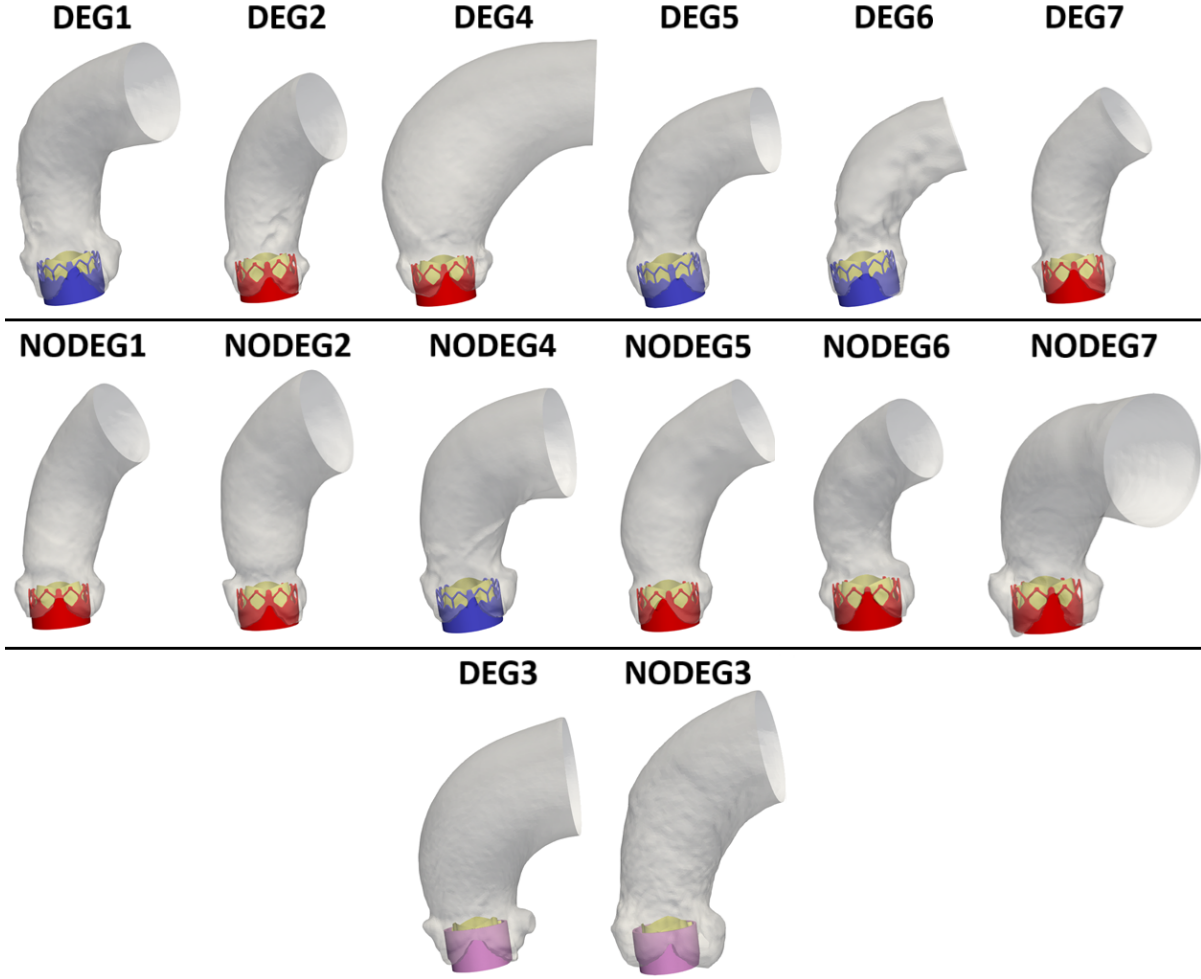


Figure 3.5: Post-TAVI virtual geometry for each patient in the study population. Blue stent: *realistic* model for SAPIEN valve (1st generation). Red stent: *realistic* model for SAPIEN-XT valve (2nd generation). Purple stent: *simplified* model for the valve. Notice that the *realistic* strategy could not be employed for patients DEG3 and NODEG3 due to a lack of information regarding the generation of the implanted SAPIEN valve (see Section 3.2.1).

the accuracy of the post-TAVI virtual geometries.

We report in Figure 3.6 a comparison between the positions and orientations of the reconstructed implanted stent (red) inside the post-operative aortic geometry and the virtually inserted stent (green) inside the deformed pre-operative geometry. Specifically, to facilitate the comparison, the CAD model used to generate the *realistic* stent (see Section 3.2.1) is shown in the figure. Moreover, the distinguished metallic structure present in the SAPIEN valves where the leaflets are sutured to the stent is used to identify the position of the bio-prosthetic leaflets commissures, and thus the radial orientation of the implanted

valve. We observe that there is a qualitative good agreement between the relative position

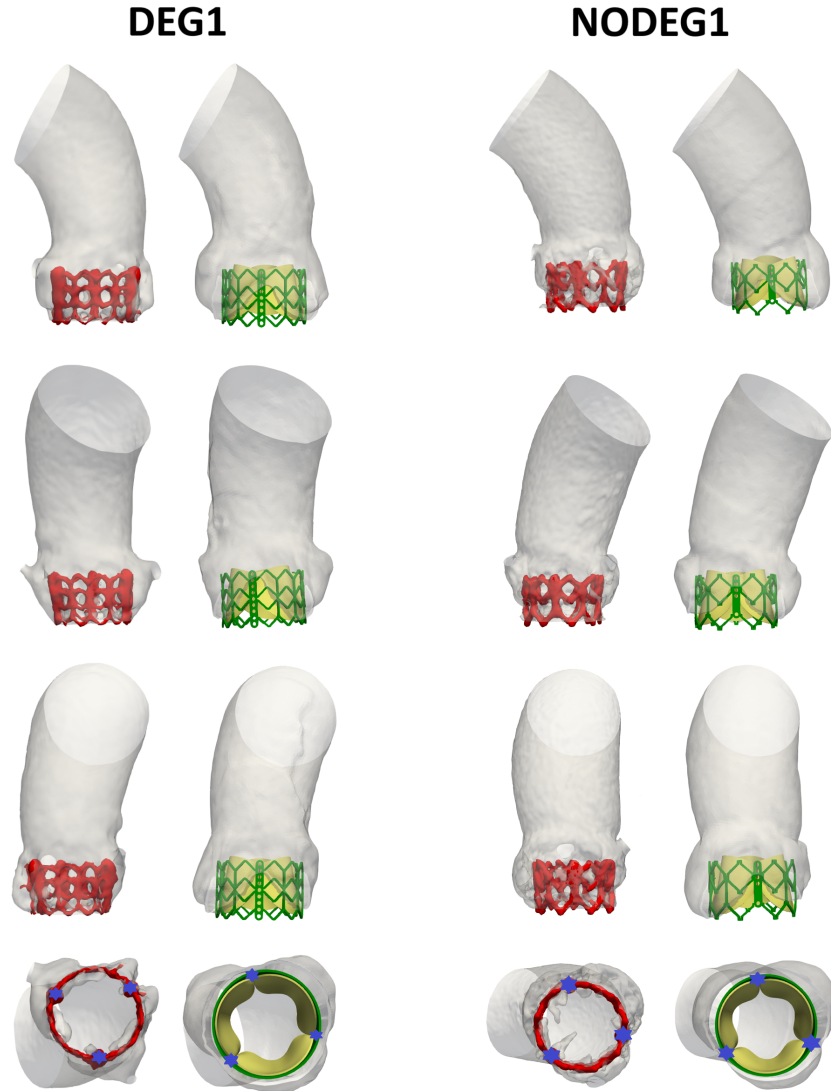


Figure 3.6: Validation of virtual stent insertion for patients DEG1 and NODEG1. Three different frontal views and the view from the left ventricle are reported in the different rows. Specifically, in the ventricle view (last row), the leaflets commissures are highlighted with a blue star. For each patient and each view we report: the aortic geometry and the implanted stent, in red, reconstructed from the post-operative CT scan (left); the deformed aortic geometry, and the virtually inserted stent, in green, and leaflets, in yellow, models (right). Notice that the CAD model used to generate the *realistic* stent model (see Section 3.2.1) is shown instead of the stent model used in the CFD simulations.

and the longitudinal orientation of the stent model inside the pre-operative geometry with respect to the those of the implanted stent inside the post-operative geometry for all the considered views. Additionally, from the view from the ventricle (last row) we see that the

radial orientation of the virtually inserted valve model is in good agreement with the one of the implanted valve for patient NODEG1, whereas this does not hold for patient DEG1 for which the radial orientations differ. We remember that we set the radial orientation of our valve model to match the orientation of the native valve as commonly done in clinical practice. This assumption turned out to be accurate for one out of two patients with available post-TAVI imaging data. Finally, the reconstructed implanted stent (in red) shows a circular cross section in the view from the left ventricle, supporting our choice to consider a cylindrical virtual stent.

3.4. Generation of the computational mesh

In Section 3.3 we considered only surface geometries. In order to perform the numerical simulations, we need to generate a volumetric computational mesh associated to the obtained post-TAVI virtual geometries (see Figure 3.5). In particular, in the following we introduce the specifics of our computational mesh (see Section 3.4.1); finally, we present the mesh sensitivity analysis performed to choose the mesh size (see Section 3.4.2).

3.4.1. Computational mesh specifics

In order to generate the computational mesh we first need a triangulation of the surface geometries introduced in Section 3.3 and then we need to build a volumetric mesh starting from the triangulation.

As for the surface triangulation, we consider triangular elements with the following superficial sizes in the different parts of our computational domain:

- Stent: the element size smoothly varies from 0.75 mm on the ventricular side of the stent (domain's inlet) to 0.375 mm on the aortic side. The smaller size on the aortic side is considered in order to properly describe the wire-frame design;
- Interface between blood and the annulus: the element size is constant and equal to 0.5 mm ;
- Aortic wall: the element size smoothly varies from 0.65 mm at the level of the annulus to 0.85 mm at the domain's outlet.

Notice that since in the numerical simulations we provide an implicit representation of the bio-prosthetic leaflets as an immersed surface, then the leaflets are not explicitly accounted for in our computational mesh. Lastly, we create a flow extension of three millimeters both at the inlet and at the outlet of our computational domain.

Starting from the surface triangulation detailed above, we generate a volumetric mesh using tetrahedral elements with a volumetric size that smoothly varies from 0.35 mm in stent region to 0.9 mm at the domain's outlet. Furthermore, on the whole aortic wall we consider a boundary layer made of three sub-layers with thicknesses $\{0.1, 0.2, 0.4\}\text{ mm}$ going from the wall to the internal domain. Lastly, we refine the mesh to a 0.25 mm size in the leaflets area to ensure a proper implicit representation of the leaflets in the numerical simulations. The resulting mesh is depicted in Figure 3.7.

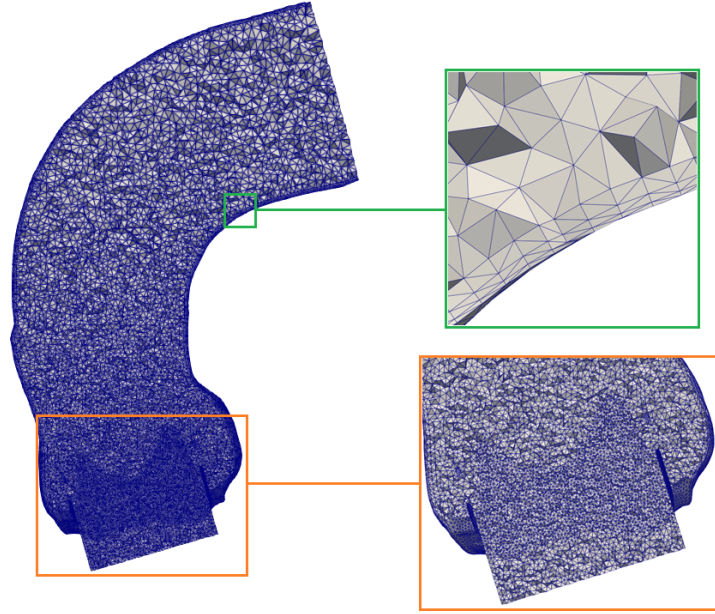


Figure 3.7: Volumetric computational mesh with a boundary layer (zoom in green box) and a local refinement in the leaflet area (zoom in orange box). Patient DEG1.

3.4.2. Mesh sensitivity analysis

In the following we present the sensitivity analysis performed to choose the mesh size of our computational mesh. This is done to ensure that our numerical results do not strongly depend on the chosen mesh while allowing for a sustainable computational cost of the simulations. The analysis is carried out only for patient DEG1, as a representative of the study population, and we numerically simulate two complete heartbeats, analyzing only the results of the second one (the details regarding the numerical simulations will be provided in Chapter 4).

In our computational mesh the elements size is minimum at the level of the aortic annulus and a maximum at the level of the outlet section (see Section 3.4.1). We select the minimum superficial element size on the aortic wall as the characteristic mesh size H

and perform sequential refinements of the mesh by decreasing the value of H , while keeping the same ratio between the maximum and minimum superficial element sizes, and between the superficial and volumetric element sizes. Specifically, we consider three refinement steps associated to $\{H_1, H_2, H_3\} = \{0.82, 0.65, 0.52\} mm$, corresponding to computational meshes $\{M_1, M_2, M_3\}$, respectively. Let us define the refinement factor between two consecutive meshes as $R_i = \frac{H_{i+1}}{H_i}$, $i = 1, 2$. We deem a mesh as sufficiently refined if the relative difference between quantity of interest Q_{i+1} , computed in M_{i+1} , and Q_i , computed in M_i , is less than a tolerance $T(Q, R_i)$ which depends on the quantity of interest and the refinement factor. In particular, as we proposed in [71], we define the tolerance as follows:

$$T(Q, R_i) = \hat{T}(Q) \cos\left(\frac{\pi}{2} R_i\right), \quad (3.1)$$

where $\hat{T}(Q)$ represents an acceptable error with respect to the real measured quantity Q in the limit $R_i \rightarrow 0$, e.g. the uncertainty related to a clinical measure. This framework stresses the importance of taking into account the amount of refinement between meshes when quantifying the tolerance, with values of $R_i \approx 1$ resulting in $T(Q, R) \approx 0$.

We are interested in studying the Wall Shear Stress (WSS) on the aortic wall, which highly depends on the mesh size. Thus, let us take as a quantity of interest the temporal average of the maximum-in-space WSS value on the aortic wall $\overline{WSS^{max}}$ and set $\hat{T}(\overline{WSS^{max}}) = 10\%$, since accurately computing the WSS is challenging even with the most sophisticated imaging techniques. Notice that we choose this quantity since the post-processing of the numerical results presented in the next chapters is strictly related to the WSS and since we expect the maximum-in-space WSS value to be more sensible to a mesh refinement with respect to an average-in-space value. We report in Table 3.3 the results of our analysis, showing that mesh M_2 is appropriately refined for our study. For the sake of completeness,

Table 3.3: Mesh sensitivity analysis. i : refinement step; H_i : minimum element size on the aortic wall; R_i : refinement factor; $T(\overline{WSS^{max}}, R_i)$: tolerance; $E_i = \frac{|\overline{WSS^{max}}_{i+1} - \overline{WSS^{max}}_i|}{|\overline{WSS^{max}}_i|}$ relative difference.

i	Mesh	H_i	R_i	$T(\overline{WSS^{max}}, R_i)$	E_i
1	M_1	0.82 mm	0.79	3.24%	10.64%
2	M_2	0.65 mm	0.80	3.09%	1.16%
3	M_3	0.52 mm			

in Figure 3.8 we plot the WSS on the aortic wall at the peak systolic flow instant for all the meshes, highlighting the similar results obtained for meshes M_2 ($H = 0.65 mm$) and

M_3 ($H = 0.52 \text{ mm}$).

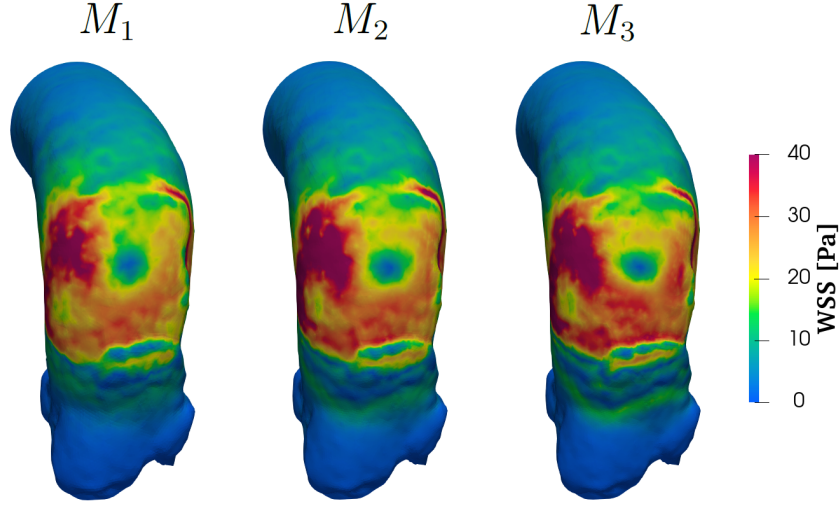


Figure 3.8: WSS on the aortic wall at the peak systolic flow instant in meshes M_1 ($H_1 = 0.82 \text{ mm}$, left), M_2 ($H_2 = 0.65 \text{ mm}$, center) and M_3 ($H_3 = 0.52 \text{ mm}$, right)

Lastly, in Figure 3.9 we report, only for the *realistic* stent and leaflets models, the computational meshes obtained with $H = 0.65 \text{ mm}$ in the whole study population.

3.5. Personalized flow rate profile

We want to prescribe a personalized flow rate profile in the numerical simulations based on early post-TAVI PW Doppler TTE data, which are routinely acquired in the TAVI framework to assess post-TAVI hemodynamics. In particular, in this thesis we consider two strategies also to derive the personalized flow rate profile, namely a *simplified* strategy and a *realistic* strategy.

Simplified strategy In the *simplified* strategy we start from the physiological waveform taken from [45] (see Figure 3.10) and we adapt its magnitude to match the patient-specific cardiac output computed in the clinics. Specifically, in the clinical settings the patient's cardiac output is computed from PW Doppler data as follows:

$$CO_{clin} = \pi \left(\frac{D_{LVOT}}{2} \right)^2 * VTI_{LVOT} * HR, \quad (3.2)$$

where CO_{clin} is the cardiac output computed in the clinics, D_{LVOT} is the diameter of the Left Ventricular Outflow Tract (LVOT), VTI_{LVOT} is the approximated time integral of the velocity magnitude at the center of the LVOT, and HR is the heart rate. By using this

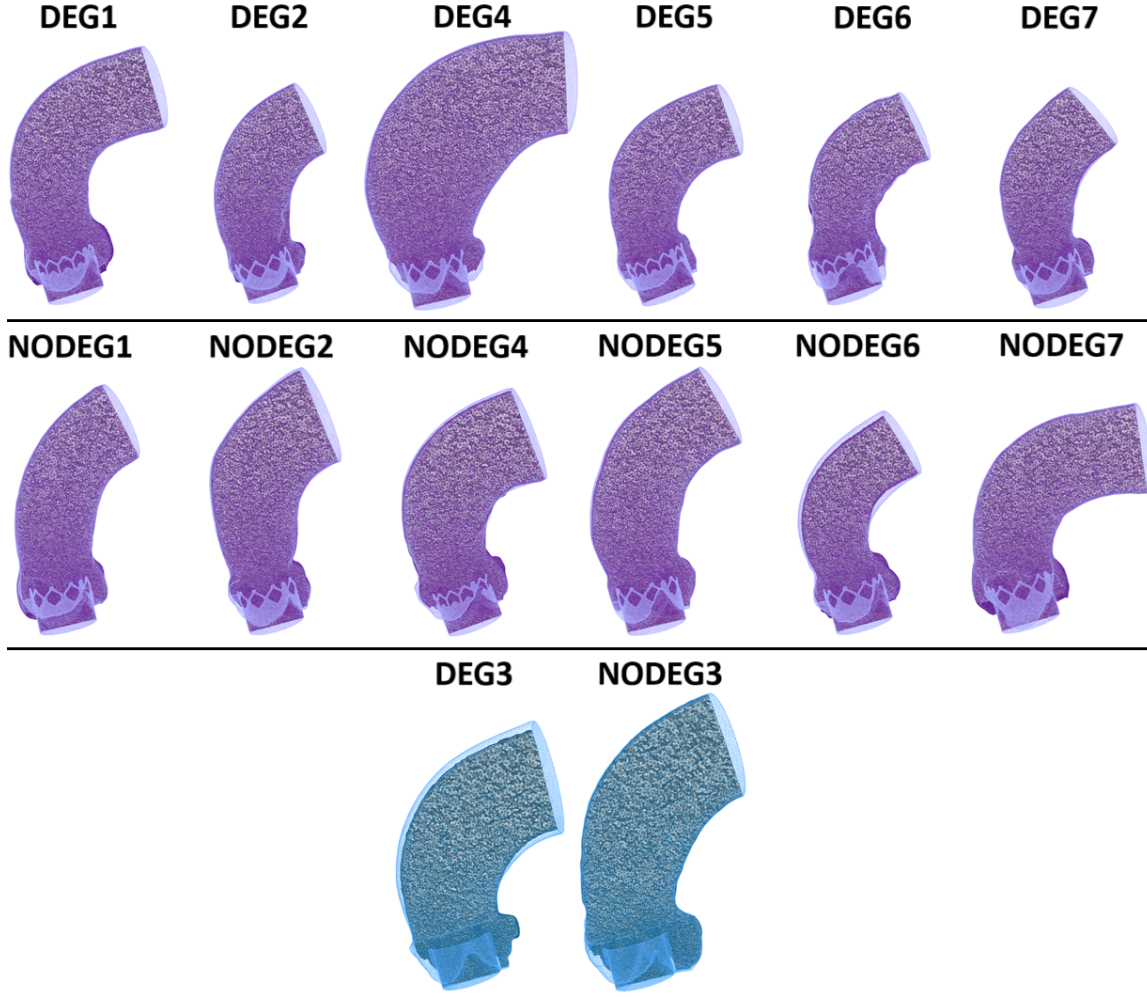


Figure 3.9: For each patient in the study population we report a longitudinal slice of the associated computational mesh together with the external surface edges. Purple: *realistic* strategy for stent model. Blue: *simplified* strategy for stent model. Notice that the *realistic* strategy could not be employed for patients DEG3 and NODEG3 due to a lack of data (see Section 3.2.1).

formula clinicians assume a circular cross-section of the LVOT and a flat velocity profile in the LVOT. Notice that the cardiac output for patients DEG3 and NODEG3 could not be computed due to the unavailability of the early post-TAVI PW Doppler TTE data (see Table 3.2), thus the average of the cardiac outputs in the study population is considered for these two patients

Realistic strategy In the *realistic* strategy we correct the cardiac output clinical measure and we exploit the PW Doppler TTE image, which provides a temporal measurement of the blood velocity at the center of the LVOT for consecutive heartbeats (see Figure

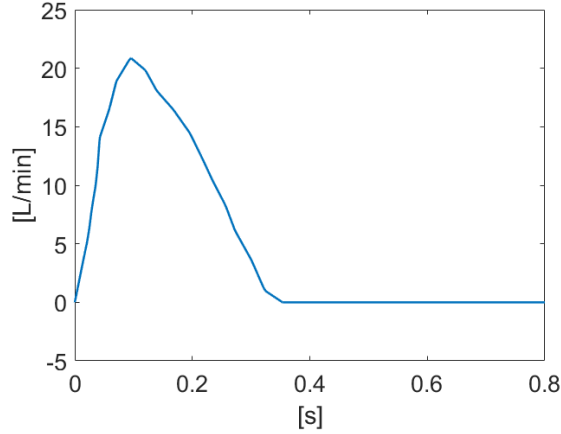


Figure 3.10: Physiological flow rate profile taken from [45] and used to derive a personalized flow rate profile. *Simplified* strategy.

3.11-(A.)). Notice that, due to the unavailability of the PW Doppler TTE image for patients DEG3 and NODEG3 (see Table 3.2), we could only employ the *simplified* strategy for these patients and not the *realistic* one.

Let us notice that Equation (3.2) tends to overestimate the real cardiac output by about 15% [204] due to the skewness of the real velocity profile. Accordingly, in the *realistic* strategy we correct the clinical cardiac output so to eliminate this overestimation (for simplicity assumed to be equal to 15% in all the patients).

Furthermore, we assume that the inlet flow rate shares the same temporal evolution profile as the blood velocity inside the LVOT, that we reconstruct from the available PW Doppler TTE image. Finally, we scale the profile to match the patient’s corrected cardiac output. The resulting flow rate is characterized by a patient-specific mean value (i.e. the corrected cardiac output), heart rate, and partition between systolic and diastolic phase.

More specifically, for each visible heartbeat, we manually draw on the PW Doppler TTE image the velocity temporal evolution during systole, following the Doppler signal’s contour and the drawings performed by clinicians, if present. These manual drawings were validated by an expert clinician for the whole study population. Then, using *WebPlot-Digitizer*, we digitalize the drawn profiles and we identify the end of the heartbeat. In particular, the end of the heartbeat is identified exploiting the electrocardiographic signal, available in the image, and the start of the velocity signal of the following heartbeat. Finally, we average the digitalized signals between the different heartbeats and we scale the averaged profile to match the patient-specific cardiac output and heart rate. The full procedure is schematized in Figure 3.11.

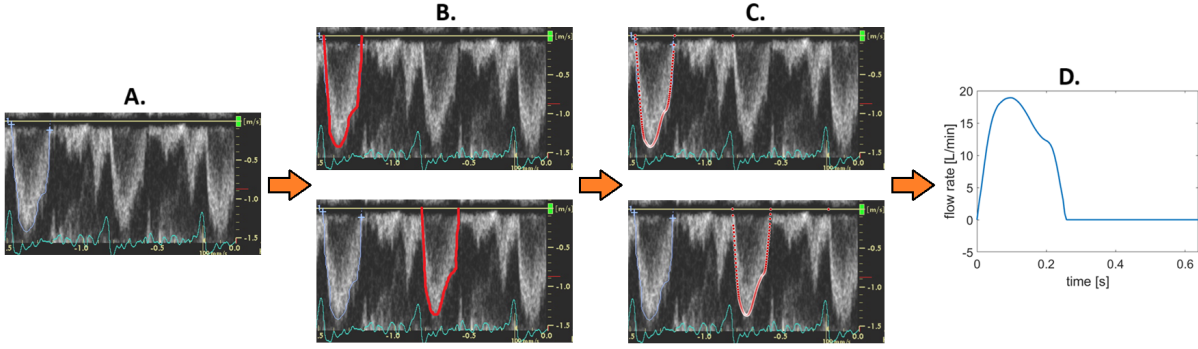


Figure 3.11: Derivation of the personalized flow rate profile. Starting from a PW Doppler TTE image (A.), we manually draw the temporal evolution of the blood velocity during systole for each visible heartbeat (B.), we digitalize each drawing and identify the end of the heartbeat (C.), we average the digitalized profiles between the heartbeats and we rescale the averaged profile to match the patient's cardiac output and heart rate (D.). *Realistic* strategy.

We report in Figure 3.12 the personalized flow rate profiles obtained for each patient with available data following the *realistic* strategy presented above.

We notice that in the *Realistic* strategy we are assuming that the flow rate profile shares the same temporal trend of the blood velocity in the LVOT, measured for the patient by Echo Doppler. The accuracy of this assumption depends on the skewness of the velocity profile, which is not known. However, the phase discrepancy between the two signals is expected to be small, and this strategy is anyway patient-specific, thus more accurate than considering a flow rate taken from the literature, as done in the *Simplified* strategy.

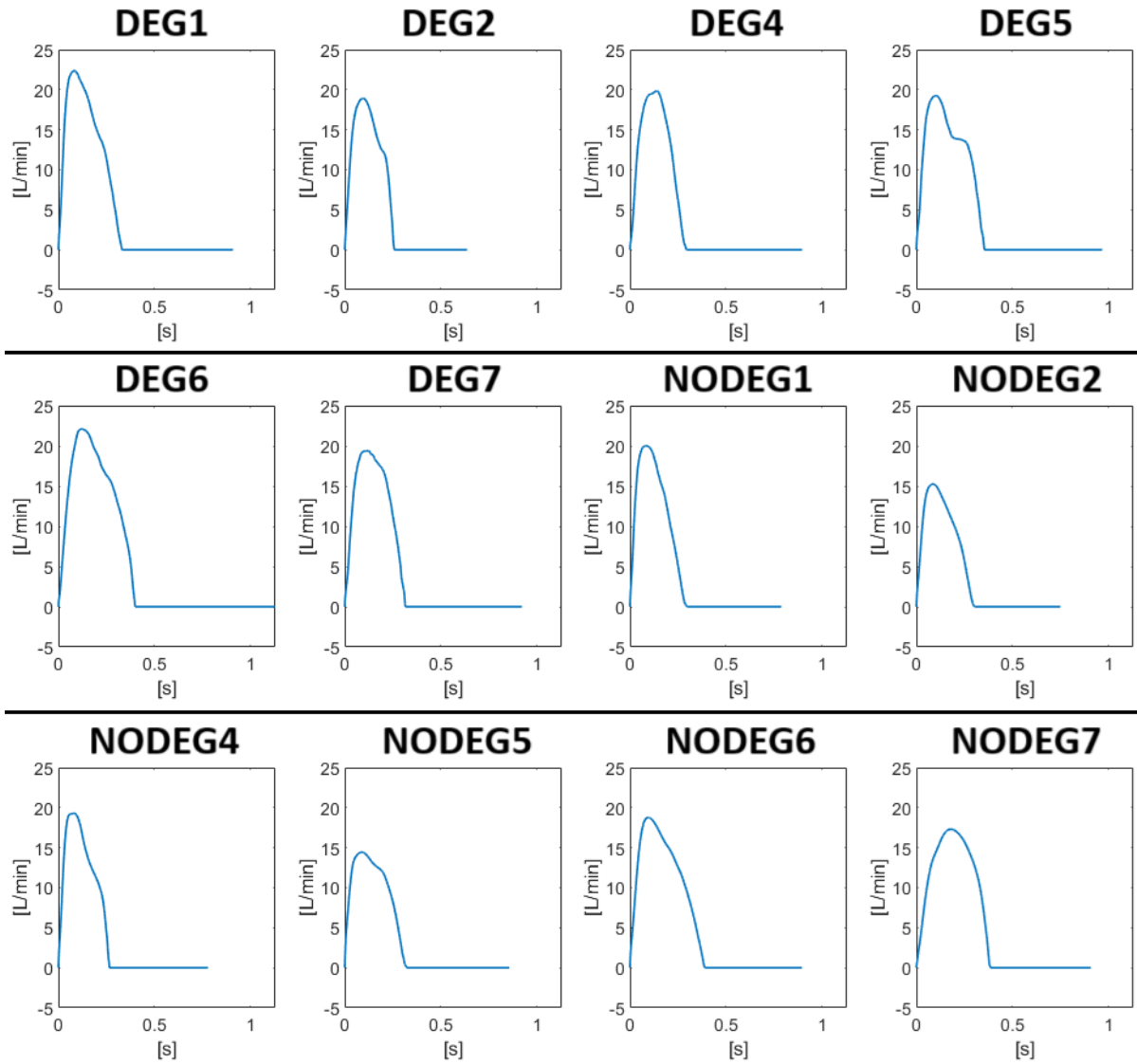


Figure 3.12: For each patient in the study population we report the associated personalized flow rate profile. *Realistic* strategy.

4 | Mathematical modeling and numerical methods for post-TAVI hemodynamics

This chapter introduces the mathematical model and associated numerical methods characterizing our Computational Fluid Dynamics (CFD) analysis. In particular, we present the mathematical equations describing post-TAVI hemodynamics with a moving immersed surface (Section 4.1); finally, we deal with the temporal and spatial discretization of these equations and we discuss the solution of the resulting linear system (Section 4.2).

4.1. Mathematical model for hemodynamics with a moving immersed surface

In this thesis we are interested in studying aortic blood-dynamics in presence of the TAVI bio-prosthetic valve. To this aim, we need a suitable system of mathematical equations describing hemodynamics in presence of a moving immersed surface. In particular, in the following we present our modeling choices (Section 4.1.1), and the boundary conditions (Section 4.1.2); we introduce the strong formulation of the continuous problem (Section 4.1.3); finally we discuss the modeling of the leaflets opening/closure dynamics (Section 4.1.4).

4.1.1. Modeling choices

Blood is modeled as an incompressible homogeneous Newtonian fluid, thus describing its dynamics with the Navier-Stokes (NS) equations. Blood is a two-phase fluid made of cellular components (e.g. red blood cells) and a liquid solution (plasma). However, in large vessels like the aorta the incompressible homogeneous Newtonian assumption is commonly accepted [43, 136, 190], due to the small dimension of the cellular elements with respect to the vessel. This assumption allows us to reduce the modeling complexity,

and the computational cost of the numerical simulations.

The aortic wall is modeled as rigid, thus neglecting its compliance. This choice significantly reduces the computational cost related to the numerical simulations and it is motivated by the fact that we study elderly patients which are usually characterized by a limited tissue elasticity due to stiffening and calcifications.

The blood flow in the ascending aorta is expected to be turbulent due to the high Reynolds number and its pulsatile nature, as shown in [218]. Turbulence acts at very small length scales, thus a very refined computational mesh is needed to explicitly capture its effect, but this is unfeasible due to the associated computational cost. For this reason in this thesis we employ a Large Eddy Simulation (LES) turbulence model, which is most suitable due to its capability to capture the laminar, transitional, and turbulence features characterizing the cardiac cycle [151]. This approach is based on the application of a low-pass filter to the NS equations, which allows to avoid the simulation of the small length scales while retaining information on their effect through the modeling of the nonlinear filtered advection term [26]. Different LES models have been proposed based on different approaches to model this term and we consider the LES σ -model [170], which proved to perform well in closed channel configurations (which is the case of interest in this thesis), showing accurate results in the near wall region [200]. The σ -model was also chosen due to its simple implementation, since it only adds a numerical viscosity to the NS equations (4.1).

The bio-prosthetic leaflets are implicitly represented as an immersed surface with the Resistive Immersed Implicit Surface (RIIS) method [79, 94]. This method surrogates the obstruction to the flow given by the presence of the leaflets by adding to the NS momentum equation a local penalization term which represents the adherence of the blood to the leaflets. In particular, a smoothed Dirac delta function is used to impose the penalization term only in a neighborhood of the immersed surface.

4.1.2. Boundary conditions

We report in Figure 4.1 our computational domain Ω , which is the post-TAVI virtual geometry described in Section 3.3. The domain's boundary $\partial\Omega$ comprises the external wall Σ_{wall} , the inlet section Σ_{in} , and the outlet section Σ_{out} . Specifically we impose the following boundary conditions:

- Σ_{wall} : the external wall, made of the aortic wall, the interface between blood and the stent, and the interface between blood and the annulus, is treated as rigid boundary imposing a homogeneous Dirichlet condition (zero velocity), thus employing a CFD framework;

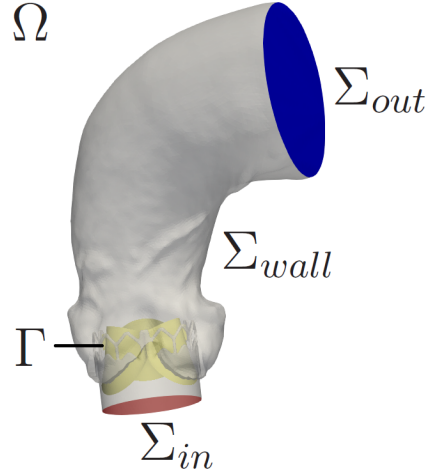


Figure 4.1: Representation of the computational domain Ω with its boundaries: the external wall Σ_{wall} (gray), the inlet section Σ_{in} (red), and the outlet section Σ_{out} (blue). The bio-prosthetic leaflets surface Γ is also reported (yellow).

- Σ_{in} : a flow rate condition, prescribing the personalized flow rate profile derived in Section 3.5, is imposed at the inlet boundary. This condition does not provide enough information to close the NS system and we will discuss its prescription in Section 4.2.2;
- Σ_{out} : a homogeneous Neumann condition (zero stress) is imposed at the outlet boundary Σ_{out} . The outlet condition morally sets a zero pressure at the outlet, which is non physiological. This is done since, in a CFD setting, the NS pressure is defined up to a constant, thus solving for a physiological pressure or a zero pressure is equivalent in terms of the velocity field and the pressure gradient.

4.1.3. Strong formulation of the continuous problem

The resulting strong formulation of the considered mathematical model reads:

Given $Q : [0, T] \rightarrow \mathbb{R}$ and the initial blood velocity $\mathbf{u}^0 : \Omega \rightarrow \mathbb{R}^3$, for each time $t \in (0, T]$ find the filtered blood velocity $\mathbf{u} : \Omega \rightarrow \mathbb{R}^3$ and the filtered blood pressure $p : \Omega \rightarrow \mathbb{R}$,

such that:

$$\rho \frac{D\mathbf{u}}{Dt} + \nabla p - \nabla \cdot [\tau(\mathbf{u}) + \tau_{sgs}(\mathbf{u})] + \delta_{\Gamma, \epsilon} \frac{R}{\epsilon} (\mathbf{u} - \mathbf{u}^\Gamma) = \mathbf{0} \quad \text{in } \Omega \quad (4.1a)$$

$$\nabla \cdot \mathbf{u} = 0 \quad \text{in } \Omega \quad (4.1b)$$

$$\mathbf{u} = \mathbf{0} \quad \text{on } \Sigma_{wall} \quad (4.1c)$$

$$-p\mathbf{n} + [\tau(\mathbf{u}) + \tau_{sgs}(\mathbf{u})] \mathbf{n} = \mathbf{0} \quad \text{on } \Sigma_{out} \quad (4.1d)$$

$$\int_{\Sigma_{in}} \mathbf{u} \cdot \mathbf{n} \, d\sigma = Q(t) \quad \text{on } \Sigma_{in} \quad (4.1e)$$

where:

- T is a finite time;
- $\rho = 1060 \, \text{kg/m}^3$ is the blood density;
- $\frac{D\mathbf{u}}{Dt} = \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u}$ is the total time derivative of the filtered velocity field;
- $\tau(\mathbf{u}) = \mu(\nabla \mathbf{u} + \nabla^T \mathbf{u})$ is the viscous stress tensor, with $\mu = 3.5 \times 10^{-3} \, \text{Pa} \cdot \text{s}$ the blood viscosity;
- $\tau_{sgs}(\mathbf{u}) = \mu_{sgs}(\mathbf{u})(\nabla \mathbf{u} + \nabla^T \mathbf{u})$ is the subgrid-scale tensor coming from the LES approach, with μ_{sgs} the subgrid-scale viscosity coming from the eddy viscosity assumption [26]. In particular, in the LES σ -model

$$\mu_{sgs}(\mathbf{u}) = \rho (C_{sgs} \Delta(\mathbf{x}, t))^2 \frac{\sigma_3(\sigma_1 - \sigma_2)(\sigma_2 - \sigma_3)}{\sigma_1^2},$$

where C_{sgs} is a suitable constant (in this work 1.5), $\Delta(\mathbf{x}, t)$ is the LES filter width (in this work equal to the diameter of the mesh element), and σ_i are the singular values of $\nabla \mathbf{u}$;

- the last term of equation (4.1a) represents the RIIS method: Γ is the bioprosthetic leaflets surface, $\mathbf{u}^\Gamma$ is the velocity of the bioprosthetic leaflets, R represents a resistance coefficient, and ϵ is a numerical parameter representing the half-thickness of a smoothed Dirac delta function $\delta_{\Gamma, \epsilon}$ centered in Γ :

$$\delta_{\Gamma, \epsilon}(\mathbf{x}, t) = \begin{cases} \frac{1}{2\epsilon} \left(1 + \cos \left(\frac{\pi \xi}{\epsilon} \right) \right) & \text{if } |\xi| \leq \epsilon, \\ 0 & \text{if } |\xi| > \epsilon, \end{cases}$$

where $\xi(\mathbf{x}, t)$ is a time-dependent signed distance function from the bio-prosthetic leaflets surface Γ . In particular, according to the definition of $\delta_{\Gamma, \epsilon}$, the RIIS pe-

nalization term is active only in the points of the mesh which are at a distance smaller than ϵ from the leaflets surface Γ . The value of the resistance coefficient $R = 10^5 \text{ Kg/m} \cdot \text{s}$ has been empirically tuned to effectively obstruct the flow close to the leaflets. Instead, notice that the smoothed delta function $\delta_{\Gamma, \epsilon}(\mathbf{x}, t)$ gives the amount of penalization that the RIIS term introduces in the point $\mathbf{x}$ at time t ; thus, points close to the delta boundary ($|\xi(\mathbf{x}, t)| \approx \epsilon$) are little penalized, whereas points at the center of the delta ($|\xi(\mathbf{x}, t)| \approx 0$) are greatly penalized. This suggests that the effective thickness of the leaflets we are introducing to obstruct the flow is (statistically) equal to half of the delta thickness, that is ϵ . For this reason, we select $\epsilon = 0.4 \text{ mm}$ which is in accordance with literature values for the Edwards SAPIEN leaflets (0.36 mm) [260]. Moreover, we set $\mathbf{u}^\Gamma = \mathbf{0}$, thus considering a quasi-static approach, to avoid numerical instabilities, as commonly done in the literature [24, 41, 266];

- equation (4.1e) prescribes that the flow rate at the inlet boundary Σ_{in} is equal to $Q(t)$, the value at time t of the personalized flow rate profile derived in Section 3.5. Notice that, being an average condition, this is a *defective* condition, i.e. it does not provide enough information to close the NS problem, thus it needs to be completed. The strategy to complete this condition is going to be discussed in Section 4.2.2.

4.1.4. Modeling leaflets dynamics

The bio-prosthetic leaflets are implicitly represented as an immersed surface using the RIIS method presented above in Section 4.1.3. In particular, in this thesis we consider two strategies also to model leaflets dynamics, namely a *simplified* strategy and a *realistic* strategy.

Simplified strategy In the *simplified* strategy the open and closed configurations of the leaflets are used to provide a quasi-static on/off modeling of opening/closure dynamics. Specifically, in the numerical simulations, at each time instant the leaflets surface Γ represents either the open configuration or the closed of the leaflets according to the flow rate profile imposed at the inlet, which identifies the systolic and diastolic phases.

Realistic strategy In the *realistic* strategy we model the transition between the closed and the open configuration of the leaflets. To this aim, in the numerical simulations we move the bio-prosthetic leaflets surface Γ according to an a-priori decided law described in the following.

We use the distance between the fully closed and the fully open configurations of the leaflet

surface, introduced in Section 3.2, to interpolate between the two configurations according to the following law: the opening and closure times are 15 ms and 45 ms , respectively, according to [23]; moreover, the transition between the two configurations is regulated by a valve opening coefficient which follows the cosine-exponential ramps

$$r(t) = \begin{cases} r_{op}(t) = 0.5 \left(1 - \cos \left(\pi \left(\frac{1 - e^{-p_{op}t}}{1 - e^{-p_{op}}} \right) \right) \right) & \text{during opening,} \\ r_{cl}(t) = 1 - 0.5 \left(1 - \cos \left(\pi \left(\frac{1 - e^{-p_{cl}t}}{1 - e^{-p_{cl}}} \right) \right) \right) & \text{during closure,} \end{cases}$$

where t is a standardized time and $p = \{p_{op}, p_{cl}\}$ is a parameter to be calibrated for each phase. We vary $p_{op} \in [2.5, 3.5]$ for the opening ramp and $p_{cl} \in [-3, -2]$ for the closure ramp according to the slope of the input flow rate profile at the opening and closure instants. Specifically, patients showing steeper flow rate profiles are associated to higher absolute values of p . For completeness, in Figure 4.2 we plot the opening and closure ramps for the extreme values of the parameter p .

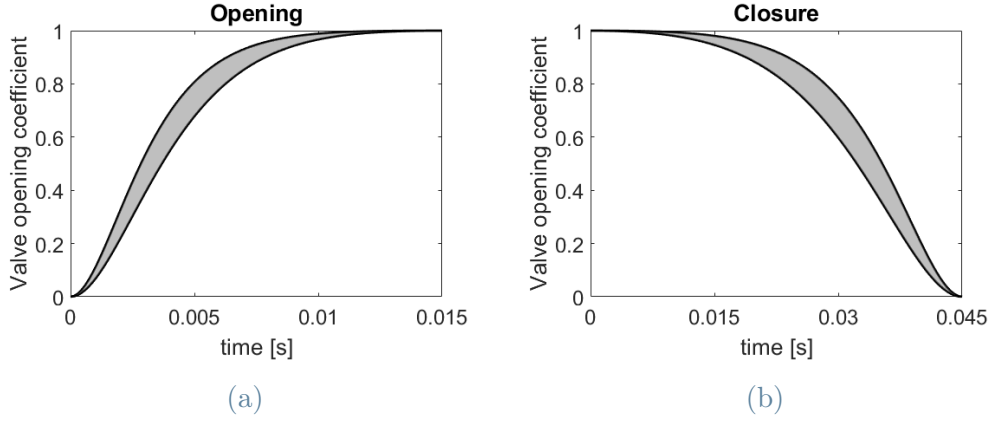


Figure 4.2: Valve opening coefficient as a function of time for the opening (a) and closure (b) phase. These ramps depend on a parameter p which varies in the study population. We plot in black the ramps associated to the extreme values of p and we color in gray the area where the ramps for intermediate values of p lay.

We stress that the leaflets geometry Γ is a surface and we provide a thickness to it directly in the numerical simulations using the smoothed Dirac delta function $\delta_{\Gamma,\epsilon}$.

4.2. Temporal and spatial discretization of the continuous problem

In order to be solved on a computer, the continuous NS equations presented above need to be discretized both in time and in space. In particular, in the following we discuss the numerical methods used to achieve the temporal (Section 4.2.1) and the spatial discretization of the problem, focusing on its Galerkin (Section 4.2.2) and algebraic (Section 4.2.3) formulations.

4.2.1. Temporal discretization

In order to achieve a temporal discretization of the strong formulation (4.1) we introduce a partition $\{t^n\}_{n=0}^N$ of the time interval $[0, T]$ such that $t^n = n\Delta t$, $n = 0, \dots, N$, with $\Delta t > 0$ and $N = \frac{T}{\Delta t}$. Accordingly, we denote as $(\mathbf{u}^n(\mathbf{x}), p^n(\mathbf{x}))$ the approximation of the exact solution $(\mathbf{u}(\mathbf{x}, t), p(\mathbf{x}, t))$ at time t^n .

The time discretization is based on a first order backward Euler scheme with a semi-implicit treatment of the convective term and an explicit treatment of the sub-grid scale viscosity $\mu_{sgs}(\mathbf{u})$.

4.2.2. Galerkin formulation

In order to write the Galerkin formulation of our problem we first need its weak formulation. To this aim, let us introduce the following functional space:

$$V = \{ \mathbf{v} \in [H^1(\Omega)]^3 : \mathbf{v} = \mathbf{0} \text{ on } \Sigma_{wall} \}.$$

The weak formulation of our problem is obtained by multiplying the NS equations (4.1a)-(4.1b) by suitable test functions $(\mathbf{v}, q) \in V \times L^2(\Omega)$, respectively, and integrate them over the whole domain Ω .

Notice that to prescribe the inlet flow rate condition (4.1e) we exploit an augmented weak formulation of the NS problem, as proposed in [87, 242]. In this approach the flow rate boundary condition is considered as a constraint for the solution and enforced using a Lagrange multiplier. Specifically, the problem is closed by imposing that the traction on Σ_{in} is normal to the surface and constant in space. From the properties of the augmented weak formulation, it is possible to show that the physical meaning of the Lagrange multiplier relies precisely in the value of this scalar traction as a function of time [87]. Thus, with this strategy we are in fact prescribing a Neumann (traction) inlet

condition where the prescribed value (the Lagrange multiplier) is at each time unknown and found by the augmented formulation. This allows us to impose the desired flow rate evolution at the inlet boundary without fixing a spatial profile for the velocity field, which would highly influence the results of the numerical simulations [242]. Notice that, in Section 5.5.2 we are going to compare the prescription of a flow rate condition by fixing the spatial velocity profile and by using a Lagrange multiplier.

We discretize our problem in space considering a Continuous Galerkin Finite Elements (FE) approximation with piece-wise linear elements for both the velocity and pressure fields, referred to as P1-P1 elements in the following. To this aim, we consider a finite tetrahedral decomposition $\mathcal{T}_h$ of the domain Ω , such that:

$$\Omega = \bigcup_{K \in \mathcal{T}_h} K,$$

where K is the tetrahedral element of the decomposition $\mathcal{T}_h$ and h is the characteristic size of the tetrahedral elements. Moreover, we introduce the linear continuous FE space:

$$\mathcal{X}_h^1 = \{\omega_h \in \mathcal{C}^0(\overline{\Omega}) : \omega_h|_K \in \mathbb{P}^1(K), \forall K \in \mathcal{T}_h\}$$

and the finite dimensional spaces

$$\begin{aligned} V_h &= V \cap [\mathcal{X}_h^1]^3, \\ M_h &= L^2(\Omega) \cap \mathcal{X}_h^1, \end{aligned}$$

with $\dim(V_h) = N_u < \infty$ and $\dim(M_h) = N_p < \infty$.

The time-discrete Galerkin formulation reads:

For each $n = 0, \dots, N-1$, given $Q^{n+1} \in \mathbb{R}$ and $\mathbf{u}_h^n \in V_h$, find $\mathbf{u}_h^{n+1} \in V_h$, $p_h^{n+1} \in M_h$ and $\lambda^{n+1} \in \mathbb{R}$ such that for all $v_h \in V_h$, $q_h \in M_h$ and $\chi \in \mathbb{R}$,

$$\begin{aligned} \rho \left(\frac{\mathbf{u}_h^{n+1} - \mathbf{u}_h^n}{\Delta t} + (\mathbf{u}_h^n \cdot \nabla \mathbf{u}_h^{n+1}), \mathbf{v}_h \right) - (p_h^{n+1}, \nabla \cdot \mathbf{v}_h) + a(\mathbf{u}_h^n; \mathbf{u}_h^{n+1}, \mathbf{v}_h) \\ + \lambda^{n+1} \int_{\Sigma_{in}} \mathbf{v}_h \cdot \mathbf{n} + \mathcal{R}(\mathbf{u}_h^{n+1}, \mathbf{v}_h) + \mathcal{S}_{mom}(\mathbf{u}_h^n, \mathbf{u}_h^{n+1}, p_h^{n+1}, v_h) = 0, \end{aligned} \quad (4.3a)$$

$$(\nabla \cdot \mathbf{u}_h^{n+1}, q_h) + \mathcal{S}_{mass}(\mathbf{u}_h^n, \mathbf{u}_h^{n+1}, p_h^{n+1}, q_h) = 0, \quad (4.3b)$$

$$\chi \int_{\Sigma_{in}} \mathbf{u}_h^{n+1} \cdot \mathbf{n} = \chi Q^{n+1}, \quad (4.3c)$$

with

$$a(\mathbf{u}_h^n; \mathbf{u}_h^{n+1}, \mathbf{v}_h) = (\mu + \mu_{sgs}(\mathbf{u}_h^n)) (\nabla \mathbf{u}_h^{n+1} + \nabla^T \mathbf{u}_h^{n+1}, \nabla v_h),$$

$$\mathcal{R}(\mathbf{u}_h^{n+1}, \mathbf{v}_h) = \left(\delta_{\Gamma, \epsilon} \frac{R}{\epsilon} \mathbf{u}_h^{n+1}, \mathbf{v}_h \right)$$

where the expression $(\cdot, \cdot)$ stands for the L^2 scalar product in Ω for scalars, vectors and tensors. Additionally, λ is the Lagrange multiplier introduced to impose the defective flow rate condition at the inlet (4.1e) as an extra row of the weak formulation (4.3c) and the terms $\mathcal{S}_{mom}(\mathbf{u}_h^n, \mathbf{u}_h^{n+1}, p_h^{n+1}, v_h)$ and $\mathcal{S}_{mass}(\mathbf{u}_h^n, \mathbf{u}_h^{n+1}, p_h^{n+1}, v_h)$ account for the stabilization terms. Specifically, we use a Streamline Upwind Petrov-Galerkin/Pressure Stabilizing Petrov-Galerkin (SUPG/PSPG) [230] stabilization for the advection-dominated regime and the use of P1-P1 spaces, which are inf-sup unstable, and a backflow stabilization [159] at the outlet to address possible numerical instabilities arising from the presence of recirculating areas.

4.2.3. Algebraic formulation

Let us introduce the vectorial Lagrangian basis function $\{\psi_j\}_{j=1}^{N_u}$ for the velocity and the scalar Lagrangian basis functions $\{\zeta_l\}_{l=1}^{N_p}$ for the pressure. Notice that vectorial basis functions can be derived from scalar basis functions [23]. Accordingly, we can write:

$$\mathbf{u}_h^{n+1}(\mathbf{x}) = \sum_{j=1}^{N_u} U_j^{n+1} \psi_j(\mathbf{x}), \quad (4.5a)$$

$$p_h^{n+1}(\mathbf{x}) = \sum_{l=1}^{N_p} P_l^{n+1} \zeta_l(\mathbf{x}). \quad (4.5b)$$

Substituting these expressions inside the Galerkin formulation (4.3a) we get the following linear algebraic system of equations:

$$\begin{bmatrix} \frac{\rho}{\Delta t} M + \rho C(\mathbf{U}^n) + A(\mathbf{U}^n) + R + Z_K & B^T + Z_B^T & \Phi^T \\ -B + Z_B & Z & 0 \\ \Phi & 0 & 0 \end{bmatrix} \begin{bmatrix} \mathbf{U}^{n+1} \\ \mathbf{P}^{n+1} \\ \lambda^{n+1} \end{bmatrix} = \begin{bmatrix} \mathbf{F}^{n+1} \\ \mathbf{0} \\ Q^{n+1} \end{bmatrix}, \quad (4.6)$$

where:

- $[M]_{ij} = (\psi_j, \psi_i)$, $i, j = 1, \dots, N_u$ is the velocity mass matrix;
- $[C(\mathbf{U}^n)]_{ij} = (\mathbf{u}_h^n \cdot \nabla \psi_j, \psi_i)$, $i, j = 1, \dots, N_u$ is the matrix associated to the convective term;

- $[A(\mathbf{U}^n)]_{ij} = (\mu + \mu_{sgs}(\mathbf{u}_h^n)) (\nabla \boldsymbol{\psi}_j + \nabla^T \boldsymbol{\psi}_j, \nabla \boldsymbol{\psi}_i)$, $i, j = 1, \dots, N_u$ is the stiffness matrix, accounting for the μ_{sgs} term;
- $[R]_{ij} = \left(\delta_{\Gamma, \epsilon} \frac{R}{\epsilon} \boldsymbol{\psi}_j, \boldsymbol{\psi}_i \right)$, $i, j = 1, \dots, N_u$ is the matrix associated to the RIIS term;
- $[B]_{l,j} = (\zeta_l, \nabla \cdot \boldsymbol{\psi}_j)$, $l = 1, \dots, N_p$, $j = 1, \dots, N_u$;
- $[\Phi]_j = \int_{\Sigma_{in}} \boldsymbol{\psi}_j \cdot \mathbf{n}$, $j = 1, \dots, N_u$;
- Z_K , Z_B , and Z account for stabilization terms;
- $[\mathbf{U}^{n+1}]_j = U_j^{n+1}$, $j = 1, \dots, N_u$ and $[\mathbf{P}^{n+1}]_l = P_l^{n+1}$, $l = 1, \dots, N_p$;
- $\mathbf{F}^{n+1} = \frac{\rho}{\Delta t} M \mathbf{U}^n$.

Notice that the system (4.6) differs from a classical 2×2 NS block system for the presence of an extra block introduced by the Lagrange multiplier method. In this thesis, the algebraic linear system (4.6) is monolithically solved at each time-step using a preconditioned GMRES iterative solver [206]. To this aim, we propose two possible extensions of a classical 2×2 block preconditioner, the SIMPLE preconditioner, to the augmented 3×3 case. Specifically, we propose a simplified extension of the SIMPLE preconditioner that was used in [58] and a complete extension of the same preconditioner that was later used in [59]. These two extension of the SIMPLE preconditioner to the augmented case are going to be discussed in Chapter 5 together with some numerical results demonstrating their performance.

For the implementation of the mathematical and numerical methods presented in this chapter we rely on the multi-physics high-performance Finite Element library life^x [3, 6], developed at MOX, Dipartimento di Matematica, with the collaboration of LaBS, Dipartimento di Chimica, Materiali ed Ingegneria Chimica (both at Politecnico di Milano).

5 | Inexact block preconditioners for incompressible fluids with flow rate conditions

This chapter deals with the numerical solution of a Navier-Stokes (NS) problem with flow rate conditions which is the case of interest in this thesis, where a flow rate condition is prescribed at the inlet section to numerically simulate post-TAVI hemodynamics (see Chapter 4). Specifically, flow rate conditions are average conditions which do not provide enough information to close the NS problem (*defective* conditions), and in this thesis we consider the Lagrange multiplier method in order to complete them. This method introduces a Lagrange multiplier to prescribe a flow rate condition, so that the algebraic block system (4.6) we are interested in solving presents an extra block related to the Lagrange multiplier. Thus, in order to efficiently solve the augmented block system (4.6) monolithically, ad-hoc numerical strategies are required. To this aim, we propose two extensions of a standard NS preconditioner, the SIMPLE preconditioner, based on an inexact block factorization of the augmented system matrix. In particular, we propose a *simplified* preconditioner that was used in [58] and a *complete* preconditioner that was later used in [59]. Lastly, we present some numerical results demonstrating the performance of the two proposed extended preconditioners.

Notice that, despite in this thesis we are interested in the prescription of one flow rate condition, in this chapter we consider the case of multiple flow rate conditions. This is done to assess the properties of the proposed preconditioners using specific test cases.

The outline of the chapter is as follows: we give an overview on defective flow rate boundary conditions and discuss the motivations to propose a preconditioner for the monolithic augmented block system (Section 5.1); we provide a review of the augmented Navier-Stokes flow rate problem (Section 5.2) and of the SIMPLE preconditioner (Section 5.3); we propose an extension of the SIMPLE preconditioner (Section 5.4), discussing its formulation (Section 5.4.1) and introducing an efficient variant used in practice (Section 5.4.2);

finally we provide some numerical results (Section 5.5), presenting the setting of our numerical experiments which involves a trivial extension of the SIMPLE preconditioner (Section 5.5.1), highlighting the advantages of treating defective flow rate condition with a Lagrange multipliers approach (Section 5.5.2), investigating the scalability properties of our preconditioner (Section 5.5.3), testing the performance of the proposed preconditioners for a varying number of Lagrange multipliers (Section 5.5.4) and in real-life hemodynamic scenarios (Section 5.5.5), and addressing the impact of the approximations used in the preconditioner's efficient variant (Section 5.5.6).

The content of this chapter is taken from the manuscript “Inexact Block LU Preconditioners for Incompressible Fluids with Flow Rate Conditions” [57] first published in Communications in Computational Physics 39(2), published by Global Science Press¹.

5.1. Overview and motivations

Incompressible Navier-Stokes equations are commonly used in engineering applications to study the dynamics of viscous fluids. Given a bounded domain $\Omega \subset \mathbb{R}^3$, classical boundary conditions impose three (one for each spatial dimension) point-wise data on the domain's boundary $\partial\Omega$, typically prescribing the components of the velocity field (Dirichlet condition), of the Cauchy normal stress (Neumann condition), or a combination of the two (Robin condition).

On the other hand, in some applications the only information available often provides average conditions which are not enough to close the problem and thus need to be completed [54]. This is the case of the defective flow rate condition (4.1e) introduced in Section 4.1.3.

Some examples arise in blood-dynamics simulations, where clinical measures often provide information on the *flow rate* [189, 242], and flow in pipes simulations, where sensors measure the fluid flow rate [33, 183]. Moreover, in the *geometric multiscale approach* [188], where mathematical models with different spatial dimensions are coupled, the information provided by the lower-dimensional problem is not enough to close the higher-dimensional one [31, 133].

Regarding defective flow rate conditions, a widely employed strategy to close the problem, thanks to its practicality, is to prescribe a Dirichlet condition by assuming a-priori a spatial profile for the velocity field. In this case, the computational domain is often extended to reduce the impact of the chosen profile on the accuracy of the numerical solution. A more mathematically sound approach was proposed in [114], where the authors

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introduced a suitable variational formulation of the problem which includes the given flow rate data. However, this approach requires the definition of non-standard finite-dimensional subspaces which makes it problematic to implement in practice [243]. Hence, several alternative approaches have been proposed in the literature [85] based on Lagrange multipliers [88, 242], control theory [89, 132] and the Nitsche method [244, 267].

The Lagrange multiplier approach was proposed in [88] and applied to a quasi-Newtonian Stokes problem [76], in a fluid-structure interaction framework [90] and in practical hemodynamic problems with patient-specific geometries [58, 245]. In this approach, flow rate boundary conditions are considered as a constraint for the solution and enforced using Lagrange multipliers, resulting in an augmented weak formulation of the Navier-Stokes problem. The problem is closed by assuming that, on the considered portion of the domain's boundary, the Cauchy normal stress has zero tangential components and its normal component is constant in space. The resulting augmented problem can be solved by splitting the computation of the velocity/pressure fields and of the Lagrange multipliers in order to resort to available standard solvers for the solution of the Navier-Stokes step [242, 243]. However, iterative procedures based on this splitting can be very expensive in complex applications. In the recent work [116], the authors proposed monolithic block preconditioners based on inexact factorizations to deal with defective conditions arising from the coupling with lumped parameter models.

In order to efficiently solve the augmented Finite Element system, in this thesis we consider a monolithic strategy and we propose a suitable block preconditioner for its efficient solution. Specifically, we start from the SIMPLE (Semi-Implicit Method for Pressure Linked Equations) iterative solution strategy [179], studied as a preconditioner in [73, 74, 138, 180], and we extend it to the augmented flow rate defective case. To test the effectiveness of our proposal, we present several numerical results in both idealized and real-life scenarios.

5.2. Review of the augmented flow rate problem

For the sake of exposition we report here a simplified version of the NS equations presented in Chapter 4 with an arbitrary number of flow rate conditions.

We are interested in solving the incompressible unsteady Navier-Stokes equations for a

homogeneous Newtonian fluid in a bounded domain $\Omega \subset \mathbb{R}^3$:

$$\begin{aligned} \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} + \nabla p - \nu \Delta \mathbf{u} &= \mathbf{f}, & t > 0, \\ \nabla \cdot \mathbf{u} &= 0, & t > 0, \\ \mathbf{u} &= \mathbf{u}_0, & t = 0, \end{aligned}$$

supplemented by the following boundary conditions:

$$\mathbf{u} = \mathbf{0} \quad \text{on } \Gamma^D \quad (5.1a)$$

$$-p\mathbf{n} + \nu \frac{\partial \mathbf{u}}{\partial \mathbf{n}} = \mathbf{0} \quad \text{on } \Gamma^N \quad (5.1b)$$

$$\int_{\Gamma_i} \mathbf{u} \cdot \mathbf{n} \, d\gamma = Q_i \quad \text{on } \Gamma_i, \, i = 1, \dots, m \quad (5.1c)$$

where $\mathbf{u}$ and p are the fluid velocity and pressure, respectively, ν is the kinematic viscosity, $\mathbf{f}$ is the forcing term, $\mathbf{u}_0$ is the velocity initial datum, $\mathbf{n}$ is the outward unit normal vector on $\partial\Omega$ and $\partial\Omega = \Gamma^D \cup \Gamma^N \cup (\bigcup_{i=1}^m \Gamma_i)$ (see Figure 5.1). Notice that, for the sake of simplicity, in this chapter we assume that the fluid density is equal to $1 \, g/cm^3$. Moreover, we are considering homogeneous Dirichlet and Neumann conditions; all the findings of this chapter could be easily extended to the non-homogeneous case as well. Equation (5.1c) expresses defective boundary conditions, imposing time-dependent flow rates $Q_i = Q_i(t)$ on sections Γ_i , $i = 1, \dots, m$. We assume $\Gamma^N \neq \emptyset$ (which is the case of interest in our numerical experiments), so that the incompressibility constraint is satisfied without any restriction on the choice of the flow rates Q_i [88].

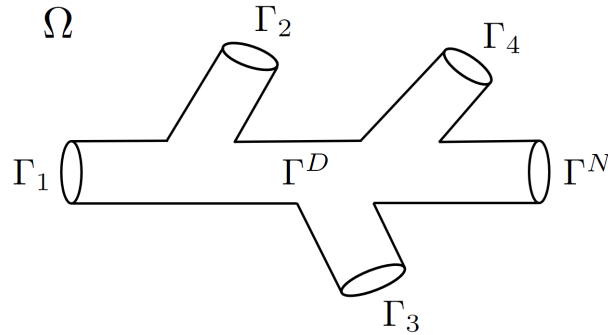


Figure 5.1: Sketch of a domain Ω , with the partition of its boundary. In this example $m = 4$.

Let us introduce the following functional space:

$$V = \{ \mathbf{v} \in [H^1(\Omega)]^3 : \mathbf{v} = \mathbf{0} \text{ on } \Gamma^D \}.$$

Then, the augmented variational formulation, corresponding to boundary conditions (5.1), as proposed in [86, 88], reads:

Given $\mathbf{f} \in L^2(\Omega)$ for almost all $t \in (0, T]$, $Q_i : [0, T] \rightarrow \mathbb{R}$, $i = 1, \dots, m$, and $\mathbf{u}_0 \in V$, find $\mathbf{u} \in V$ and $p \in L^2(\Omega)$, for almost all $t \in (0, T]$, and functions of time $\lambda_i : [0, T] \rightarrow \mathbb{R}$, $i = 1, \dots, m$, such that, for all $\mathbf{v} \in V$, $q \in L^2(\Omega)$ and $\chi \in \mathbb{R}$,

$$\begin{aligned} \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u}, \mathbf{v} \right) + \nu (\nabla \mathbf{u}, \nabla \mathbf{v}) - (p, \nabla \cdot \mathbf{v}) + \sum_{i=1}^m \lambda_i \int_{\Gamma_i} \mathbf{v} \cdot \mathbf{n} \, d\gamma &= (\mathbf{f}, \mathbf{v}), \\ (q, \nabla \cdot \mathbf{u}) &= 0, \\ \chi \int_{\Gamma_i} \mathbf{u} \cdot \mathbf{n} \, d\gamma &= \chi Q_i, \quad i = 1, \dots, m, \end{aligned} \tag{5.2}$$

with $\mathbf{u} = \mathbf{u}_0$ for $t = 0$.

In formulation (5.2), the expression $(\cdot, \cdot)$ stands for the L^2 scalar product in Ω , for scalars, vectors and tensors, whereas λ_i are the Lagrange multipliers introduced to enforce the defective flow rate boundary conditions (5.1c).

In [242] the authors proved that, for sufficiently smooth data Q_i with $\sum_i |Q_i|$ and the initial datum small enough, problem (5.2) is locally well-posed, i.e. there exists a time $T^* > 0$ such that a solution $(\mathbf{u}, p, \{\lambda_i\}_{i=1, \dots, m})$ exists for any $t \in [0, T^*]$.

We consider a Galerkin approximation of formulation (5.2) by introducing the finite-dimensional spaces $V_h \subset V$, with basis functions $\{\psi_j\}_{j=1}^{N_u}$, and $M_h \subset L^2(\Omega)$, with basis functions $\{\zeta_\ell\}_{\ell=1}^{N_p}$. Moreover, we consider a first order backward difference (BDF1) scheme for the time discretization, with a semi-implicit treatment of the convective term. Then, the augmented algebraic monolithic system associated to formulation (5.2), accounting for stabilization terms for advection dominated regimes and inf-sup condition (in our case the SUPG-PSPG strategy [231]), reads:

$$\begin{bmatrix} K & B^T & \Phi^T \\ -B & Z & 0 \\ \Phi & 0 & 0 \end{bmatrix} \begin{bmatrix} \mathbf{U} \\ \mathbf{P} \\ \mathbf{\Lambda} \end{bmatrix} = \begin{bmatrix} \mathbf{F} \\ \mathbf{0} \\ \mathbf{Q} \end{bmatrix} \tag{5.3}$$

where all the unknown vectors are evaluated at the current time t^{n+1} (the apex $n+1$ is not reported for simplicity), with $t^n = n\Delta t$, $n = 0, 1, \dots, N_T$, Δt the time-step and $N_T = \frac{T}{\Delta t}$. In particular, $\mathbf{U} \in \mathbb{R}^{N_u}$, $\mathbf{P} \in \mathbb{R}^{N_p}$ and $\mathbf{\Lambda} \in \mathbb{R}^m$ are the solution vectors for the velocity, pressure and Lagrange multipliers, respectively. Moreover, $K = \frac{1}{\Delta t}M + \zeta + C(\mathbf{U}^n) + Z_K$, where M is the velocity mass matrix, ζ is the stiffness matrix, $C(\mathbf{U}^n)$ is the matrix associated to the convective term, with $\mathbf{U}^n$ the known velocity vector at the previous time-step t^n and Z_K accounts for stabilization terms. Finally, $B = \tilde{B} + Z_B$, with $[\tilde{B}]_{\ell j} = -(\zeta_\ell, \nabla \cdot \boldsymbol{\psi}_j)$, $\ell = 1, \dots, N_p$, $j = 1, \dots, N_u$ and Z_B accounts for stabilization terms, $[\Phi]_{ij} = \int_{\Gamma_i} \boldsymbol{\psi}_j \cdot \mathbf{n} \, d\gamma$, $i = 1, \dots, m$, $j = 1, \dots, N_u$, Z accounts for stabilization terms in block (2, 2), $[\mathbf{F}]_j = (\mathbf{f}(t^{n+1}), \boldsymbol{\psi}_j) + \frac{1}{\Delta t} [M\mathbf{U}^n]_j$, $j = 1, \dots, N_u$, and $[\mathbf{Q}]_i = Q_i(t^{n+1})$, $i = 1, \dots, m$.

Analyzing the structure blocks of (5.3) this is a double saddle-point problem. The inner one (stabilized standard Navier-Stokes problem) is invertible due to the definite positive-ness of K and the presence of SUPG/PSPG stabilization terms. Now, we notice that $[\Phi^T \mathbf{\Lambda}]_j = \sum_{i=1}^m \lambda_i \int_{\Gamma_i} \boldsymbol{\psi}_j \cdot \mathbf{n} \, d\gamma$. It is trivial to prove that the latter quantity is equal to zero $\forall j = 1, \dots, N_u$ if and only if $\mathbf{\Lambda} = \mathbf{0}$. This means that $\ker \Phi^T = \mathbf{0}$, leading to the solvability of (5.3).

In such a context, the design of block preconditioners based on a block LU factorization which involves the Schur complement matrix is a standard approach [75]. Specifically, we focus on the SIMPLE preconditioner, which proved to be the most effective with respect to other preconditioners of this class for a standard Navier-Stokes problem in realistic scenarios [65]. This strategy will be at the base of our proposal for solving (5.3), see Section 5.4.1.

5.3. Review of the SIMPLE preconditioner

Let us consider the algebraic system arising from the discretization of Navier-Stokes equations with classical boundary conditions, accounting for possible stabilization terms:

$$A\mathbf{x} := \begin{bmatrix} K & B^T \\ -B & Z \end{bmatrix} \begin{bmatrix} \mathbf{U} \\ \mathbf{P} \end{bmatrix} = \begin{bmatrix} \mathbf{F} \\ \mathbf{0} \end{bmatrix} =: \mathbf{b} \quad (5.4)$$

where each matrix and vector in system (5.4) was defined at the end of Section 5.2.

The SIMPLE algorithm was proposed in [179] as an iterative method to solve system (5.4). We report here a SIMPLE-like solver algorithm which first solves for a compressible intermediate velocity, then solves for the pressure and finally compute a velocity correction

in order to impose mass-continuity:

SIMPLE-like solver algorithm:

1. Solve for the intermediate velocity: $K\tilde{\mathbf{U}} = \mathbf{F}$,
2. Solve for the pressure: $S\mathbf{P} = B\tilde{\mathbf{U}}$,
3. Compute the velocity correction: $\mathbf{U} = \tilde{\mathbf{U}} - D^{-1}B^T\mathbf{P}$,

where $S = BD^{-1}B^T + Z$ is an approximation of the pressure Schur complement $BK^{-1}B^T + Z$, with $D = \text{diag}(K)$. Note that using a diagonal approximation of K makes it possible to explicitly invert the matrix and thus to assemble the approximate Schur complement.

This algorithm can be seen as an approximate solution of problem (5.4), obtained by using the following inexact block LU factorization of A :

$$P_S = \begin{bmatrix} K & 0 \\ -B & S \end{bmatrix} \begin{bmatrix} I & D^{-1}B^T \\ 0 & I \end{bmatrix}. \quad (5.5)$$

On the other hand, one can use P_S as a preconditioner to solve problem (5.4) with a Krylov subspace method, such as GMRES [206]. So that, the computation of the preconditioned residual at the k -th iteration of the Krylov method reads

$$P_S \mathbf{z}^{(k)} = \mathbf{b} - A\mathbf{x}^{(k)} =: \mathbf{r}^{(k)},$$

that is:

$$\begin{cases} K\mathbf{y}_1^{(k)} = \mathbf{r}_1^{(k)}, \\ S\mathbf{y}_2^{(k)} = B\mathbf{y}_1^{(k)} + \mathbf{r}_2^{(k)}, \\ \mathbf{z}_1^{(k)} = \mathbf{y}_1^{(k)} - D^{-1}B^T\mathbf{z}_2^{(k)}, \\ \mathbf{z}_2^{(k)} = \mathbf{y}_2^{(k)}, \end{cases}$$

where given $\mathbf{w} \in \mathbb{R}^{N_U+N_P}$ we indicate by $\mathbf{w}_1 \in \mathbb{R}^{N_U}$ the first N_U components and by $\mathbf{w}_2 \in \mathbb{R}^{N_P}$ the last N_P components and $\mathbf{y}^{(k)}$ is an intermediate vector.

Remark 5.3.1. *Several approximate solution methods and corresponding preconditioners for system (5.4) are based on an inexact block LU factorization of the system matrix. We report here a general form of the factorization, as proposed in [187]:*

$$\begin{bmatrix} K & 0 \\ -B & BH_1B^T + Z \end{bmatrix} \begin{bmatrix} I & H_2B^T \\ 0 & I \end{bmatrix},$$

where H_1 and H_2 are approximations of K^{-1} . Some notable examples are SIMPLE ($H_1 = H_2 = \text{diag}(K)^{-1}$), Chorin-Temam ($H_1 = H_2 = \Delta t M^{-1}$) and Yosida ($H_1 = \Delta t M^{-1}$, $H_2 = K^{-1}$), where M is the velocity mass matrix.

5.4. Extension of the SIMPLE preconditioner to the flow rate augmented problem

In this section we present the main novelty of this work which is the extension, based on an inexact factorization, of the standard SIMPLE preconditioner (5.5) to the augmented problem (5.3). We stress that this extension is in principle not immediate due to the 3×3 nature of the matrix in (5.3) (vs the 2×2 nature of the standard NS matrix), which requires specific and suitable choices of the inexact factors.

5.4.1. Formulation of the preconditioner

According to the augmented algebraic system (5.3), we set:

$$A^{aug} = \begin{bmatrix} K & B^T & \Phi^T \\ -B & Z & 0 \\ \Phi & 0 & 0 \end{bmatrix}. \quad (5.6)$$

In analogy with (5.5) and according to the notation of Section 5.3, we propose the following inexact block LU factorization of matrix (5.6):

$$P_S^{aug} = \begin{bmatrix} K & 0 & 0 \\ -B & S & 0 \\ \Phi & -S_{\Lambda P} & L_{\Lambda} \end{bmatrix} \begin{bmatrix} I & D^{-1}B^T & D^{-1}\Phi^T \\ 0 & I & W^{-1}S_{P\Lambda} \\ 0 & 0 & I \end{bmatrix}, \quad (5.7)$$

where $S_{\Lambda P} = \Phi D^{-1}B^T$, $L_{\Lambda} = S_{\Lambda P}W^{-1}S_{P\Lambda} - S_{\Lambda}$, $S_{P\Lambda} = BD^{-1}\Phi^T$, $S_{\Lambda} = \Phi D^{-1}\Phi^T$ and $W = \text{diag}(S)$. In particular, as happens for the standard case, all the matrices appearing in this preconditioner can be explicitly assembled, thanks to the use of the diagonal approximations D and W .

In what follows we detail the algebraic steps needed at the k -th iteration of a Krylov method to compute the preconditioned residual associated to the augmented SIMPLE matrix (5.7):

$$P_S^{aug} \mathbf{z}^{(k)} = \mathbf{r}^{(k)},$$

that is:

$$\begin{cases} K\mathbf{y}_1^{(k)} = \mathbf{r}_1^{(k)}, \\ S\mathbf{y}_2^{(k)} = \mathbf{r}_2^{(k)} + B\mathbf{y}_1^{(k)}, \\ L_\Lambda\mathbf{y}_3^{(k)} = \mathbf{r}_3^{(k)} - \Phi\mathbf{y}_1^{(k)} + S_{\Lambda P}\mathbf{y}_2^{(k)}, \\ \begin{cases} \mathbf{z}_1^{(k)} = \mathbf{y}_1^{(k)} - D^{-1}B^T\mathbf{z}_2^{(k)} - D^{-1}\Phi^T\mathbf{z}_3^{(k)}, \\ \mathbf{z}_2^{(k)} = \mathbf{y}_2^{(k)} - W^{-1}S_{P\Lambda}\mathbf{z}_3^{(k)}, \\ \mathbf{z}_3^{(k)} = \mathbf{y}_3^{(k)}, \end{cases} \end{cases} \quad (5.8)$$

where, given $\mathbf{w} \in \mathbb{R}^{N_U+N_P+m}$, we indicate by $\mathbf{w}_1 \in \mathbb{R}^{N_U}$ the first N_U components associated to the velocity d.o.f.'s, by $\mathbf{w}_2 \in \mathbb{R}^{N_P}$ the following N_P components associated to the pressure d.o.f.'s, and by $\mathbf{w}_3 \in \mathbb{R}^m$ the last m components associated to the Lagrange multipliers d.o.f.'s.

Remark 5.4.1. We notice that in [116] the authors just very recently proposed a monolithic preconditioner for a similar 3×3 block system arising from the discretization of the 3D-0D problem, associated with the coupling with a lumped parameter model. However, in their case, the last block row accounts for the coupling constraint equations, resulting in a form of the 3×3 system's block matrix and of the corresponding inexact factorization which are different from ours.

Remark 5.4.2. Let us extend the general form of the inexact block LU factorization, reported in Remark 5.3.1, to the augmented case:

$$P_G^{aug} = \begin{bmatrix} K & 0 & 0 \\ -B & BH_1B^T + Z & 0 \\ \Phi & -\Phi H_1B^T & \Phi H_1B^T E_1BH_1\Phi^T - \Phi H_1\Phi^T \end{bmatrix} \begin{bmatrix} I & H_2B^T & H_2\Phi^T \\ 0 & I & E_2BH_2\Phi^T \\ 0 & 0 & I \end{bmatrix} \quad (5.9)$$

where H_1, H_2 are approximations of K^{-1} and E_1, E_2 are approximations of $(BK^{-1}B^T + Z)^{-1}$. Similarly to what is done in [74], it is easy to show that:

$$P_G^{aug} = \begin{bmatrix} K & KH_2B^T & KH_2\Phi^T \\ -B & B(H_1 - H_2)B^T + Z & -(I - (BH_1B^T + Z)E_2)BH_2\Phi^T \\ \Phi & -\Phi(H_1 - H_2)B^T & -\Phi(H_1 - H_2)\Phi^T + \Phi H_1B^T(E_1BH_1\Phi^T - E_2BH_2\Phi^T) \end{bmatrix},$$

and that we have the following error associated to the use of the general form (5.9) as a

solver, i.e. considering only one preconditioned iteration of the Krylov method:

$$A^{aug} - P_G^{aug} = \begin{bmatrix} 0 & (I - KH_2)B^T & (I - KH_2)\Phi^T \\ 0 & -B(H_1 - H_2)B^T & (I - (BH_1B^T + Z)E_2)BH_2\Phi^T \\ 0 & \Phi(H_1 - H_2)B^T & \Phi(H_1 - H_2)\Phi^T - \Phi H_1 B^T (E_1 B H_1 \Phi^T - E_2 B H_2 \Phi^T) \end{bmatrix}.$$

In particular, the augmented SIMPLE preconditioner (5.7) is obtained by choosing $H_1 = H_2 = D^{-1}$ and $E_1 = E_2 = W^{-1}$, thus considering only diagonal approximations to be able to explicitly invert these matrices and implement all the preconditioner's blocks, coherently to what is done for the standard SIMPLE. This is a practical choice that allows for an easy implementation of the preconditioner in a Finite Element code. According to Remark 5.3.1, other preconditioners based on an inexact block LU factorization of the Navier Stokes matrix (e.g. Chorin-Temam, Yosida) can be extended to the augmented case by considering different approximations of the inverse matrices. Moreover, the augmented SIMPLE preconditioner P_S^{aug} results in the following error matrix:

$$A^{aug} - P_S^{aug} = \begin{bmatrix} 0 & (I - KD^{-1})B^T & (I - KD^{-1})\Phi^T \\ 0 & 0 & (I - SW^{-1})S_{P\Lambda} \\ 0 & 0 & 0 \end{bmatrix}.$$

Hence, the associated augmented SIMPLE solver introduces an error in both the momentum and continuity equations, thus it loses the “mass-preserving” property which holds true for the standard case. On the other hand, the defective flow rate boundary conditions are imposed exactly. Finally, we observe that if matrices K and S are well approximated by their diagonal, then P_S^{aug} is a good approximation of A^{aug} .

Alternatively, to avoid an error in the momentum equation, one should consider $H_2 = K^{-1}$ (as done for Yosida), but this choice calls for the numerical solution of several linear systems in K , which can be very expensive in practice. Moreover, to obtain a “mass-preserving” preconditioner, one should take $H_1 = H_2$ and $E_2 = (BH_1B^T + Z)^{-1}$, calling for the solution of linear systems in the approximate Schur complement $(BH_1B^T + Z)$, which is non-diagonal in general. In the context of “mass-preserving” preconditioners, one could consider $E_1 \neq E_2$ introducing an error in the last block related to the prescription of flow rates conditions, or $E_1 = E_2$ leading to the numerical solution of additional linear systems in $(BH_1B^T + Z)$. The “mass-preserving” choice is less computationally expensive than the “momentum-preserving” one, given the smaller dimension and dense nature of the approximate Schur complement. On the other hand, it does not allow for an explicit implementation of all the terms appearing in the inexact block LU factorization (5.9), due to the presence of the inverse of non-diagonal matrices, thus it is practically less appealing

than the proposed augmented SIMPLE preconditioner P_S^{aug} .

Remark 5.4.3. *The aim of this remark is to provide some preliminary theoretical insights about the effectiveness of the proposed preconditioner under some simplifying assumptions. Specifically, we consider the limit where matrix S is well approximated by W .*

Let us consider the simplified algebraic problem where the stabilization matrices Z_K , Z_B and Z are set to 0; moreover, invert the sign of the second block row. Then the augmented system matrix reads:

$$\bar{A}^{aug} = \begin{bmatrix} K & B^T & \Phi^T \\ B & 0 & 0 \\ \Phi & 0 & 0 \end{bmatrix}.$$

Referring to (5.7), let us now neglect the diagonal approximation W of the approximated Schur complement S (so take $W = S$), so that the resulting preconditioner becomes:

$$\begin{aligned} \bar{P}_S^{aug} &= \begin{bmatrix} K & 0 & 0 \\ B & \bar{S} & 0 \\ \Phi & -S_{\Lambda P} & -S_{\Lambda P}\bar{S}^{-1}S_{P\Lambda} - S_{\Lambda} \end{bmatrix} \begin{bmatrix} I & D^{-1}B^T & D^{-1}\Phi^T \\ 0 & I & -\bar{S}^{-1}S_{P\Lambda} \\ 0 & 0 & I \end{bmatrix} \\ &= \begin{bmatrix} K & KD^{-1}B^T & KD^{-1}\Phi^T \\ B & 0 & 0 \\ \Phi & 0 & 0 \end{bmatrix}, \end{aligned}$$

where $\bar{S} = -BD^{-1}B^T$. By calling $G^T = [B^T \ \Phi^T]$ we obtain:

$$\bar{A}^{aug} = \begin{bmatrix} K & G^T \\ G & 0 \end{bmatrix}, \quad \bar{P}_S^{aug} = \begin{bmatrix} K & KD^{-1}G^T \\ G & 0 \end{bmatrix},$$

thus recovering the same formulation structure of the standard SIMPLE preconditioner studied in [138], where an eigenvalue analysis of the preconditioned matrix was performed. In particular, the authors provided some eigenvalue bounds and the estimation of the spectral condition number in the symmetric case. Thus, we have, in analogy with [138], an eigenvalue analysis of our preconditioner (at least in the case without stabilization terms) for the limit case $W = S$.

5.4.2. An efficient variant of the augmented SIMPLE preconditioner

We observe that the solution of the L-step (5.8) requires to solve linear systems in K , S and L_Λ , which may present in general some difficulties due to the ill-conditioning of matrix K and the dense nature of matrices S and L_Λ . Hence, inspired by the aSIMPLE preconditioner presented in [65], in our numerical experiments we substitute matrices K , S and L_Λ in P_S^{aug} (5.7) with approximations $\hat{K}$, $\hat{S}$ and $\hat{L}_\Lambda$.

5.5. Numerical results

5.5.1. Setting of the numerical experiments

For the numerical solution of the augmented monolithic system (5.3), we aim to investigate the performance of the augmented aSIMPLE preconditioner (introduced in Section 5.4.2):

$$P_{aS}^{aug} = \begin{bmatrix} \hat{K} & 0 & 0 \\ -B & \hat{S} & 0 \\ \Phi & -S_{\Lambda P} & \hat{L}_\Lambda \end{bmatrix} \begin{bmatrix} I & D^{-1}B^T & D^{-1}\Phi^T \\ 0 & I & W^{-1}S_{P\Lambda} \\ 0 & 0 & I \end{bmatrix}. \quad (5.10)$$

To this aim, we will also compare it with a trivially implementable extension of the standard aSIMPLE preconditioner [65], built as follows. We observe that in system (5.3) the dimension of the Lagrange multipliers block (m) is given by the number of defective flow rate conditions prescribed with Lagrange multipliers, which is usually significantly smaller than the dimension of the velocity (N^U) and pressure (N^P) blocks. Thus, one could be tempted to extend to the augmented case the standard aSIMPLE preconditioner (obtained from (5.5) with suitable approximations of K and S [65]) by simply adding identity blocks on the diagonals:

$$P_{aS-I}^{aug} = \begin{bmatrix} \hat{K} & 0 & 0 \\ -B & \hat{S} & 0 \\ 0 & 0 & I \end{bmatrix} \begin{bmatrix} I & D^{-1}B^T & 0 \\ 0 & I & 0 \\ 0 & 0 & I \end{bmatrix}. \quad (5.11)$$

In the following we will refer to the *complete* preconditioner P_{aS}^{aug} (5.10) as *aug-aS* and to the *simplified* preconditioner P_{aS-I}^{aug} (5.11) as *aug-aS-I*. Notice that, for the study of post-TAVI hemodynamics, the *simplified* preconditioner *aug-aS-I* has been used in [58] and the *complete* preconditioner *aug-aS* has been used in [59].

In the numerical experiments we employ piecewise linear finite elements for the velocity

and pressure fields with a SUPG/PSPG [231] stabilization scheme, considering a kinematic viscosity $\nu = 3.3 \times 10^{-6} \frac{m^2}{s}$ and setting $\mathbf{f} = \mathbf{0}$ in the NS momentum equation. Moreover, we solve the monolithic augmented system (5.3) using a preconditioned GMRES iterative solver with both preconditioners aug-aS and aug-aS-I. Finally, all the numerical experiments are performed using the multi-physics high-performance library life^x [4, 5] (<https://lifex.gitlab.io>, <https://doi.org/10.5281/zenodo.7852088>), developed at MOX, Dipartimento di Matematica, with the collaboration of LaBS, Dipartimento di Chimica, Materiali ed Ingegneria Chimica (both at Politecnico di Milano). The library life^x relies on deal.II [11] to provide general-purpose software facilities for finite elements. The linear algebra backend is offered by Trilinos [232], as wrapped by deal.II. This includes the implementation of the linear solver (GMRES) and of the black-box preconditioners (AMG, additive Schwarz and block Jacobi). Specifically, approximations $\hat{K}$, $\hat{S}$ and $\hat{L}_A$ are based on the Algebraic Multigrid (AMG) method, using one multi-grid cycle, an aggregation threshold of 10^{-4} , two smoother sweeps, no smoother overlap, the Chebyshev smoother [97] and the Amesos KLU solver [207] for coarse level.

In Section 5.5.2 we deal with the imposition of a Dirichlet condition for flow rate problems, in Section 5.5.3 we investigate the scalability of preconditioner aug-aS (Test S), in Sections 5.5.4-5.5.5 we compare preconditioners aug-aS and aug-aS-I by considering the following tests:

- Test I: idealized geometry to assess the influence of the number of Lagrange multipliers;
- Test II: simulation in a stenotic carotid artery ($m = 2$);
- Test III: simulation in coronary arteries in presence of a double bypass ($m = 3$);
- Test IV: simulation in an aorta with bicuspid aortic valve ($m = 4$);

and in Section 5.5.6 we investigate the use of different black-box preconditioners for approximations $\hat{K}$, $\hat{S}$ and $\hat{L}_A$.

5.5.2. On the Dirichlet approach for flow rate conditions

In this subsection we highlight the main advantages of treating defective flow rate conditions following the Lagrange multipliers approach instead of prescribing a selected Dirichlet condition. In particular, we consider a toy problem and a real-life application.

Toy problem: Let us consider a cylindrical domain (radius 4 mm) and impose a homogeneous Dirichlet condition at the lateral wall (no-slip), a homogeneous Neumann condition

at the outlet section and a flow rate condition at the inlet section, prescribing the pulsatile flow rate in Figure 5.2a. We are interested in studying the velocity spatial profile obtained

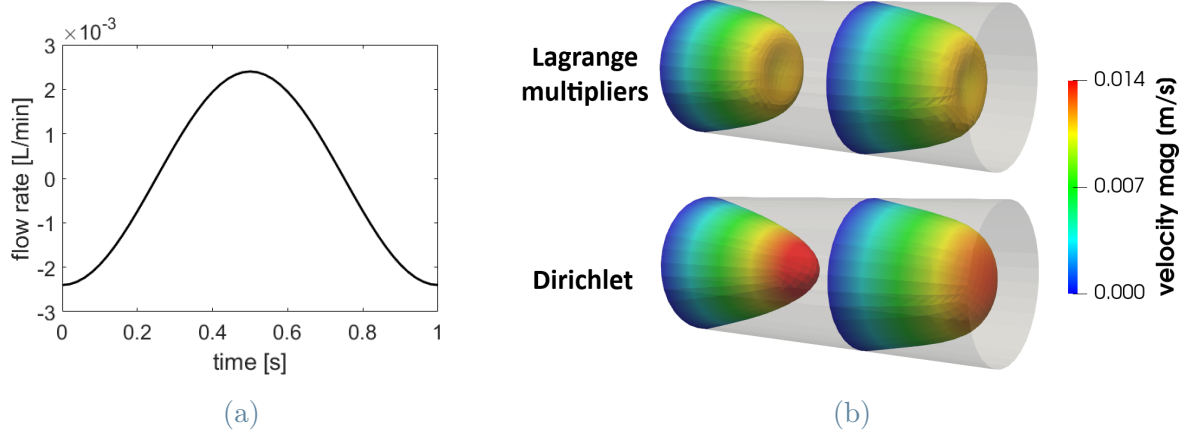


Figure 5.2: (a) Temporal evolution of the sinusoidal pulsatile flow rate imposed at the inlet boundary of the cylinder. (b) Numerical velocity profile, colored by velocity magnitude, in the cylindrical domain at $t = 0.5$ s (peak flow rate time-instant) for both the Lagrange multipliers and Dirichlet treatment of the inlet flow rate condition. Notice that the cylinder has been stretched along its longitudinal direction for visualization purposes.

by employing two different approaches for the prescription of the inlet condition: using a Lagrange multiplier or assigning a Dirichlet condition, assuming a parabolic profile. Being an axi-symmetric cylindrical domain subject to a sinusoidal periodic flow rate, there is an analytical solution given by the Womersley solution [27, 259]. In particular, it was already proven in [242] that the numerical solution obtained with the augmented formulation (5.2) matches the analytical one. We consider an average mesh size $h \approx 0.7$ mm, resulting in 41 451 velocity d.o.f.'s and 13 817 pressure d.o.f.'s, and a time-step $\Delta t = 0.001$ s.

In Figure 5.2b we show, for both the Lagrange multipliers and the Dirichlet approach, the numerical velocity spatial profiles on two different cross-sections (one at the inlet and one inside the domain) at the peak flow rate time-instant. Since in [242] has been shown that the augmented formulation is able to perfectly match the Womersley analytical solution, the plot at the top of Figure 5.2b displays the exact/reference solution. By observing the Dirichlet solution reported at the bottom we notice that the velocity profile differs from the reference solution also inside the domain, due to the influence of the parabolic profile prescribed at the inlet. This shows the need to use Lagrange multipliers to achieve accurate numerical solutions also in a regular geometry.

Real-life application: We consider a patient-specific aortic domain, taken from [34], going from the aortic root to the aortic arch, including the three sovra-aortic branches.

We consider the Large Eddy Simulation (LES) σ -model [130, 170] to account for the presence of turbulence inside the aorta [218]. Moreover, in order to prevent numerical instabilities, we add a backflow stabilization, as proposed in [78], at both the aortic inlet and the descending aorta outlet. The average mesh size is $h \approx 1.3 \text{ mm}$, resulting in 361 368 velocity d.o.f.'s and 120 456 pressure d.o.f.'s.

We impose an inflow condition, prescribing the physiological flow rate taken from [45] (see Figure 5.3a) entering the aorta. In particular, we compare the numerical solutions

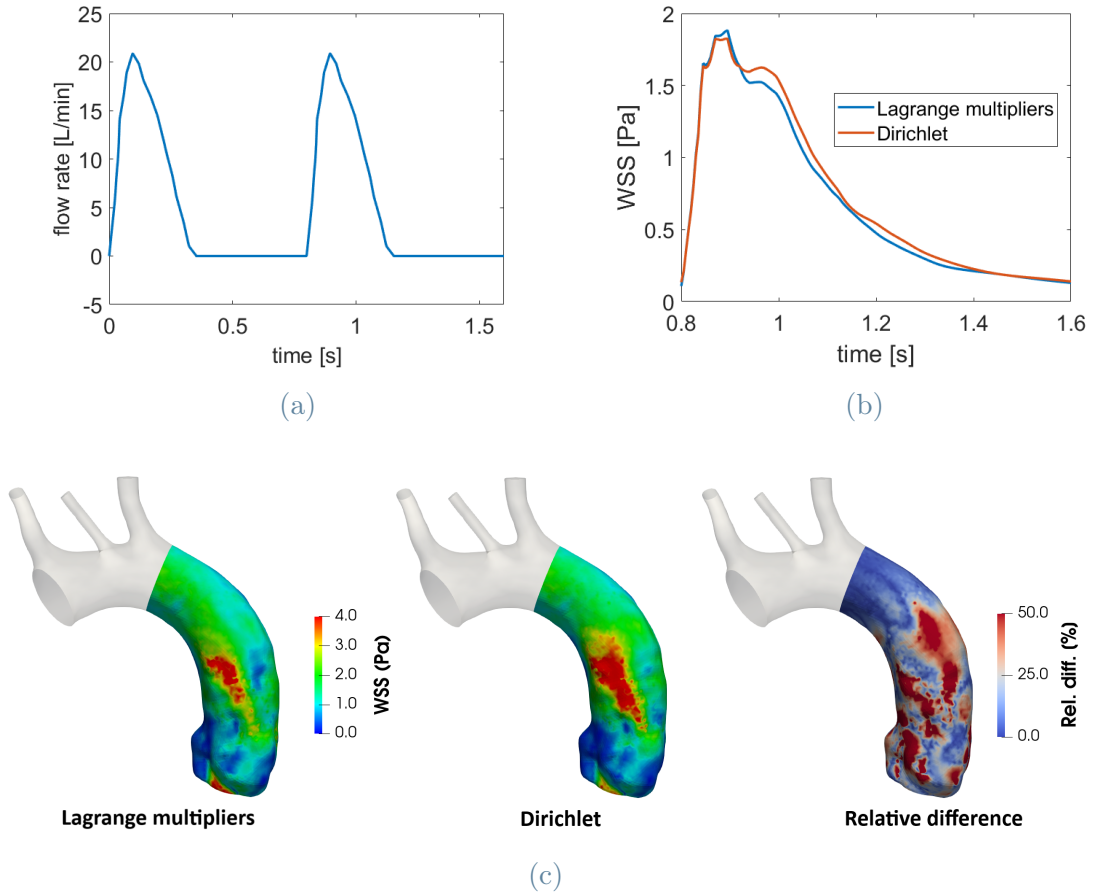


Figure 5.3: (a) Physiological flow rate [45] prescribed at the aortic inlet. (b)-(c) For both the Lagrange multipliers and Dirichlet treatment of the inlet flow rate condition we report: the temporal evolution of the average WSS on the aortic wall (b) and the WSS pattern on the aortic wall at $t = 1 \text{ s}$ together with the relative difference between the two solutions (c).

obtained by imposing such condition using a Lagrange multiplier and using a Dirichlet condition, assuming a flat velocity spatial profile (as commonly done in the aortic root [204]). Moreover, we impose three outflow conditions at the sovra-aortic arteries using Lagrange multipliers and we close the problem by imposing a homogeneous Neumann

condition at the descending aorta outlet.

In Figure 5.3b we report, only for the second cycle, the temporal evolution of the average Wall Shear Stress (WSS) on the aortic wall for both inlet condition treatments. During the first part of the simulation, when the inlet flow rate is increasing (see Figure 5.3a), the two numerical solutions coincide, suggesting that the flat profile assumption is accurate in this period of the cycle. On the other, after this acceleration phase, the Dirichlet solution starts showing non-negligible differences with respect to the Lagrange multipliers one. This can be explained by a change of the velocity spatial profile in the aortic root, which we are able to capture only following the Lagrange multipliers approach.

This is confirmed by the results reported in Figure 5.3c, where we depict the WSS pattern on the aortic wall at a time-instant after the acceleration phase ($t = 1\text{ s}$), together with the relative difference of the Dirichlet solution with respect to the Lagrange multipliers one. This figure highlights significant differences between the two approaches, with a relative difference greater than 50% in distributed areas of the aortic wall. Since using Lagrange multipliers has been previously shown to provide more accurate results in terms of the velocity profile than prescribing a Dirichlet condition, then we expect the WSS distribution, which depends on the gradient of the velocity field, to be more accurate for the Lagrange multipliers case.

We conclude that imposing a flow rate by prescribing a Dirichlet boundary condition can influence the accuracy of the numerical solution even far away from the boundary.

5.5.3. Test S - Scalability properties of the augmented aSIMPLE preconditioner

In this subsection we investigate the properties of preconditioner aug-aS. In particular, we assess the performance of this preconditioner by varying the discretization parameters, the Reynolds number and the number of parallel cores used to perform the numerical simulations.

We consider a cylindrical domain (radius 1 m and length 6 m , see Figure 5.4a) and we impose a homogeneous Dirichlet condition at the lateral wall (no-slip), a homogeneous Neumann condition at the outlet section and a flow rate condition at the inlet section using one Lagrange multiplier. The inlet condition prescribes a flow rate which follows a sinusoidal ramp profile (see Figure 5.4b). All the numerical simulations were run in parallel on Intel Sapphire Rapids@2.00GHz CPU's, using the computational resources provided by the CINECA supercomputing center, Italy.

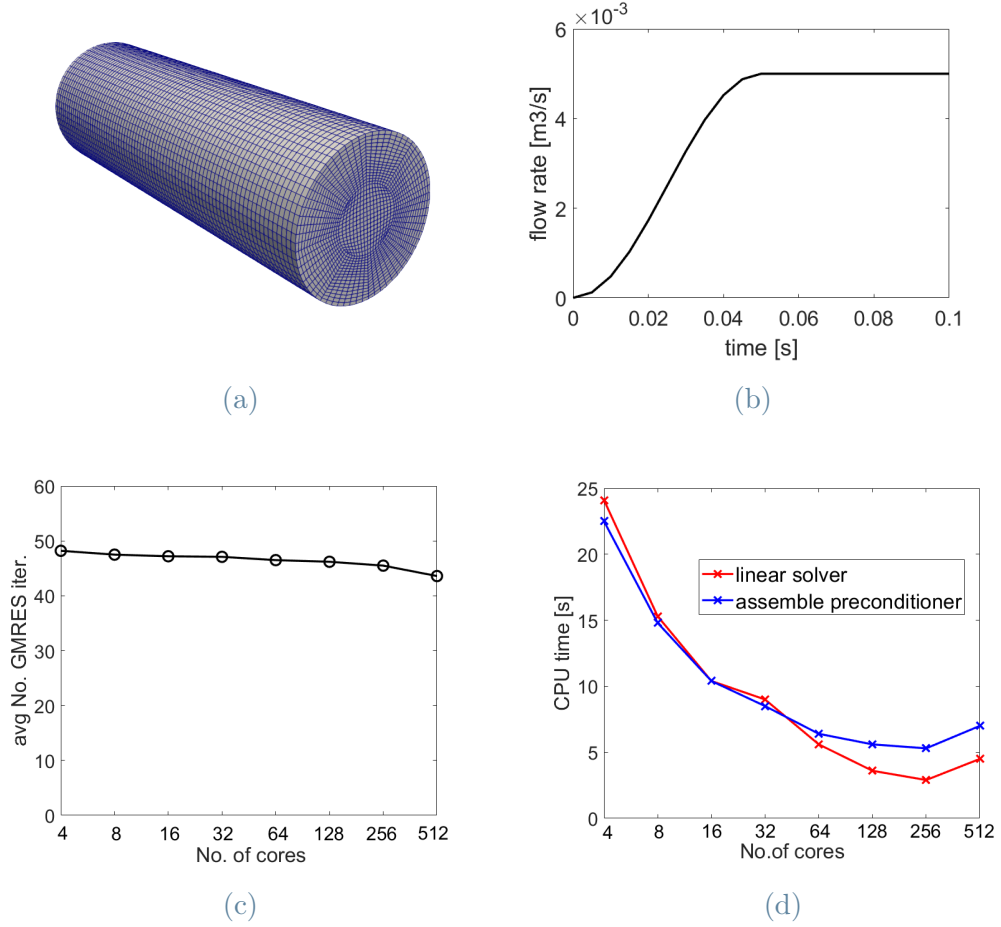


Figure 5.4: (a) Cylindrical domain discretized with hexahedral elements ($h = 0.109\text{ m}$). (b) Time-evolving flow rate prescribed at the cylinder inlet section ($Q_{max} = 5 \times 10^{-3} \frac{\text{m}^3}{\text{s}}$). (c)-(d) Average-in-time number of GMRES iterations (c) and total computing time needed to solve the linear systems and assemble the preconditioner (d), as a function of the number of cores. Test S.

We start from reference values of the parameters and we vary them individually to perform each scalability study: mesh size $h = 0.109\text{ m}$ (425,413 d.o.f.'s), time-step $\Delta t = 10^{-2}\text{ s}$, maximum flow rate value $Q_{max} = 5 \times 10^{-3} \frac{\text{m}^3}{\text{s}}$ ($Re \approx 1200$) and number of cores equal to 20.

First, we study the influence of the mesh size on the number of GMRES iterations needed to solve the problem. We consider hexahedral meshes with different mesh sizes $h \in \{0.432\text{ m}; 0.217\text{ m}; 0.109\text{ m}; 0.054\text{ m}\}$, corresponding to $\{7,477; 55,269; 425,413; 3,339,140\}$ d.o.f.'s, respectively. Moreover, we perform the same numerical experiments by prescribing the inlet flow rate with a Dirichlet condition to compare the behavior of the augmented

aSIMPLE preconditioner with the one of the standard aSIMPLE preconditioner. We report the results in Table 5.1. The table shows that the average-in-time number of GMRES

Table 5.1: Average-in-time number of GMRES iterations for each mesh size using the augmented aSIMPLE and the standard aSIMPLE preconditioners ($Q_{max} = 5 \times 10^{-3} \frac{m^3}{s}$, $\Delta t = 10^{-2} s$). Test S.

h	d.o.f.'s	avg GMRES iter. (augmented aSIMPLE)	avg GMRES iter. (standard aSIMPLE)
$0.217 m$	55,269	38.1	32.7
$0.109 m$	425,413	47.2	39.3
$0.054 m$	3,339,140	58.8	47.6

iterations increases with the refinement of the mesh. This behavior is the same for the standard aSIMPLE preconditioner, highlighting that the sub-optimality of the preconditioner is not due to the presence of the Lagrange multiplier, but was inherent to the aSIMPLE preconditioner [65]. Moreover, we notice an extra cost, in terms of the number of iterations, when using Lagrange multipliers with respect to the Dirichlet case. This is not surprising since we are introducing an extra saddle-point problem.

Secondly, we investigate the impact of the time-step by considering $\Delta t \in \{1 \times 10^{-2} s; 5 \times 10^{-3} s; 2.5 \times 10^{-3} s; 1 \times 10^{-3} s\}$. In Table 5.2 we report the average-in-time number of GMRES iterations and the total computing time needed to solve the linear systems together with the assembly of the preconditioner. The table shows that the GMRES iterations decrease with the time-step (since the mass matrix becomes more significant). However, as expected, the overall time needed to solve the linear systems and assemble the preconditioner shows an opposite trend since there is twice (or more) the amount of linear systems to be solved at each refinement step.

To assess the scaling properties of the augmented aSIMPLE preconditioner with respect to the Reynolds number, we consider different maximum flow rate values $Q_{max} \in \{2.5 \times 10^{-3} \frac{m^3}{s}; 5 \times 10^{-3} \frac{m^3}{s}; 1 \times 10^{-2} \frac{m^3}{s}; 2 \times 10^{-2} \frac{m^3}{s}\}$, corresponding to $Re \in \{600; 1200; 2400; 4800\}$, respectively. We report in Table 5.2 the results in terms of average-in-time number of GMRES iterations and total computing time to solve the linear systems and assemble the preconditioner. We notice that in both cases the computational effort very mildly depends on the Reynolds number, thus we argue that the augmented aSIMPLE preconditioner shows good scaling properties with respect to this parameter.

Finally, we are interested in the parallel scalability properties of the augmented aSIMPLE

Table 5.2: Average-in-time number of GMRES iterations and total computing time needed to solve the linear systems and assemble the preconditioner for different time-steps ($Q_{max} = 5 \times 10^{-3} \frac{m^3}{s}$, $h = 0.11 m$) and different Reynolds numbers ($\Delta t = 1 \times 10^{-2} s$, $h = 0.11 m$). Test S.

	avg GMRES iter.	total time [s]
Δt		
$1.0 \times 10^{-2} s$	47.2	19.8
$5.0 \times 10^{-3} s$	43.2	37.1
$2.5 \times 10^{-3} s$	38.1	68.8
$1.0 \times 10^{-3} s$	35.4	167.3
Re		
600	45.6	19.6
1200	47.2	19.8
2400	48.6	20.0
4800	50.3	20.4

preconditioner, thus we perform numerical simulations using different numbers of parallel computing cores. The results of this analysis are reported in Figure 5.4c-5.4d, where we plot the average-in-time number of GMRES iterations and the total computing time needed to solve the linear systems and assemble the preconditioner as functions of the number of cores. The figures show that the number of GMRES iterations is almost independent of the number of cores. Moreover, the computing time needed to solve the linear systems and assemble the preconditioner decreases with the number of cores up to a bottleneck of 256 cores, corresponding to ≈ 1661 d.o.f.'s per core. These results prove a good parallel scalability of the augmented aSIMPLE preconditioner.

5.5.4. Test I - Varying the number of Lagrange multipliers

We are interested in assessing the numerical performance of preconditioners aug-aS and aug-aS-I for an increasing number of flow rate conditions prescribed with Lagrange multipliers, thus an increasing dimension of the Lagrange multipliers block (m) in the augmented system (5.3). We consider the star-shape domain depicted in Figure 5.5a, which comprises six cylinders with radius $1 mm$ and length $10 mm$ connected to a sphere with radius $2 mm$. We impose a homogeneous Dirichlet condition at the wall, a homogeneous

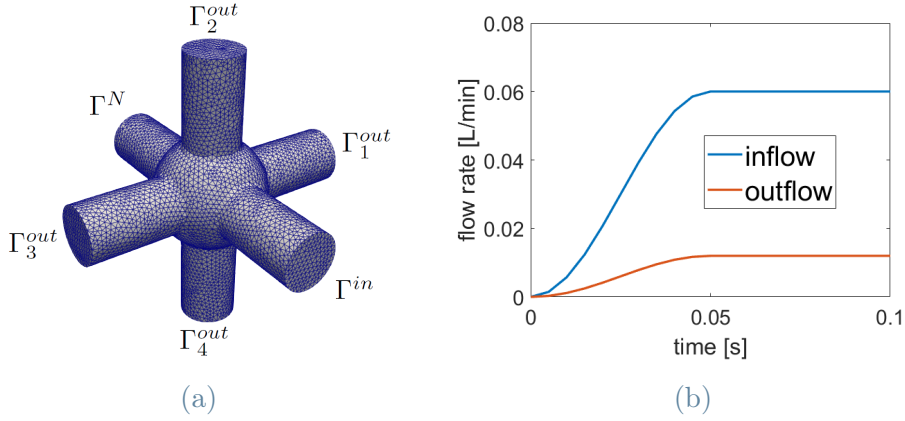


Figure 5.5: (a) Star-shape domain comprising six cylinders and a sphere ($h \approx 0.2 \text{ mm}$). (b) Time-evolving flow rates prescribed at the inlet section Γ^{in} (inflow) and at each outlet section Γ_i^{out} , $i = 1, \dots, 4$ (outflow). Test I.

Neumann condition at Γ^N , an inflow condition at Γ^{in} prescribed with a Lagrange multiplier, and four outflow conditions at Γ_i^{out} , $i = 1, \dots, 4$, prescribed either with Lagrange multipliers or assuming a parabolic Dirichlet profile. For the latter cases, we impose the time-evolving flow rates depicted in Figure 5.5b. We perform several numerical experiments varying the number of Lagrange multipliers by employing the different approaches for the prescription of the outflow conditions. We consider a tetrahedral mesh with size $h \approx 0.2 \text{ mm}$, resulting in 141 720 velocity d.o.f.'s and 47 240 pressure d.o.f.'s, and a time-step $\Delta t = 0.01 \text{ s}$. All the numerical simulations were run in parallel on 20 cores of Xeon E5-2640 v4 @2.4GHz CPU's, using the computational resources available at MOX, Dipartimento di Matematica, Politecnico di Milano.

In Figure 5.6 we report the average-in-time number of GMRES iterations and the total CPU time needed to solve the linear systems and assemble the preconditioner as a function of the number of Lagrange multipliers m . We compare the performance of the proposed block preconditioners with an AMG preconditioner applied directly to the monolithic system, as standard reference for non-functional preconditioners. For the latter we use the same implementation as for the application to the single blocks described in Section 5.5.1. The figure shows that by using the *simplified* preconditioner aug-aS-I and the AMG preconditioner we obtain comparable results, with both the analyzed quantities tending to increase with the number of Lagrange multipliers. On the other hand, by using the *complete* preconditioner aug-aS, we notice that the average number of GMRES iterations does not depend on the size of the Lagrange multipliers block, providing an "optimality" result for the proposed extension. Moreover, the total CPU time needed to solve the linear systems and assemble the preconditioner very slightly increases with the number of

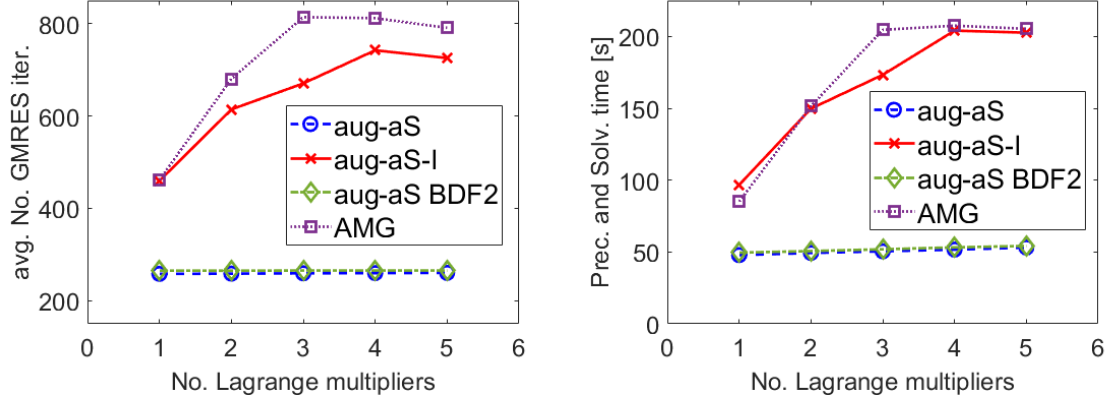


Figure 5.6: Numerical simulations were run in the star-shape domain (see Figure 5.5a) varying the number of Lagrange multipliers. For preconditioners aug-aS, aug-aS-I and an Algebraic Multigrid (AMG) preconditioner we report as a function of the number of Lagrange multipliers: the average-in-time number of GMRES iterations (left) and the total CPU time needed to solve the linear systems and assemble the preconditioner (right). In green the performance of the aug-aS preconditioner for BDF2. Test I.

Lagrange multipliers. Nonetheless, we can always notice a significant speed-up by using preconditioner aug-aS instead of the other two preconditioners. These results stress the importance of designing a preconditioner that properly captures the double saddle-point structure of our problem of interest, even in the "small" extra block related to Lagrange multipliers.

To assess the performance of the aug-aS preconditioner when using other time discretizations, in Figure 5.6 we also report the number of GMRES iteration and total CPU time needed to solve the linear systems and assemble the preconditioner as a function of the number of Lagrange multipliers for the case of a second order backward difference scheme (BDF2), with a second-order semi-implicit treatment of the convective term. From these results we observe that the performance of the proposed preconditioner only slightly depends on the order of the time discretization.

5.5.5. Real-life hemodynamic applications

We aim to test the numerical performance of preconditioners aug-aS and aug-aS-I in real-life hemodynamic scenarios. In particular, we perform blood-dynamics numerical simulations in patient-specific geometries, representing three different districts of the human body: carotid arteries (Test II), coronary arteries (Test III) and thoracic aorta (Test IV).

We notice that, in accordance to the augmented problem presented in Section 5.2, we always impose a homogeneous Dirichlet condition at the lateral wall (physical boundary) of the computational domains. Moreover, at least at one artificial (not physical) boundary we prescribe a Neumann condition. Here one should prescribe a physiological pressure. However, in the rigid wall context considered in this thesis, the pressure is defined up to a constant. For this reason on such boundaries we consider homogeneous Neumann conditions.

All the numerical simulations were run in parallel on 56 cores of Xeon Gold 6238R @2.20GHz CPU's, using the computational resources available at MOX, Dipartimento di Matematica, Politecnico di Milano, with a time-step $\Delta t = 0.001 s$.

In the forthcoming three paragraphs we qualitatively describe the numerical results obtained in each real-life scenario, whereas in the last paragraph of the section we discuss the performance of our preconditioners in the three numerical tests together.

Test II - Carotid arteries. We consider a computational domain, taken from [107], representing a patient-specific stenotic carotid artery bifurcation, made of the Common Carotid Artery (CCA), the External Carotid Artery (ECA) and the Internal Carotid Artery (ICA) (see Figure 5.7a). The average mesh size is $h \approx 0.5 mm$ with a local refinement close to the stenosis, resulting in 45 555 velocity d.o.f.'s and 15 185 pressure d.o.f.'s.

We have at disposal patient-specific flow rate measurements in the CCA and the ICA [107] (see Figure 5.7b) and we use them to prescribe an inflow condition at the CCA boundary and an outflow condition at the ICA boundary using two Lagrange multipliers. Moreover, we close the problem by imposing a homogeneous Neumann condition at the ECA boundary.

In Figure 5.7c-5.7d we report the numerical pressure distribution and velocity streamlines at the time-instant of peak flow rate in the CCA. The figure shows a significant pressure drop at the level of the bifurcation, due to a severe narrowing of the cross-sectional area of the domain. Such a narrowing gives rise to high-velocity jets at the bifurcation level and the formation of vortical structures in the bifurcating branches (ICA and ECA) due to another sudden change of the domain's morphology.

Test III - Coronary arteries. We consider a patient-specific post-surgical geometry, taken from [108], representing a district of the left coronary tree comprising three coronary arteries (LAD, M1 and LCX) and a double bypass. A bypass creates a new path for blood to flow around a partially blocked (stenotic) artery restoring a normal blood flow

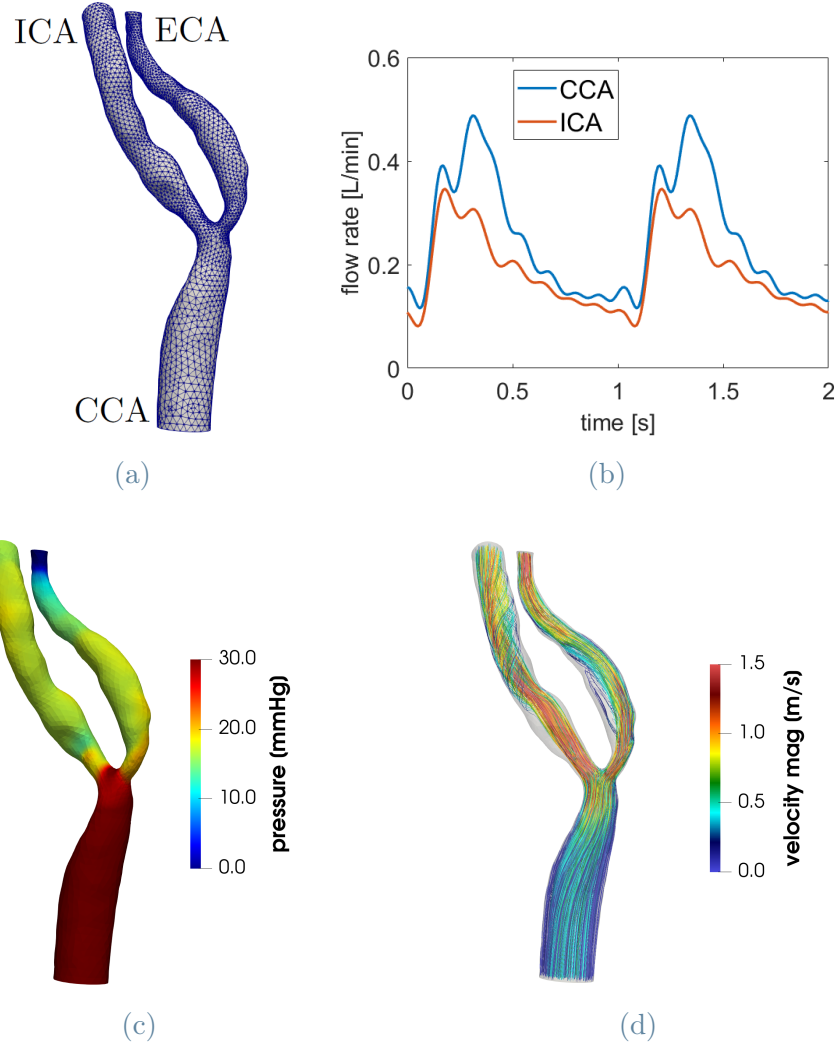


Figure 5.7: (a) Carotid arteries computational domain (average mesh size $h \approx 0.5 \text{ mm}$). (b) Patient-specific flow rate measurements in CCA and ICA, prescribed as inflow at the CCA boundary and as outflow at the ICA boundary. (c)-(d) At the time-instant of peak flow rate in the CCA we report: the pressure distribution (c) and the velocity streamlines, colored by velocity magnitude, (d) obtained in the numerical simulation. Test II.

downstream of the blockage (stenosis). In our case, a double bypass, originating from the boundary Γ_{in}^1 , was needed to treat the patient since both the LAD and M1 arteries present stenoses (see Figure 5.8a). The average mesh size is $h \approx 0.6 \text{ mm}$ with a local refinement close to the stenoses, resulting in 90 015 velocity d.o.f.'s and 30 005 pressure d.o.f.'s.

The domain presents two inlet sections, the bypass inlet Γ_{in}^1 and the left coronary artery inlet Γ_{in}^2 , where we impose homogeneous Neumann conditions, thus assuming to have the same pressure upstream the stenoses. Moreover, we guarantee the physiological flow

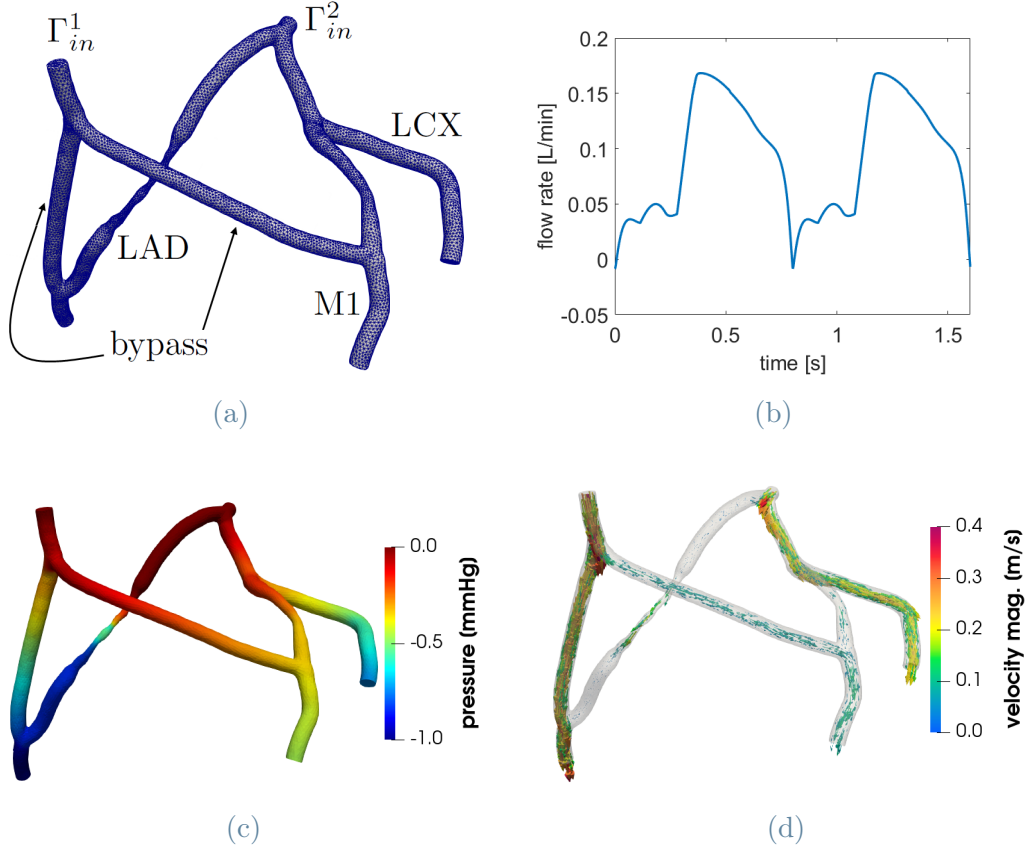


Figure 5.8: (a) Coronary arteries domain comprising three left coronary arteries (LAD, M1 and LCX) and a double bypass originating from the boundary Γ_{in}^1 ($h \approx 0.6 \text{ mm}$). (b) Physiological flow rate in left coronary tree [67], partitioned between the three outlet boundaries. (c)-(d) At the time-instant of peak flow rate in the left coronary tree we report: the pressure distribution (c) and the velocity streamlines, colored by velocity magnitude, (d) obtained in the numerical simulation. Test III.

rate taken from [67] (see Figure 5.8b) inside the left coronary tree by imposing three outflow conditions, with three Lagrange multipliers, which partition the total flow in such a way that it goes: $\frac{1}{6}$ through the M1 outlet, $\frac{1}{3}$ through the LCX outlet, and $\frac{1}{2}$ through the remaining outlet. By doing so we are assuming that the double bypass restores a physiological flow downstream the stenoses.

In Figure 5.8c-5.8d we report the numerical pressure distribution and velocity streamlines at the time-instant of peak flow rate in the left coronary tree. From the velocity visualization we see that the majority of the flow is passing through the bypasses and not through the stenotic tracts of the LAD and M1 arteries. This results in a moderate pressure gradient, around 1 mmHg , between inlet and outlet sections, thus avoiding significant pressure losses across the stenoses which would be present without the bypasses.

Test IV - Thoracic aorta. We consider the thoracic aorta problem presented in Section 5.5.2, introducing a representation of the aortic valve's leaflets. In particular, the patient under consideration has a native bicuspid aortic valve, which differs from a normal aortic valve for the presence of two valve's leaflets instead of three (see Figure 5.9a). The aor-

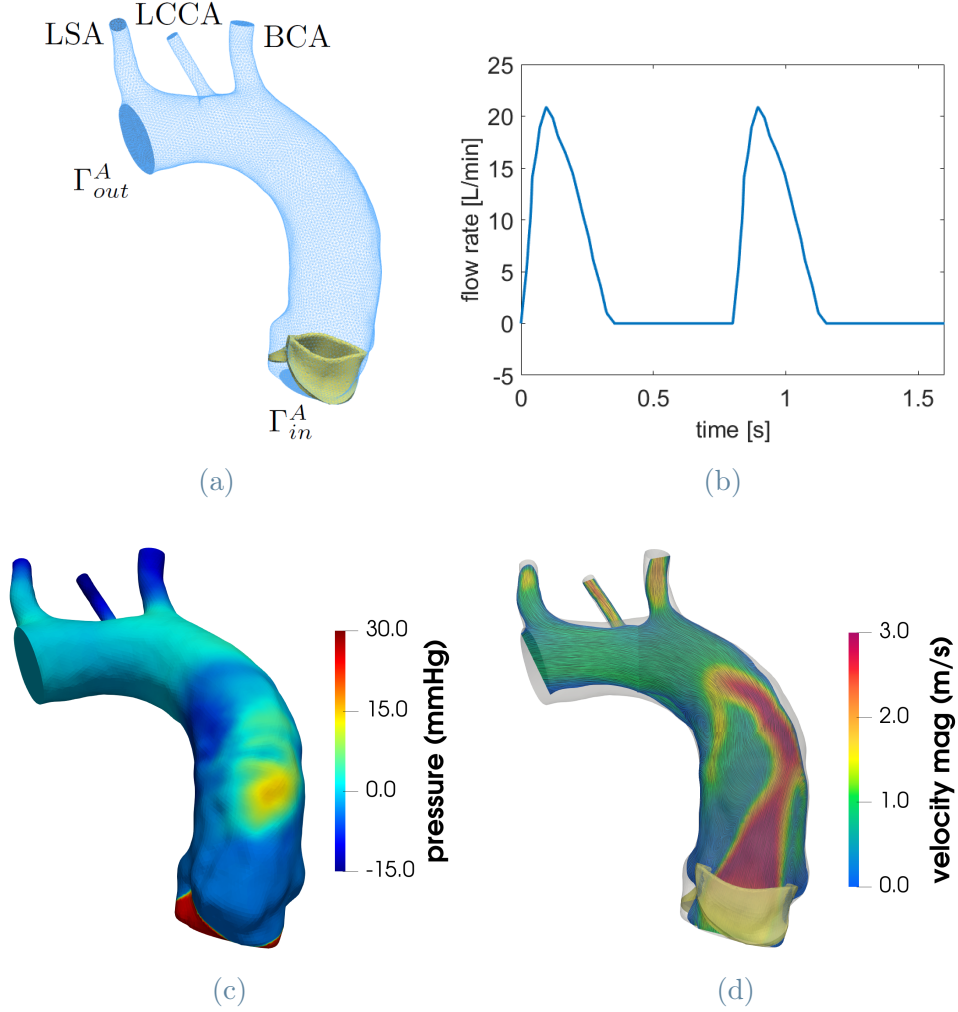


Figure 5.9: (a) Thoracic aorta domain with the bicuspid aortic valve's leaflets in yellow ($h \approx 1.3 \text{ mm}$). (b) Physiological flow rate [45] prescribed at Γ_{in}^A and partitioned between the BCA, LCCA and LSA outlet boundaries. (c)-(d) At the time-instant of peak flow rate in the thoracic aorta we report: the pressure distribution (c) and the velocity streamlines, colored by velocity magnitude, on a longitudinal section (d) obtained in the numerical simulation. Test IV.

tic valve's leaflets in their open configuration are implicitly represented in the numerical simulation as an obstruction to the flow using the Resistive Implicit Immersed Surface (RIIS) method [13, 79, 80, 94]. This consists in adding a local penalization term inside the momentum equation of the Navier-Stokes system to model the adherence of blood to

the leaflets. RIIS, LES and backflow stabilization introduce specific changes in the first block row of system (5.3) (see Appendix 5.6, where the value of specific parameters are also reported). In this case, preconditioners (5.10) and (5.11) are simply adapted by considering such changes without any approximations. The average mesh size is $h \approx 1.3 \text{ mm}$ with a local refinement of 0.4 mm in the leaflets area, resulting in 377 673 velocity d.o.f.'s and 125 891 pressure d.o.f.'s.

We impose the inflow condition at Γ_{in}^A , prescribing the physiological flow rate in Figure 5.9b entering the aorta, and three outflow conditions at the BCA, LCCA and LSA boundaries, guaranteeing that 30% of the total flow goes to these sovra-aortic arteries. Specifically, we split the flow between each sovra-aortic branch according to the area of its outlet boundary. As a result, the inlet flow is partitioned in such a way that it goes: 17.0% through the BCA outlet, 4.8% through the LCCA outlet, and 8.2% through the LSA outlet. All these flow rate conditions are prescribed using four Lagrange multipliers. Moreover, we close the problem by imposing a homogeneous Neumann condition at Γ_{out}^A .

In Figure 5.9c-5.9d we report the numerical pressure distribution in the domain and velocity streamlines on a longitudinal section at the time-instant of peak flow rate in the aorta. Bicuspid aortic valves are characterized by a smaller orifice area with respect to the normal tricuspid valves. In our numerical results this translates in a significant pressure drop across the valve and in the formation of a high-velocity jet inside the first tract of the aorta. This jet collides against the aortic wall giving rise to high pressure areas on the wall. Moreover, we observe the formation of vortical structures along side the jet, giving rise to complex hemodynamic patterns in the aorta.

Performance of the augmented aSIMPLE preconditioner. Let us first stress that the solutions reported in Figure 5.7-5.8-5.9 are the same (up to the GMRES tolerance) for the two preconditioners aug-aS and aug-aS-I, since we are in both cases at convergence. In the following we discuss the performance in terms of efficiency of the two preconditioners.

In Table 5.3 we report the average-in-time number of GMRES iterations and the detailed CPU times for each real-life hemodynamic problem presented above using both the *complete* and *simplified* preconditioners. The table shows that in all the applications the average number of GMRES iterations for the aug-aS case is much smaller than for the aug-aS-I case. This is also confirmed by the results reported in Figure 5.10, where the number of GMRES iterations as a function of time is shown. Indeed, we can see that at almost each time-step the number of iterations associated to aug-aS is smaller than the one associated to aug-aS-I.

We can also observe that in all the numerical experiments considering preconditioner aug-

Table 5.3: Average-in-time number of GMRES iterations and detailed computing times in each real-life hemodynamic application using preconditioners aug-aS and aug-aS-I.

	avg GMRES iter.	total time [s]	setup system [s]	assemble system [s]	assemble prec. [s]	solve system [s]
Carotid						
aug-aS	75.8	1430.9	2.9	718.6	196.0	491.9
aug-aS-I	150.6	2139.1	2.8	711.3	193.9	1208.6
Coronary						
aug-aS	48.0	1845.7	16.6	1222.6	293.2	341.5
aug-aS-I	70.8	1923.1	16.6	1215.3	237.6	426.9
Aorta						
aug-aS	55.3	10594.7	420.0	6833.8	1248.9	1962.3
aug-aS-I	175.7	14747.3	409.1	6748.9	1254.7	6213.8

aS-I² the number of GMRES iterations is highly variable and presents severe oscillations during the time evolution; such behavior is not present for preconditioner aug-aS. This highlights the better stability of aug-aS due to the proper approximation of the blocks related to the Lagrange multipliers (third row in L and third column in U in the block LU factorization (5.9)).

Moreover, from Figure 5.10 it emerges that for both preconditioners the number of iterations is higher in the time-instants characterized by a high flow rate. This can be explained by the fact that the diagonal approximation does not capture enough information about the convection operator [74], thus poor performance of the SIMPLE preconditioner, which is based on such approximation, are to be expected in a convection-dominated regime. In particular, this behavior is mitigated for preconditioner aug-aS.

From the detailed CPU times reported in Table 5.3 we observe that, as expected, the use of the two different preconditioning strategies mainly affects the computing time needed to solve the linear systems. The solving time obtained by using preconditioner aug-aS-I instead of aug-aS increases by more than 2-fold in Test II and by more than 3-fold in Test IV, whereas a less significant increase is observed in Test III.

To better understand the reasons behind these differences, in Table 5.4 we summarize

²Notice that, in each sub-plot, the red stars are all related to one numerical simulation

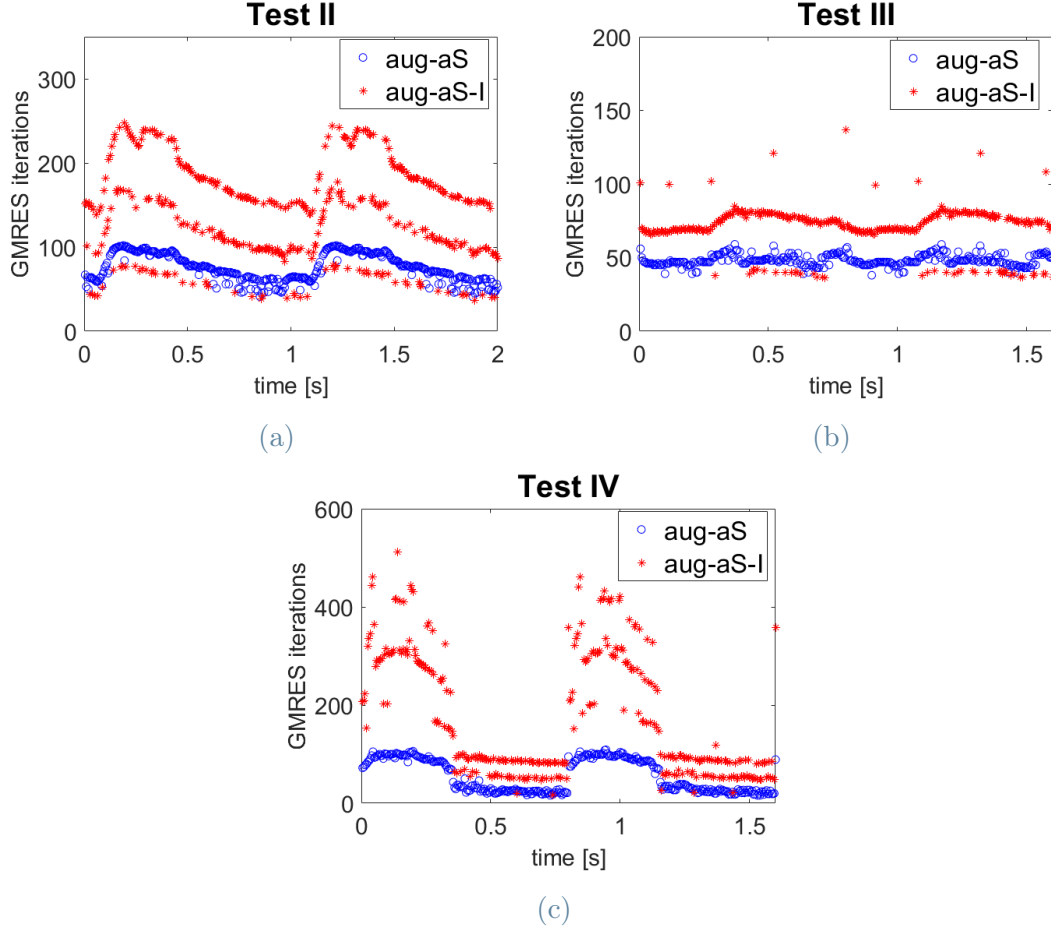


Figure 5.10: Number of GMRES iterations as a function of time needed to monolithically solve each real-life hemodynamic problem using preconditioner aug-aS (blue) and aug-aS-I (red). Notice that, in each sub-plot, the red stars are all related to one numerical simulation.

our findings. The results reported in Table 5.4 suggest that it is particularly significant to employ preconditioner aug-aS when the boundaries at which flow rate conditions are prescribed using Lagrange multipliers contain a great number of mesh points (represented in the table by the maximum number of mesh points $N_{\text{points}}^{\text{max}}$ among these boundaries). Indeed, the percentage of savings in the number of GMRES iterations $d_{\text{GMRES}}^{\%}$ increases with $N_{\text{points}}^{\text{max}}$. This is due to matrix Φ in (5.6) which has several non-zero entries when $N_{\text{points}}^{\text{max}}$ is large and thus aug-aS-I preconditioner introduces in this case a too rough approximation. Furthermore, the percentage of savings in the number of GMRES iterations $d_{\text{GMRES}}^{\%}$ shows the same trend with respect to the maximum Reynolds number Re^{max} . This trend is not observed for the percentage of savings in total CPU time $d_{\text{CPU}}^{\%}$, since the Carotid test shows higher values than the Aorta one. This is due to the fact that the

Table 5.4: Application: real-life hemodynamic application; Re^{max} : maximum Reynolds number in the simulation; N_{points}^{max} : maximum number of mesh points among the boundaries where flow rate conditions are prescribed using Lagrange multipliers; $N_{LagMult}$: number of Lagrange multipliers considered in the numerical simulation; $d_{GMRES}^{\%}$: relative difference between the average number of GMRES iterations obtained using preconditioner aug-aS with respect to preconditioner aug-aS-I; $d_{CPU}^{\%}$: relative difference between the total CPU time using preconditioner aug-aS with respect to preconditioner aug-aS-I.

Application	Re^{max}	N_{points}^{max}	$N_{LagMult}$	$d_{GMRES}^{\%}$	$d_{CPU}^{\%}$
Carotid	554	70	2	-49.67%	-33.11%
Coronary	184	36	3	-32.16%	-4.03%
Aorta	4730	408	4	-68.54%	-28.16%

setup and assembly times, which do not significantly depend on the preconditioner, have a bigger influence on the total CPU time in the Aorta test, as shown in Table 5.3.

On the other hand, from Table 5.4 we also observe that the dependence on the number of Lagrange multipliers $N_{LagMult}$ of the speed-up in terms of GMRES iterations and CPU time allowed by the use of the *complete* preconditioner aug-aS seems to not have a clear trend.

To conclude, this analysis suggests that the improvement gained by properly preconditioning the extra Lagrange multipliers block does not strictly depend on the size of this block (i.e. the number of multipliers), but it is linked to the number of mesh points on the boundaries where flow rate conditions are imposed and the Reynolds number. Therefore, the proposed trivial extension of the standard aSIMPLE preconditioner aug-aS-I can be suited in applications where Re^{max} and N_{points}^{max} are small, e.g. Test III which shows a speed-up in terms of CPU time of just 4.03% (against much larger values in the other cases, see last column of Table 5.4) by using preconditioner aug-aS instead of aug-aS-I. In all other applications the *complete* preconditioner aug-aS should be preferred.

5.5.6. On the approximation of the L diagonal blocks

Throughout Section 5.5 we worked with approximations of the L matrix diagonal blocks, $\hat{K}$, $\hat{S}$ and $\hat{L}_\Lambda$ in (5.10), based on the AMG method, as presented in Section 5.5.1. In this subsection we investigate the use of other non-functional preconditioners implemented in

Trilinos, as wrapped by deal.II, for the approximation of these blocks. Specifically, we use additive Schwarz preconditioners with an ILU [61] or a SSOR [62] internal solvers, and a block Jacobi preconditioner [63]. For simplicity we fix their parameters to the default values reported in the documentations cited above.

We consider the same problem setup as in Test I (Section 5.5.4), fixing the number of Lagrange multipliers to five, investigating only the aug-aS preconditioner and using the same CPU's as in Test I. In order to assess the impact of each specific approximation, we perform numerical experiments by setting an AMG based preconditioner for all but one diagonal blocks and a different non-functional preconditioner for the remaining diagonal block and we compare the results with the use of AMG for all the diagonal blocks.

In Table 5.5 we report the average in time number of GMRES iterations and the total computing time needed to solve the linear systems and assemble the preconditioner for all the experiments. We notice from this table that the only choice that significantly improves the overall performance of the augmented aSIMPLE preconditioner, with respect to the standard AMG case, is given by an additive Schwarz preconditioner for $\widehat{K}$, in particular with an ILU solver.

We conclude that an approximation based on an additive Schwarz preconditioner should be preferred for $\widehat{K}$, whereas an AMG approximation is well-suited for both $\widehat{S}$ and $\widehat{L}_\Lambda$.

5.6. Main outcomes and limitations of the chapter

In this chapter we presented a new preconditioner for an augmented formulation related to an incompressible fluid in presence of flow rate conditions. Specifically, we extended the SIMPLE preconditioner [73, 179] introducing an inexact block LU factorization of the 3×3 block matrix. We applied the proposed method in several test cases, highlighting the suitability of the preconditioner for an arbitrary number of flow rate sections and in different hemodynamic realistic scenarios, and investigating its scalability with respect to the discretization parameters, the Reynolds number and the number of parallel cores.

The analysis presented in this chapter is characterized by some main limitations, which are discussed in what follows:

- although in Remark 5.4.3 we provide some preliminary insights regarding the effectiveness of our preconditioner under suitable hypothesis, a general theoretical analysis on the properties of the preconditioner is nowadays missing. A possible strategy is to follow [138] and to extend their analysis to our 3×3 block case, or to exploit the existing results for double saddle-point problems;

Table 5.5: Average-in-time number of GMRES iterations and total computing time needed to solve the linear systems and assemble the preconditioner varying individually the non-functional preconditioners used for approximations $\widehat{K}$, $\widehat{S}$ and $\widehat{L}_\Lambda$. Where not specified, AMG is intended to be used to approximate the non-indicated blocks. AMG: Algebraic Multigrid; AS-ILU: additive Schwarz with ILU solver; AS-SSOR: additive Schwarz with SSOR solver; BJ: block Jacobi. Test I with different block approximations.

	avg GMRES iter.	total time [s]
$\widehat{K}, \widehat{S}, \widehat{L}_\Lambda$		
AMG	260.3	53.0
$\widehat{K}$		
AS-ILU	115.8	18.9
AS-SSOR	165.0	31.0
BJ	312	56.2
$\widehat{S}$		
AS-ILU	269.3	51.2
AS-SSOR	295.2	60.9
BJ	313.9	60.1
$\widehat{L}_\Lambda$		
AS-ILU	260.3	53.0
AS-SSOR	260.3	52.9
BJ	260.3	53.0

- our choice on how to approximate the Schur complements appearing in our preconditioner is simply based on the standard Jacobi diagonal one. More reliable choices may be investigated in future works to better exploit their spectral properties;
- we do not perform any comparison with other methods to impose flow rate conditions, e.g. Nitsche, control-based, and corresponding specific preconditioners. Future studies may account for this point to complete the work started in this analysis about the Lagrange multipliers technique;
- we do not perform any comparison with other ad-hoc block preconditioners specifically designed for our problem and inspired by Navier-Stokes, such as Yosida, al-

gebraic Chorin-Temam, PCD. This is possible argument of future studies on the topic.

Appendix: Algebraic system for Test IV - Thoracic aorta

In this appendix we provide additional details on the RIIS, LES σ -model and backflow stabilization methods considered in "Test IV - Thoracic aorta" (see Section 5.5.5) and in the computational model to study post-TAVI hemodynamics (see Chapter 4). Specifically, we will focus on how these methods change the augmented variational formulation (5.2), the corresponding augmented monolithic system (5.3), preconditioner aug-aS (5.10) and preconditioner aug-aS-I (5.11).

Each of these methods introduces a term in the left hand side of the first equation of the augmented variational formulation (5.2). In particular, following the same notation as in Section 5.2 and Section 5.5.5, the introduced terms are:

- RIIS:

$$\left(\delta_{\Sigma, \epsilon} \frac{R}{\epsilon} (\mathbf{u} - \mathbf{u}_{\Sigma}), \mathbf{v} \right),$$

where Σ is the leaflets surface, $R = 10^5 \text{ Kg/m} \cdot \text{s}$ represents a resistance coefficient, $\epsilon = 7 \times 10^{-4} \text{ m}$ is a numerical parameter representing the half-thickness of a smoothed Dirac delta function $\delta_{\Sigma, \epsilon}$ centered in Σ and $\mathbf{u}_{\Sigma} = \mathbf{0} \text{ m/s}$ is the velocity of the bioprosthesis leaflets that we set to zero since we do not consider leaflets' dynamics [24, 79]. In Test IV this RIIS term is active only during the ejection phase (positive values of the inlet flow rate in Figure 5.9b);

- LES σ -model:

$$(\nu_{sgs}(\mathbf{u}) \nabla \mathbf{u}, \nabla \mathbf{v}),$$

where $\nu_{sgs} = C h^2 \sigma_3 (\sigma_1 - \sigma_2) (\sigma_2 - \sigma_3) / \sigma_1^2$ (with σ_j the singular values of $\nabla \mathbf{u}$, $C = 1.5$) is a sub-grid scale viscosity which accounts for the non-resolved scales [170];

- Backflow stabilization:

$$-\frac{1}{2} \int_{\Gamma_{in}^A \cup \Gamma_{out}^A} |\mathbf{u} \cdot \mathbf{n}|_- \mathbf{u} \cdot \mathbf{v} \, d\gamma,$$

where $|\mathbf{u} \cdot \mathbf{n}|_- = \frac{\mathbf{u} \cdot \mathbf{n} - |\mathbf{u} \cdot \mathbf{n}|}{2}$, so that this term is different from zero only in the points where $\mathbf{u} \cdot \mathbf{n} < 0$.

Considering the same spatial and temporal discretizations presented in Section 5.2 with a semi-implicit treatment of the LES σ -model and backflow stabilization terms, the resulting monolithic system reads:

$$\begin{bmatrix} K + G(\mathbf{U}^n) & B^T & \Phi^T \\ -B & Z & 0 \\ \Phi & 0 & 0 \end{bmatrix} \begin{bmatrix} \mathbf{U} \\ \mathbf{P} \\ \mathbf{\Lambda} \end{bmatrix} = \begin{bmatrix} \mathbf{F} \\ \mathbf{0} \\ \mathbf{Q} \end{bmatrix}, \quad (5.12)$$

showing the same block structure as in (5.3). The only difference is given by the addition of matrix G in the momentum equation accounting for RIIS, LES, backflow stabilization: $G(\mathbf{U}^n) = M_{RIIS} + A_{LES}(\mathbf{U}^n) + M_{bf}(\mathbf{U}^n)$, where $[M_{RIIS}]_{kj} = (\delta_{S,\epsilon} \frac{R}{\epsilon} \boldsymbol{\psi}_j, \boldsymbol{\psi}_k)$, $[A_{LES}]_{kj} = (\nu_{sgs}(\mathbf{U}^n) \nabla \boldsymbol{\psi}_j, \nabla \boldsymbol{\psi}_k)$, and $[M_{bf}(\mathbf{U}^n)]_{kj} = -\frac{1}{2} \int_{\Gamma_{in}^A \cup \Gamma_{out}^A} |\mathbf{U}^n \cdot \mathbf{n}|_- \boldsymbol{\psi}_j \cdot \boldsymbol{\psi}_k \, d\gamma$, $j, k = 1, \dots, N_U$.

The addition of matrix G in the first diagonal block results in the following expression of the augmented SIMPLE preconditioner:

$$P_S^{aug} = \begin{bmatrix} K + G(\mathbf{U}^n) & 0 & 0 \\ -B & \tilde{S} & 0 \\ \Phi & -\tilde{S}_{\Lambda P} & \tilde{L}_{\Lambda} \end{bmatrix} \begin{bmatrix} I & \tilde{D}^{-1} B^T & \tilde{D}^{-1} \Phi^T \\ 0 & I & \tilde{W}^{-1} \tilde{S}_{P\Lambda} \\ 0 & 0 & I \end{bmatrix}, \quad (5.13)$$

where $\tilde{D} = \text{diag}(K + G(\mathbf{U}^n))$, $\tilde{S} = B\tilde{D}^{-1}B^T + Z$, $\tilde{S}_{\Lambda P} = \Phi\tilde{D}^{-1}B^T$, $\tilde{L}_{\Lambda} = \tilde{S}_{\Lambda P}\tilde{W}^{-1}\tilde{S}_{P\Lambda} - \tilde{S}_{\Lambda}$, $\tilde{S}_{P\Lambda} = B\tilde{D}^{-1}\Phi^T$, $\tilde{S}_{\Lambda} = \Phi\tilde{D}^{-1}\Phi^T$ and $\tilde{W} = \text{diag}(\tilde{S})$. Following the same arguments of Sections 5.4.2-5.5.1, preconditioner aug-aS is obtained by suitably approximating the diagonal blocks of the lower triangular matrix in (5.13) and preconditioner aug-aS-I is obtained by setting an identity row and column in third block related to Lagrange multipliers in both the lower and upper triangular matrices.

6 | Analysis of post-TAVI hemodynamics

This chapter deals with a general analysis of the numerical results regarding post-TAVI hemodynamics, the results regarding the discrimination between DEG and NODEG patients will be later presented in Chapter 7. In particular, we introduce some quantities of interest used to analyze the numerical results (Section 6.1); we present two different computational models used in the thesis to numerically simulate post-TAVI hemodynamics (Section 6.2); we quantitatively validate the numerical results obtain with both the considered computational models (Section 6.3); finally we analyze the hemodynamics patterns obtain from the numerical results (Section 6.4).

6.1. Quantities of interest

In this section we introduce some quantities of interest used for the post-processing of the numerical results. We highlight that we introduce them as they were continuous functions of space and time. It goes without saying that, in fact, we will compute all these quantities of interest from numerical solutions discretized both in space and time.

Due to the turbulent nature of the analyzed flow, in this thesis we numerically simulate several complete heartbeats, discarding the first ones to avoid the influence of the null initial condition and computing average values on the remaining heartbeats $j = 1, \dots, N_{HB}$. In particular, using the *Paraview* software, we compute the *phase-average* (also named as *ensemble*) quantities, i.e., the average at each time over N_{HB} heartbeats:

$$\phi(\mathbf{x}, t) = \frac{1}{N_{HB}} \sum_{j=1}^{N_{HB}} \phi_j(\mathbf{x}, t),$$

where ϕ_j is either the velocity or the pressure at the j -th heartbeat, and N_{HB} is the number of heartbeats for which the average is computed. Notice that all the analyses presented in this and the following chapters are based on the *phase-average* velocity and

the *phase-average* pressure fields.

In the following we define some quantities of interest that are going to be used both to analyze post-TAVI hemodynamics (see Section 6.4) and to propose computational hemodynamic indices and scores that correlate with a premature onset of SVD (see Chapter 7).

Let us define the fluid viscous traction on a surface as:

$$\boldsymbol{\tau} = 2\mu D(\mathbf{u})\mathbf{n},$$

where μ is the blood viscosity, $D(\mathbf{u}) = \frac{\nabla \mathbf{u} + \nabla^T \mathbf{u}}{2}$, $\mathbf{u}$ is the (phase-average) blood velocity and $\mathbf{n}$ is the surface normal. Accordingly, the Wall Shear Stress (WSS) vector and its magnitude read, respectively:

$$\begin{aligned}\boldsymbol{\tau}_{WSS} &= \boldsymbol{\tau} - (\boldsymbol{\tau} \cdot \mathbf{n}) \mathbf{n}, \\ WSS &= \|\boldsymbol{\tau}_{WSS}\|,\end{aligned}$$

where $\|\mathbf{v}\|$ is the magnitude of a generic vector $\mathbf{v}$. This allows us to define the following quantities:

- Time-Averaged WSS (*TAWSS*):

$$TAWSS(\mathbf{x}; [T_1, T_2]) = \frac{1}{T_2 - T_1} \int_{T_1}^{T_2} \|\boldsymbol{\tau}_{WSS}\| dt,$$

where T_1 and T_2 identify the time-period (systole, diastole or complete heartbeat);

- Oscillatory Shear Index (*OSI*):

$$OSI(\mathbf{x}; [T_1, T_2]) = \frac{1}{2} \left(1 - \frac{\|\int_{T_1}^{T_2} \boldsymbol{\tau}_{WSS} dt\|}{\int_{T_1}^{T_2} \|\boldsymbol{\tau}_{WSS}\| dt} \right).$$

It provides a measure of the oscillatory nature of the WSS vector;

- Topological Shear Variation Index (*TSVI*):

$$TSVI(\mathbf{x}; [T_1, T_2]) = \sqrt{\frac{1}{T_2 - T_1} \int_{T_1}^{T_2} \left(\nabla \cdot \boldsymbol{\tau}_{WSS}^N - \overline{\nabla \cdot \boldsymbol{\tau}_{WSS}^N} \right)^2 dt},$$

where $\nabla \cdot$ is the divergence operator, $\boldsymbol{\tau}_{WSS}^N = \frac{\boldsymbol{\tau}_{WSS}}{\|\boldsymbol{\tau}_{WSS}\|}$ the normalized WSS vector, and $\overline{\nabla \cdot \boldsymbol{\tau}_{WSS}^N} = \frac{1}{T_2 - T_1} \int_{T_1}^{T_2} \nabla \cdot \boldsymbol{\tau}_{WSS}^N dt$ the average in time of the divergence of the normalized WSS vector. It represents the variation in the WSS action on the vessel

expansion/contraction [160].

Moreover we define the Q-criterion:

$$Q(\mathbf{x}, t) = \frac{1}{2} (\|W(\mathbf{u})\|^2 - \|D(\mathbf{u})\|^2),$$

where $W(\mathbf{u}) = \frac{\nabla \mathbf{u} - \nabla^T \mathbf{u}}{2}$ is the vorticity tensor. Positive values of this quantity identify regions where vorticity dominates over laminar friction.

6.2. Different computational models for post-TAVI hemodynamics

For the numerical simulation of post-TAVI hemodynamics in this thesis we consider two different computational models which differ for the level of detail and accuracy. In particular, we consider a *Simplified* model, namely *Model S*, and a *Realistic* model, namely *Model R*.

6.2.1. Simplified computational model for post-TAVI hemodynamics (*Model S*)

In *Model S* we consider:

1. the *simplified* strategy to geometrically model the SAPIEN valves' stent, based on the use of a hollow cylinder, introduced in Section 3.2.1;
2. the *simplified* strategy to geometrically model the SAPIEN valves' leaflets, mimicking a native aortic valve, introduced in Section 3.2.2;
3. the *simplified* strategy to derive a personalized flow rate profile, only based on the clinical cardiac output measure, introduced in Section 3.5. Such flow rate profile is imposed at the inlet boundary in the numerical simulations;
4. the *simplified* strategy to model leaflets dynamics, based on an on-off modality, introduced in Section 4.1.4;
5. the *aug-aS-I* SIMPLE preconditioner introduced in Section 5.5.1;
6. a slightly coarser superficial element size on the external wall of the domain with respect to the computational mesh specifics introduced in Section 3.4.1. For the sake of simplicity, we refer to [58] for the details on the mesh and for the associated mesh sensitivity analysis;

7. a time-step $\Delta t = 10^{-3} s$ for all the patients since the same heartbeat period is considered for each patient according to the *simplified* personalized flow rate profile imposed at the inlet.

These choices allow us to perform an analysis on all the 14 patients of the study population, comprising patients DEG3 and NODEG3 for which the *realistic* modeling strategy cannot be always employed. Notice that *Model S* was employed in [58].

Using *Model S*, numerical simulations of six complete heartbeats were run in parallel on 56 cores of Xeon E5-2640v4@2.4 GHz CPU's, using the computational resources available at MOX, Dipartimento di Matematica, Politecnico di Milano. The average computational time for each simulation (i.e. for six complete heartbeats) is 28.3 ± 4.2 hrs. In particular, for the computation of the phase-average fields from the numerical results obtained with *Model S* we consider $N_{HB} = 5$, thus discarding only the first heartbeat.

6.2.2. *Realistic computational model for post-TAVI hemodynamics (Model R)*

In *Model R* we consider:

1. the *realistic* strategy to geometrically model the SAPIEN valves' stent, accounting for the wire-frame design, introduced in Section 3.2.1;
2. the *realistic* strategy to geometrically model the SAPIEN valves' leaflets, based on a SAPIEN-like leaflets geometry, introduced in Section 3.2.2;
3. the *realistic* strategy to derive a personalized flow rate profile, exploiting both the cardiac output measure and the PW Doppler TTE image, introduced in Section 3.5. Such flow rate profile is imposed at the inlet boundary in the numerical simulations;
4. the *realistic* strategy to model leaflets dynamics, accounting for the transition between the closed and the open configuration, introduced in Section 4.1.4;
5. the *aug-aS* SIMPLE preconditioner introduced in Section 5.5.1;
6. the computational mesh obtained with the strategy presented in Section 3.4;
7. a different time-step Δt for each patient according to the duration of the patient's systolic phase given by the *realistic* personalized flow rate profile imposed at the inlet. Specifically, a time-step $\Delta t = 10^{-3} s$ is used for patient NODEG6 who shows the longest systolic period ($0.4 s$) and for the other patients the time-step is scaled so that we have roughly the same number of time instants during systole;

These choices allow us to perform an analysis on 12 out of the 14 patients of the study population, excluding patients DEG3 and NODEG3 for which the *realistic* modeling strategy cannot be employed for the stent model and the personalized flow rate profile due to a lack of data (see Table 3.2). Notice that *Model R* was employed in [59].

Using *Model R*, numerical simulations of eight complete heartbeats were run in parallel on 112 cores of Intel Sapphire Rapids@2.00GHz CPU's, using the computational resources provided by the CINECA supercomputing center, Italy. The average computational time for each simulation (i.e. for eight complete heartbeats) is 17.0 ± 5.3 hrs. In particular, for the computation of the phase-average fields from the numerical results obtained with *Model R* we consider $N_{HB} = 6$, thus discarding the first two heartbeats.

Notice that *Model R* is characterized by a finer computational mesh and the simulation of eight complete heartbeats (six in *Model S*). Nonetheless, the increased number of computing cores employed and the use of the *complete* preconditioner *aug-aS* allow for a significant speed-up in the total simulation time proving the efficiency of the library life^x and of the proposed *aug-aS* SIMPLE preconditioner.

6.3. Validation of the numerical results

To validate the numerical results of our CFD models we use the maximum blood velocity measurements through the bio-prosthetic valve taken from early post-TAVI CW Doppler TTE data, available for eleven patients in the study population (all but DEG2, DEG3, and NODEG3, see Table 3.2). During CW Doppler TTE a transducer continuously transmits ultrasound waves and receives echoes in order to measure blood velocities along an entire beam θ oriented as the valve and passing through its center (Section 1.3.1). The maximum blood velocity through the valve is identified as the maximum velocity magnitude obtained along the beam θ during the heartbeat, and we compare it with the same quantity extracted from the CFD results, assuming a Doppler-like beam θ with a radius of 1 mm. We report in Figure 6.1 an example of the beam θ , for both the Doppler and CFD measures.

6.3.1. Validation of the numerical results with *Model S*

In table 6.2 we report the maximum blood velocity obtained from CW Doppler TTE and from the CFD results with *Model S*.

In particular, out of the eleven patients with available clinical data, the table shows that: in four patients (DEG4, NODEG1, NODEG4, NODEG5) there is a good agreement with

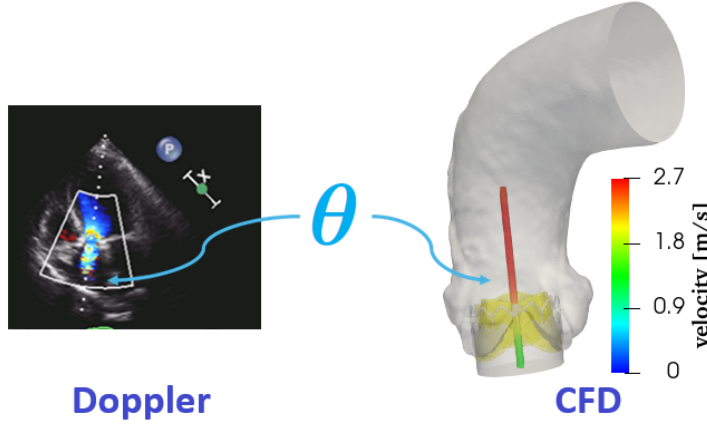


Figure 6.1: Left: visualization of the Doppler image and the Doppler beam θ . Right: example of the region θ where the maximum blood velocity magnitude is computed from the CFD results.

Table 6.1: Numerical blood velocity validation. Early post-TAVI maximum blood velocity magnitude through the bio-prosthetic valve taken from CW Doppler TTE data ($V_{max}^{Doppler}$) and from the CFD results (V_{max}^{CFD}), and relative difference between the two measures ($Diff$). Notice that the Doppler velocity is truncated after the first decimal digit, thus we compute a range of difference by considering $V_{max}^{Doppler} \pm 0.05 [\frac{m}{s}]$. *Model S*

ID	$V_{max}^{Doppler} [\frac{m}{s}]$	$V_{max}^{CFD} [\frac{m}{s}]$	$Diff [\%]$
DEG1	2.6	2.88	9.1-12.9
DEG4	2.6	2.54	0.4-3.8
DEG5	2.5	2.63	3.5-7.3
DEG6	2.6	2.78	5.3-9.0
DEG7	2.4	2.53	3.7-7.7
NODEG1	2.5	2.55	0.4-4.1
NODEG2	2.0	2.20	7.8-12.8
NODEG4	2.5	2.54	0-3.6
NODEG5	2.3	2.27	0-3.0
NODEG6	2.1	2.85	33.2-39.0
NODEG7	2.5	2.38	2.9-6.3

maximum difference values smaller than 5%; in four patients (DEG5, DEG6, DEG7, NODEG7) there is an acceptable agreement with average difference values smaller than

10%; in the remaining three patients we experience increased differences with DEG1, NODEG2 having average difference values smaller than 15%, and NODEG6 having an average difference value around 35%.

6.3.2. Validation of the numerical results with *Model R*

In table 6.2 we report the maximum blood velocity obtained from CW Doppler TTE and from the CFD results with *Model R*.

Table 6.2: Numerical blood velocity validation. Early post-TAVI maximum blood velocity magnitude through the bio-prosthetic valve taken from CW Doppler TTE data ($V_{max}^{Doppler}$) and from the CFD results (V_{max}^{CFD}), and relative difference between the two measures ($Diff$). Notice that the Doppler velocity is truncated after the first decimal digit, thus we compute a range of difference by considering $V_{max}^{Doppler} \pm 0.05 [\frac{m}{s}]$. *Model R*

ID	$V_{max}^{Doppler} [\frac{m}{s}]$	$V_{max}^{CFD} [\frac{m}{s}]$	$Diff [\%]$
DEG1	2.6	2.92	10.6-14.5
DEG4	2.6	2.51	1.6-4.9
DEG5	2.5	2.33	4.9-8.2
DEG6	2.6	2.62	0.0-2.7
DEG7	2.4	2.39	0.0-2.0
NODEG1	2.5	2.54	0.0-3.7
NODEG2	2.0	2.04	0.0-4.6
NODEG4	2.5	2.51	0.0-2.4
NODEG5	2.3	1.85	17.8-20.9
NODEG6	2.1	2.29	7.0-11.7
NODEG7	2.5	2.08	15.1-18.1

In particular, out of the eleven patients with available clinical data, the table shows that: in three patients (DEG6, DEG7, NODEG4) the agreement is excellent with maximum differences smaller than 3%; in three patients (DEG4, NODEG1, NODEG2) there is a good agreement with maximum difference values smaller than 5%; in two patients (DEG5, NODEG6) there is an acceptable agreement with average difference values smaller than 10%; in the remaining three patients we experience increased differences with DEG1 having an average difference value smaller than 15%, and NODEG5, NODEG7 having average difference values smaller than 20%.

6.3.3. Discussion on the validation of the numerical results

Doppler-based blood velocity measurements showed a variability up to 9% between different measurements performed by the same experienced vascular technologist in an idealized in-vitro setting [144]. Thus, we deem as acceptable all the differences between the CW Doppler TTE and CFD measures which are lower or close to the 9% threshold.

We report in Table 6.3, for both *Model S* and *Model R*, the number of patients showing different levels of agreement between the CW Doppler TTE and CFD maximum blood velocity.

Table 6.3: For both *Model S* and *Model R* we report the number of patients showing an agreement between the CW Doppler TTE and CFD maximum blood velocity which is: excellent, good, acceptable, non-acceptable. Excellent: maximum difference below 3%. Good: maximum difference below 5%. Acceptable: average difference below 10%. Non-acceptable: average difference above 10%.

Agreement	<i>Model S</i>	<i>Model R</i>
Excellent	0	3
Good	4	3
Acceptable	4	2
Non-acceptable	3	3

The table shows that both models result in a satisfactory quantitative validation with eight out eleven patients with available clinical data having differences lower or close to the 9% threshold. In particular, *Model R* performs better than *Model S* due to the increased number of patients showing at worst a good agreement between the two measures (6 for *Model R* vs 4 for *Model S*) and the lower maximum difference between the patients (20.9% for *Model R* vs 39.0% for *Model S*). On the other hand, both models result in non-acceptable differences in three patients: DEG1, NODEG2, and NODEG6 for *Model S* and DEG1, NODEG5, and NODEG7 for *Model R*.

The fact that different patients are associated with non-acceptable differences by employing the different models is due to the different strategies used to derive the flow rate profile imposed at the inlet section, and to the different geometries used to model the bio-prosthetic leaflets. Specifically, we deem *Model R* to be more accurate since it includes more patient-specific information in the derivation of the flow-rate profile and a more realistic representation of the leaflets. This is particularly relevant in patients for which the

flow rate profile derived with the *realistic* strategy significantly differs from the literature profile considered in the *simplified* strategy. This is the case for patient NODEG6 who is characterized by a longer systolic period using *Model R*, leading to a smaller maximum flow rate value and thus to a smaller maximum velocity value which drastically improves the comparison with the clinical data. On the other hand, the *realistic* strategy to derive the flow rate profile is based on a manual reconstruction of the blood velocity magnitude at the center of the LVOT assuming that it shares the same temporal evolution with the flow rate coming into the aorta. A sub-optimal manual reconstruction or a mismatch between the flow rate and the velocity temporal trends result in the derivation of an inaccurate flow rate, leading to a poor comparison with the clinical data. This could be the case for patients NODEG5 and NODEG7 which shows non-acceptable differences only using *Model R*. Another possible explanation for the discrepancies between the CFD and clinical data is an under/over expansion of the real implanted TAVI valve, that we cannot model since we do not have at disposal any intra-procedural data. This could be the case for patient DEG1 for which both models result in an overestimation of the maximum blood velocity with respect to the Doppler measurement.

6.4. Analysis of the post-TAVI hemodynamic patterns

In order to analyze the post-TAVI hemodynamic patterns captured with our CFD models, we first focus on a single patient, as a representative of the study population, and on the *Realistic* CFD model, but analogous considerations can be made also for the other patients and for the *Simplified* CFD model. In particular, considering patient NODEG4, in Figure 6.2 we report at different time-steps during the cardiac cycle the velocity streamlines and the pressure field on a longitudinal plane, the region where the Q-criterion $Q > 50000 [Hz^2]$, and the WSS magnitude on the aortic wall. Let us notice that the pressure field is to be interpreted as a pressure difference with respect to the pressure at the outlet section since we impose a zero pressure at the outlet in our CFD setting (see Section 4.1.2). From the velocity plots we can observe that the presence of a small size TAVI valve (23 mm in external diameter) gives rise to a high-velocity jet forming across the implanted valve, together with a doughnut-shaped vortical structure along side the jet, in early systole (i.e. when the flow rate is increasing). Specifically, the vortical structure can be better visualized in 3D by isolating positive values of the Q-criterion ($Q > 50000 [Hz^2]$ in the figure). Let us note that, the velocity magnitude obtained inside the jet strictly depends on the personalized flow rate profile (see Section 3.5) prescribed

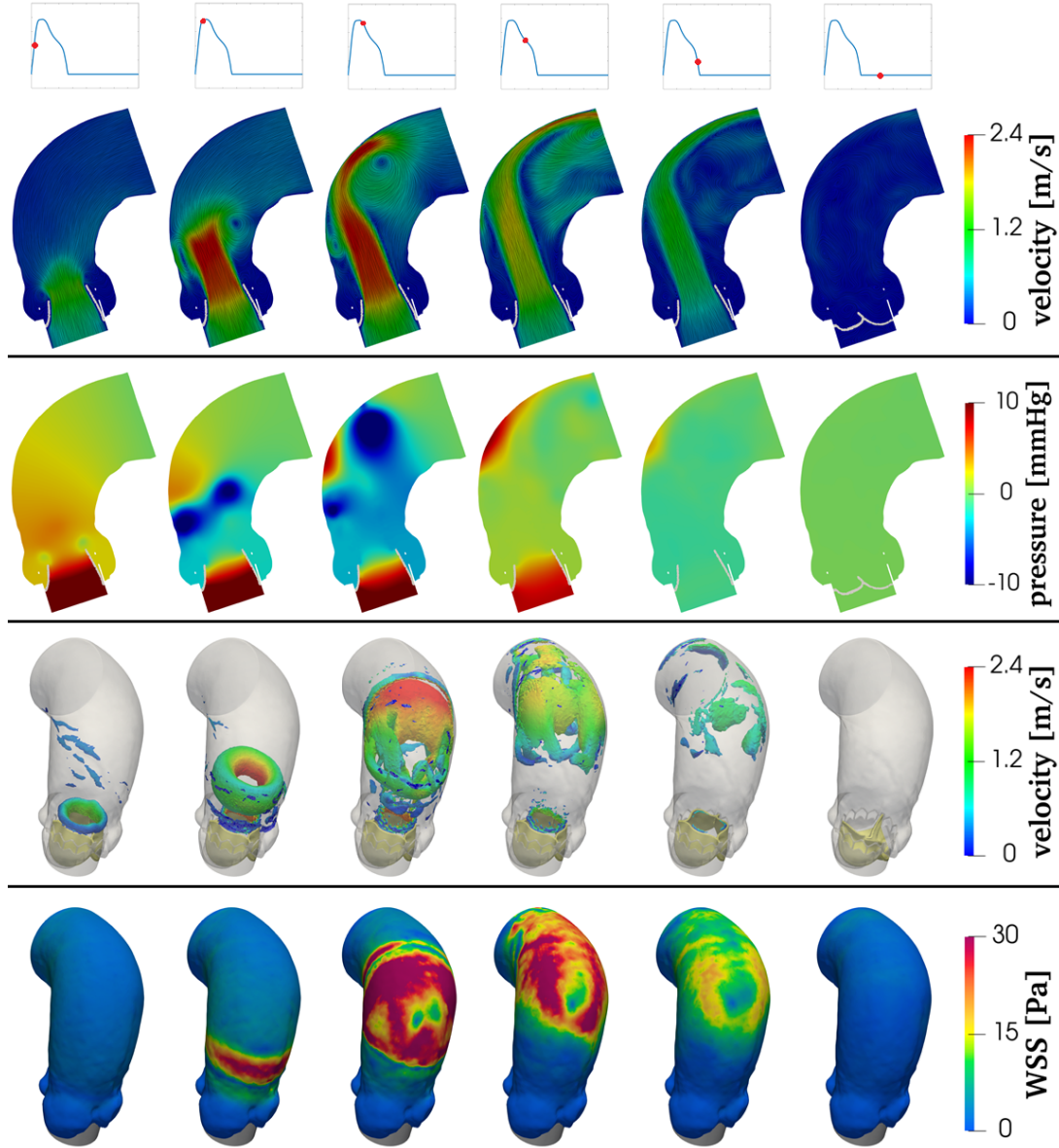


Figure 6.2: For patient NODEG4 we report at different time-steps during the cardiac cycle (indicated on top) the velocity streamlines and the pressure field on a longitudinal plane, the region where the Q-criterion $Q > 50000 [Hz^2]$ (colored by velocity), and the WSS magnitude on the aortic wall. *Model R*.

at the inlet, since the geometric opening area of the valve is the same for each patient in our model. The impingement of the jet and vortices on the aortic wall results in very chaotic hemodynamic patterns with recirculating areas in the ascending aorta forming in late systole (i.e. when the flow rate is decreasing). Additionally, the accelerated flow results in significant pressure gradients across the valve, with maximum values around $20 [mmHg]$. In particular, in the second and third time instants, low pressure values are

obtained in the vortices inside the ascending aorta, with a pressure recovery towards the outlet section. Furthermore, high values of the WSS vector magnitude are obtained on the aortic wall, with the WSS patterns following the collision of the vortices on the wall. Finally, the diastolic time instant (i.e. when the flow rate is zero) is characterized by chaotic velocity streamlines throughout the computational domain and low pressure and WSS magnitude values.

This analysis highlights the mildly stenotic scenario that follows the implantation of a balloon-expandable, small size TAVI valve (Edwards SAPIEN 23 mm), characterized by high velocity magnitudes and a pressure recovery distal to the aortic valve [171]. This is consistent with the observation that all stented bio-prosthetic valves result in a residual stenosis of up to 20% [212]. Specifically, the formation of a high-velocity jet in the ascending aorta leads to complex and disturbed hemodynamic patterns possibly speeding up SVD pathogenesis through inflammatory reaction and infiltration of host cells in the leaflets.

For the sake of completeness, in Figure 6.3 we report for the whole study population the velocity streamlines (see Figure 6.3a) and the pressure field (see Figure 6.3b) on a longitudinal plane at the instant of peak flow rate during systole. The figure shows that the presence of the high-velocity jet, the vortical structures, and the pressure recovery is a common feature in all the patients. In particular, we notice that the morphology of the jet and of the vortical structures depends on the patient-specific geometries and inlet flow rate profiles. Moreover, the same main flow features can be captured also with the *Simplified* CFD model, as shown by the results obtained with *Model S* for patients DEG3 and NODEG3.

Lastly, in Figure 6.4 we discuss the differences in the numerical results obtained with the *Simplified* and *Realistic* CFD models, considering patient NODEG2 as a representative of the study population. From Figure 6.4a we can see how the *Simplified* and *Realistic* strategies to obtain the personalized flow rate profiles imposed at the inlet section, and to obtain the leaflets geometry influence the morphology of the jet and the velocity magnitude inside the jet. Moreover the zoom in the stent's struct area highlights that, by considering a wire-frame design for the stent (*Model R*), blood is able to flow within the stent's struct, resulting in different streamlines in the valve area. Finally, Figure 6.4b shows that using the *Simplified* CFD model the leaflets instantaneously pass from the fully closed to the fully open configuration, whereas using the *Realistic* CFD model a smoother transition between these configurations can be achieved. In particular, with *Model R* we observe an higher pressure gradient across the valve and an higher velocity magnitude in the first time instants of the numerical simulation since blood is constrained

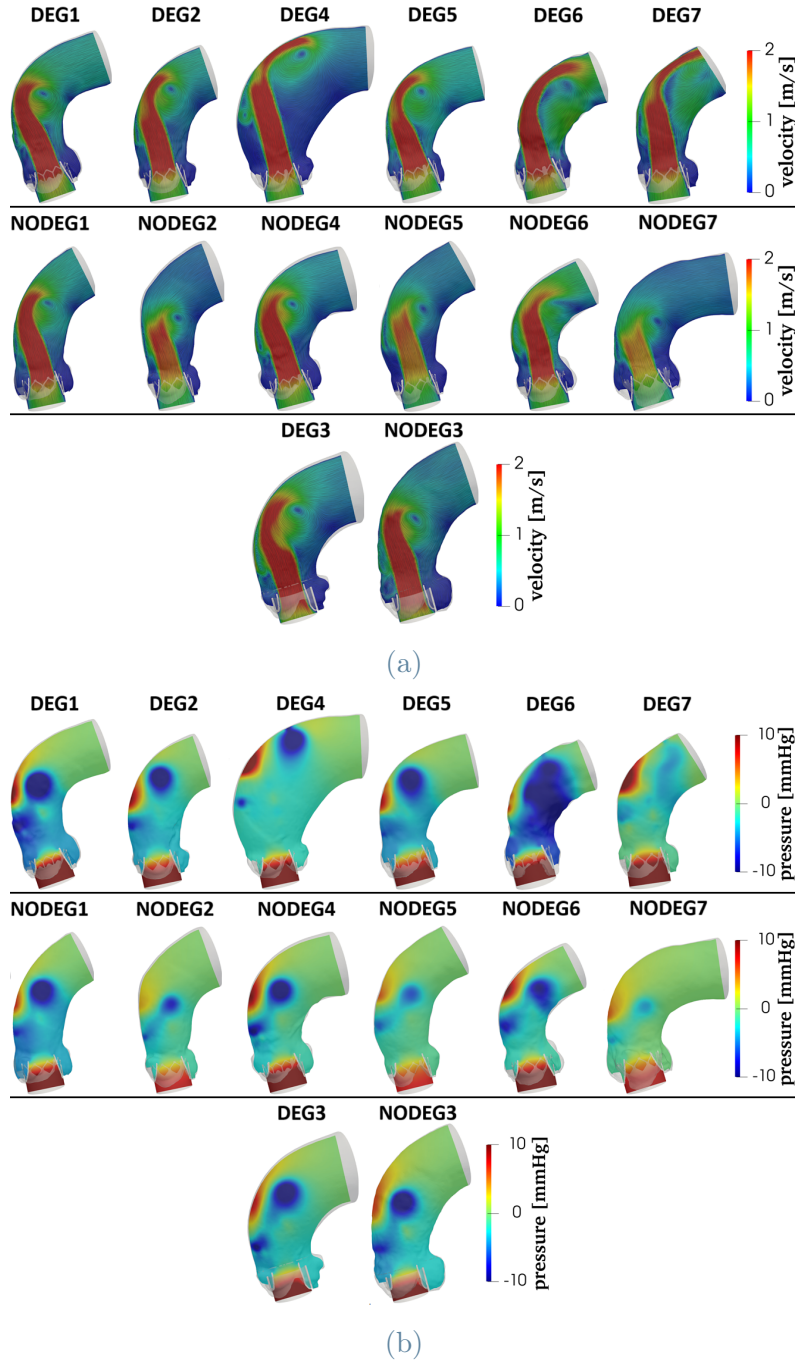


Figure 6.3: For each patient in the study population we report the velocity streamlines (a) and the pressure field (b) on a longitudinal plane at the instant of peak flow rate during systole. The results obtained with *Model R* are reported for every patient except for DEG3 and NODEG3 for which the results with *Model S* are reported since these two patients could not be analyzed with *Model R*.

to flow through a smaller opening area.

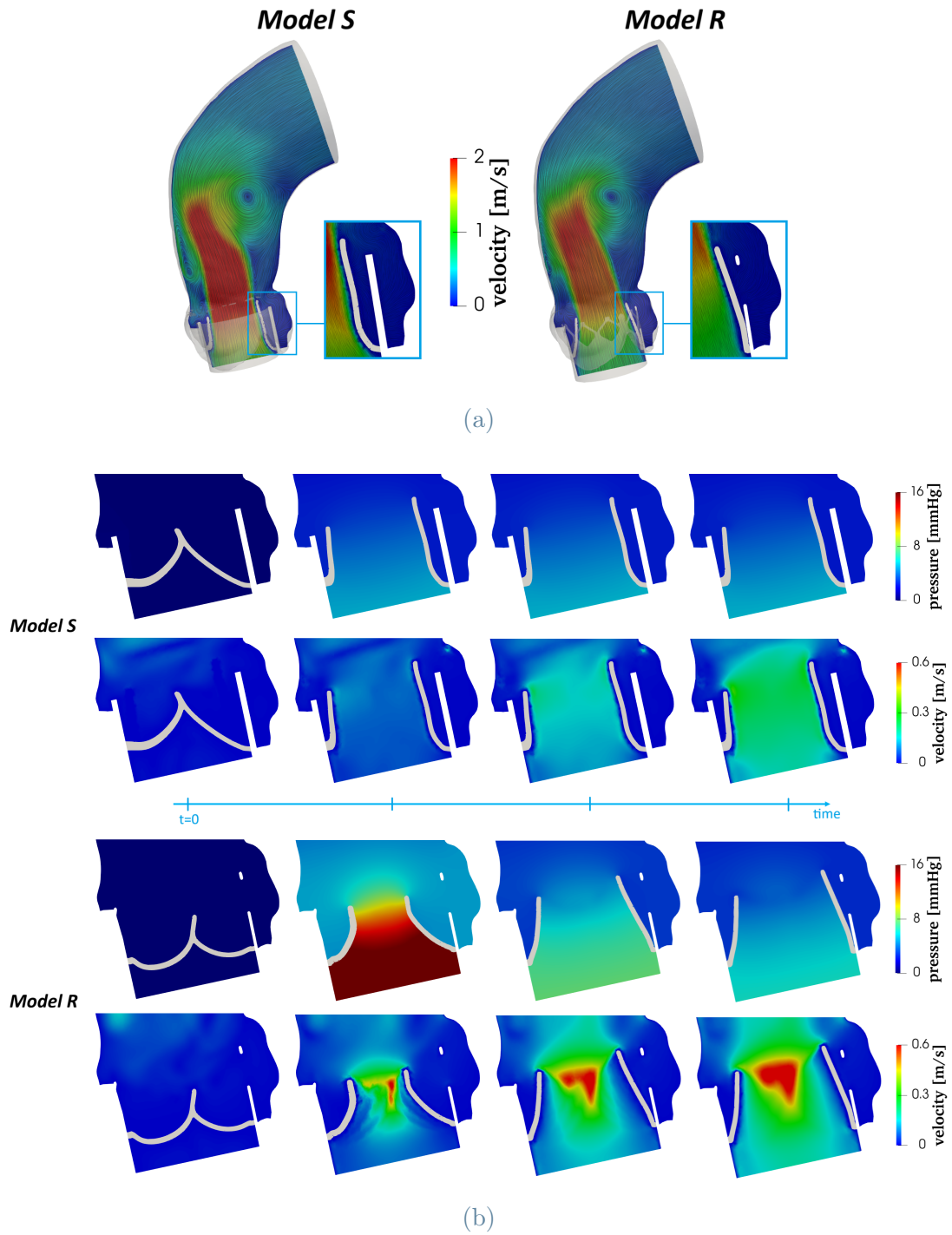


Figure 6.4: For both the *Simplified* and *Realistic* CFD models we report: (a) the velocity streamlines on a longitudinal plane with a zoom in the stent's struct area; (b) a zoom in the valve area of the pressure field and velocity streamlines in the first time-steps of the numerical simulation. Patient NODEG2

7 | Computational scores for Structural Valve Deterioration

This chapter deals with the computational hemodynamic indices and associated scores, computed in early post-TAVI scenarios, in order to discriminate between patients with and without Structural Valve Deterioration (SVD), identified at long-term follow-up exam. In particular, we detail the definition of SVD adopted in this study (Section 7.1); finally we present the formulation and results of the computational scores identified with both the *Realistic* model (Section 7.2) and the *Simplified* model (Section 7.3).

7.1. On the definition of SVD

In this section we show that the definition of SVD adopted in this thesis is in agreement with both the "stage 3 SVD" definition proposed by Dvir et al in [72] and the definition of SVD with "Stage 3 Hemodynamic Valve Deterioration" proposed by the Valve Academic Research Consortium (VARC) 3 in [53].

We report in Table 7.1 the PW and CW Transthoracic Echocardiography (TTE) data used to identify the onset of SVD at long-term follow-up exam in all the patients in our study population. In particular, these data were acquired both early post-TAVI to have baseline measurements and at long-term follow-up to assess valve deterioration after some years. Additionally, we report in Table 7.2 the absolute and relative difference between the long-term follow-up and the early post-TAVI data, for each type of data reported in Table 7.1.

Dvir et al defined "stage 3 SVD" as the development of severe stenosis and/or regurgitation in the implanted valve. In particular, severe stenosis is identified by the following characteristics [72]:

- Maximum blood velocity through the bio-prosthetic valve $V_{max} \geq 4.0 [\frac{m}{s}]$;
- Mean transvalvular pressure gradient $\Delta P_{mean} \geq 40 [mmHg]$;

Table 7.1: Patients' data used to identify the onset of SVD. This data was obtained from early post-TAVI and long-term follow-up Pulsed Wave and Continuous Wave Transthoracic Echocardiography (TTE). The superscripts B and F identify the baseline and follow-up measurements, respectively. V_{max}^* : maximum velocity through the bio-prosthetic valve. ΔP_{mean}^* : mean transvalvular pressure gradient. EOA^* : Effective Orifice Area. DVI^* : Doppler Velocity Index.

ID	Early post-TAVI TTE				Long-term follow-up TTE			
	V_{max}^B [$\frac{m}{s}$]	ΔP_{mean}^B [$mmHg$]	EOA^B [cm^2]	DVI^B [-]	V_{max}^F [$\frac{m}{s}$]	ΔP_{mean}^F [$mmHg$]	EOA^F [cm^2]	DVI^F [-]
DEG1	2.6	15	1.67	0.48	4.0	40	1.02	0.36
DEG2	-	-	-	-	3.9	40	0.94	0.33
DEG3	-	-	-	-	-	-	-	-
DEG4	2.6	13	1.64	0.43	4.0	40	0.81	0.26
DEG5	2.5	13	1.79	0.63	4.0	40	0.61	0.18
DEG6	2.6	14	1.87	0.45	4.0	35	1.18	0.34
DEG7	2.4	13	1.63	0.52	4.2	36	0.81	0.26
NODEG1	2.5	14	1.44	0.35	2.2	6	1.59	0.38
NODEG2	2.0	9	1.61	0.51	2.2	10	1.14	0.36
NODEG3	-	-	-	-	-	-	-	-
NODEG4	2.5	11	1.65	0.53	2.5	14	1.25	0.40
NODEG5	2.3	11	1.39	0.49	2.6	16	1.08	0.38
NODEG6	2.1	9	1.88	0.54	2.6	13	1.50	0.36
NODEG7	2.5	14	1.48	0.43	2.7	13	1.89	0.55

- Absolute difference in mean gradient $D_{\Delta P}^{abs} \geq 20 mmHg$;
- Doppler Velocity Index $DVI \leq 0.25$;
- Effective Orifice Area $EOA \leq 1.00$.

From Tables 7.1-7.2 we can see that, at the long-term follow-up exam, each DEG patients satisfies at least one of these conditions, whereas each NODEG does not satisfy any of these conditions.

On the other hand, the VARC 3 defined "Stage 3 Hemodynamic Valve Deterioration" as an

Table 7.2: Differences between the long-term follow-up and early post-TAVI TTE data reported in Table 7.1. The superscripts *abs* and *rel* identify the absolute and relative differences, respectively. D_V^* difference in terms of V_{max} . $D_{\Delta P}^*$ difference in terms of ΔP_{mean} . D_{EOA} difference in terms of EOA . D_{DVI} difference in terms of DVI .

ID	Absolute difference				Relative difference			
	D_V^{abs} [$\frac{m}{s}$]	$D_{\Delta P}^{abs}$ [$mmHg$]	D_{EOA}^{abs} [cm^2]	D_{DVI}^{abs} [-]	D_V^{rel} [%]	$D_{\Delta P}^{rel}$ [%]	D_{EOA}^{rel} [%]	D_{DVI}^{rel} [%]
DEG1	1.4	25	-0.65	-0.12	53.8	166.7	-38.9	-25.0
DEG2	-	-	-	-	-	-	-	-
DEG3	-	-	-	-	-	-	-	-
DEG4	1.4	27	-0.83	-0.17	53.8	207.7	-50.6	39.5
DEG5	1.5	27	-1.18	-0.45	0.6	207.7	-65.9	-71.4
DEG6	1.4	21	-0.69	-0.11	53.8	150.0	-36.9	-24.4
DEG7	1.8	23	-0.82	-0.26	75.0	176.9	-50.3	-50.0
NODEG1	-0.3	-8	0.15	0.04	-12.0	-57.1	10.4	10.4
NODEG2	0.2	1	-0.47	-0.15	9.1	11.1	-29.2	-29.3
NODEG3	-	-	-	-	-	-	-	-
NODEG4	0.0	3	-0.40	-0.13	0.0	27.3	-24.2	-24.5
NODEG5	0.3	5	-0.31	-0.11	13.0	45.5	-22.3	-22.1
NODEG6	0.5	4	-0.38	-0.18	23.8	44.4	-20.2	-33.2
NODEG7	0.2	-1	0.41	0.12	8.0	-7.1	27.7	28.0

absolute difference in mean transvalvular pressure gradient $D_{\Delta P}^{abs} \geq 20 mmHg$ resulting in a mean gradient $\Delta P_{mean}^F \geq 30 [mmHg]$ with concomitant differences in Effective Orifice Area (EOA) $D_{EOA}^{abs} \leq -0.60 cm^2$ or $D_{EOA}^{rel} \leq -50.0\%$ and/or differences in Doppler Velocity Index (DVI) $D_{DVI}^{abs} \leq -0.20$ or $D_{DVI}^{rel} \leq -40.0\%$. From Tables 7.1-7.2 we can see that, at the long-term follow-up exam, each DEG patients satisfies these conditions, whereas each NODEG does not satisfy these conditions.

Notice that the onset of SVD in patients DEG2, DEG3 and NODEG3 has been identified using the same criteria as for the other patients, but the specific data for these patients were not available at the time of this study. Specifically, for patient DEG2 we are lacking only the early post-TAVI CW TTE data, thus we could not report only the differences

between the long-term follow-up and the baseline measures.

7.2. Computational scores for SVD with the *Realistic* model

We start by presenting the computational indices and scores for SVD identified from the post-processing of the numerical results obtained with *Model R*. This is done to stress the fact that with *Model R* we are able to formulate computational indices and scores that have a clearer phenomenological interpretation and that show better results in terms of their correlation with a premature onset of SVD. In particular, we first define the computational hemodynamic indices and associated scores identified with *Model R* (Section 7.2.1) and then we present their results in terms of discriminating power between DEG and NODEG patients (Section 7.2.2).

7.2.1. Definition of hemodynamic and synthetic scores (*Model R*)

In this thesis we aim to propose computational hemodynamic indices and scores in early post-TAVI scenarios that correlate with a premature onset of SVD, identified at long-term follow-up exam. To this aim, we perform a post-processing of the numerical results obtained with *Model R*, based on the *phase-average* velocity field, to identify indices that discriminate between DEG and NODEG patients.

Let us remember that SVD has been associated with an increased infiltration of host cells (e.g. immune cells, cell debris) in the bio-prosthetic leaflets [38, 239, 255] (see Section 1.5). Accordingly, in what follows we introduce three hemodynamic indices, based on the quantities of interest defined in Section 6.1, that can be associated to different mechanisms promoting an infiltration of host cells in the leaflets. In particular:

- A diffuse damage/inflammation of the aortic wall can lead to the recruitment of immune cells to the aortic root [49], thus facilitating their infiltration in the leaflets. To quantify this damage we propose the Wall Damage Index (*WDI*) computed on the aortic wall:

$$WDI(\mathbf{x}) = TAWSS(\mathbf{x}; [0; T]) \times TSVI(\mathbf{x}; [0; T]),$$

where T is the duration of the whole heartbeat. It is known that high WSS, here associated with high *TAWSS* values, on the vessel wall can result in endothelial

changes, possibly promoting inflammation [77]. Additionally, significant variations in WSS directionality, corresponding to high $TSVI$ values, can affect vascular diseases by influencing endothelial cells [12]. Thus, we associate high WDI values with a possible damage of the aortic wall.

- High stresses on the bio-prosthetic leaflets can cause the delamination of the connective tissue, promoting the infiltration of immune cells [128]. For this reason, we propose the Leaflet Delamination Index (LDI) computed on the ventricular side of the leaflets:

$$LDI(\mathbf{x}) = TAWSS(\mathbf{x}; [0; T_S]),$$

where T_S is the systolic end instant.

- Low and oscillatory WSS is known to impair endothelial integrity, thus increasing its permeability [50]. Accordingly, we propose the Leaflet Permeability Index (LPI) computed on the aortic side of the leaflets:

$$LPI(\mathbf{x}) = OSI(\mathbf{x}; [T_S; T]) \times (0.05 - TAWSS(\mathbf{x}; [T_S; T])).$$

Notice that, high OSI and low $TAWSS$ values result in high LPI values.

To investigate the correlation between the proposed indices and a premature onset of SVD, we define a hemodynamic score associated to each index by spatially averaging the index on the corresponding surface. Specifically, WDI is averaged on the whole aortic wall to obtain $\widehat{WDI}$, LDI is averaged on the ventricular side of the leaflets to obtain $\widehat{LDI}$, and LPI is averaged on the aortic side of the leaflets to obtain $\widehat{LPI}$.

We notice that in the literature combinations of $TAWSS$ and OSI to identify vessels regions subject to low and oscillatory shear stresses are commonly based on the use of the Endothelial Cell Activation Potential ($ECAP$) [66, 251] and Relative Residence Time (RRT) [238], which depend on the inverse of $TAWSS$. Our numerical results are often characterized by values of $TAWSS \approx 0$ in some very localized areas of the leaflets during diastole, leading to very high $ECAP$ and RRT values that would dominate over the spatial average needed to define the hemodynamic score. For this reason, in this study we proposed LPI which does not have a singularity for $TAWSS = 0$.

In order to clearly separate between patients with and without SVD at long-term follow-up exam (DEG vs NODEG), we define a global synthetic score, which combines the proposed hemodynamic scores. This is done with the aim of proposing a robust score which synthetically comprises different mechanisms facilitating immune cells infiltration (aortic wall damage/inflammation, leaflet delamination, leaflet increased permeability).

Since the three hemodynamic scores take values in significantly different ranges, then in order to be combined they have to first be normalized. To do so we compute the 25th percentile (Ψ_1), the 75th percentile (Ψ_3), and the inter-quartile range ($IQR = \Psi_3 - \Psi_1$) for each hemodynamic score in the whole study population and we linearly project the interval $[\Psi_1 - IQR, \Psi_3 + IQR]$ into the interval $[-1, 1]$.

The global synthetic score SVD_{score}^R of *Model R* reads:

$$SVD_{score}^R = \frac{(\widehat{WDI}_N + \widehat{LDI}_N + \widehat{LPI}_N)}{3},$$

where the subscript N identifies the hemodynamic normalized score.

7.2.2. Results of the hemodynamic and synthetic scores (Model R)

In Figure 7.1 we report for patient DEG1, as a representative of the study population, the spatial distribution of the hemodynamic indices for *Model R* presented in Section 7.2.1, which is driven by the complex hemodynamics described in Section 6.4. Indeed, the high stresses on the aortic wall and the disturbed flow patterns, leading to significant topological variations of the WSS vectors, are the main determinants for the *WDI* distribution. Furthermore, the accelerated flow across valve affects the stress intensity on the ventricular side of the leaflets during systole, thus the *LDI*. Finally, the chaotic flow patterns, characterized by several vortical structures in the aorta, leads to low and oscillatory stresses on the aortic side of the leaflets during diastole, thus influencing the *LPI* intensity and patterns.

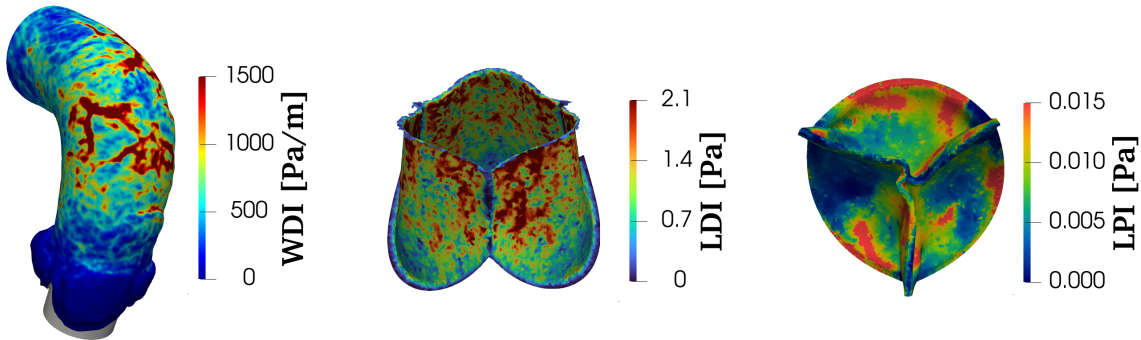


Figure 7.1: Hemodynamic indices *WDI*, *LDI* and *LPI* for *Model R* (see Section 7.2.1). Patient DEG1.

In Table 7.3 we report, for the 12 patients analyzed with *Model R*, the values of the

hemodynamic scores introduced in Section 7.2.1. From the table it is clear that different

Table 7.3: Values of the hemodynamic scores $\widehat{WDI}$, $\widehat{LDI}$ and $\widehat{LPI}$ defined in Section 7.2.1 for the 12 patients analyzed with *Model R*.

ID	$\widehat{WDI} [\frac{Pa}{m}]$	$\widehat{LDI} [Pa]$	$\widehat{LPI} [Pa]$
DEG1	5.10×10^2	1.08×10^0	7.27×10^{-3}
DEG2	5.31×10^2	1.12×10^0	5.58×10^{-3}
DEG4	4.03×10^2	1.12×10^0	7.49×10^{-3}
DEG5	5.28×10^2	1.07×10^0	4.81×10^{-3}
DEG6	5.83×10^2	1.24×10^0	6.11×10^{-3}
DEG7	4.50×10^2	1.17×10^0	6.14×10^{-3}
NODEG1	3.98×10^2	1.06×10^0	3.36×10^{-3}
NODEG2	2.69×10^2	0.81×10^0	4.64×10^{-3}
NODEG4	3.85×10^2	0.98×10^0	7.14×10^{-3}
NODEG5	3.07×10^2	0.82×10^0	5.29×10^{-3}
NODEG6	4.31×10^2	0.99×10^0	4.39×10^{-3}
NODEG7	5.03×10^2	0.95×10^0	3.11×10^{-3}

scores take value in significantly different ranges, thus stressing the importance of the normalization procedure, described in Section 7.2.1, in order to combine them.

In Figure 7.2 we plot using boxplots the distribution of the hemodynamic scores obtained with *Model R* in the DEG and NODEG sub-populations. The figure shows that each score tends to be characterized by greater values for DEG patients with respect to NODEG patients.

In order to properly assess the observed trend, for each individual hemodynamic score we employ a right-tailed Wilcoxon rank-sum test having as alternative hypothesis that the median of the DEG distribution is statistically greater than the median of the NODEG distribution. In particular, this is a non-parametric test which evaluates if the distribution of one group is significantly higher than the other, and it is chosen due to the limited amount of observations. The p-values resulting from the right-tailed Wilcoxon rank-sum tests are: $p = 0.0076$ for $\widehat{WDI}$, $p = 0.0011$ for $\widehat{LDI}$, and $p = 0.0206$ for $\widehat{LPI}$. Thus, with respect to each hemodynamic score the DEG distribution is statistically greater than the NODEG distribution at a 2.06% significance level. This is a very promising

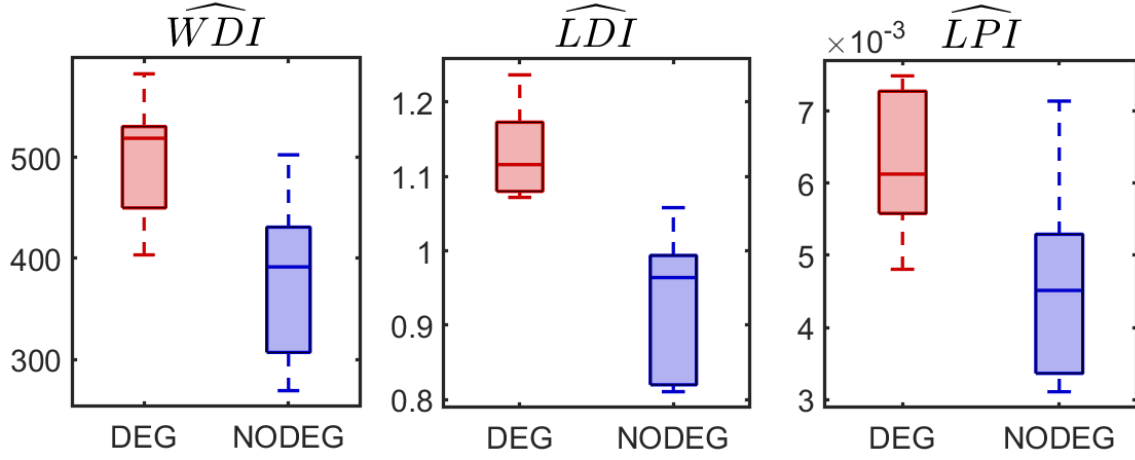


Figure 7.2: Boxplot distributions the hemodynamic scores $\widehat{WDI}$, $\widehat{LDI}$ and $\widehat{LPI}$ in the DEG and NODEG sub-populations. *Model R*.

result showing that patients with a prematurely degenerated valve belong to a different statistical distribution with respect to the considered hemodynamic scores even when the valve is not degenerated yet. Therefore, this analysis represents a preliminary proof of the influence of aortic hemodynamics on the development of SVD, which could be considered for a thorough assessment of SVD and has been rarely investigated with computational models.

Additionally, in Table 7.4 we report, for the 12 patients analyzed with *Model R*, the values of the global synthetic score SVD_{score}^R introduced in Section 7.2.1. The SVD_{score}^R is able

Table 7.4: For the 12 patients analyzed with *Model R* we report the value of the global synthetic score SVD_{score}^R defined in Section 7.2.1. *Model R*.

ID	SVD_{score}^R	ID	SVD_{score}^R
DEG1	0.33	NODEG1	−0.30
DEG2	0.24	NODEG2	−0.76
DEG4	0.22	NODEG4	−0.04
DEG5	0.09	NODEG5	−0.61
DEG6	0.57	NODEG6	−0.23
DEG7	0.24	NODEG7	−0.31

to clearly separate between the two sub-populations, with each DEG patient showing positive values and each NODEG patient showing negative values of this score.

The global synthetic score $SV D_{score}^R$ turns out to be more robust than the three individual hemodynamic scores in discriminating between DEG and NODEG patients, probably since it takes into account multiple mechanisms facilitating immune cells infiltration (aortic wall damage/inflammation, leaflet delamination, leaflet increased permeability). We notice that also the individual $\widehat{LDI}$ score alone is able to separate the two sub-populations (see Figure 7.2-middle), even if with a less evident separation (0.13 for $SV D_{score}$, see Table 7.4, vs 0.06 for the standardized $\widehat{LDI}_S$, not reported here for the sake of exposition).

The proposed synthetic $SV D_{score}^R$ could be easily translated into clinical practice to identify, early after the intervention, those patients who are at higher risk of a premature onset of SVD. This could drive a patient-specific planning of follow-up exams to closely monitor the high SVD risk patients, trying to avoid their dispersion after the procedure.

7.3. Computational scores for SVD with the *Simplified model*

In this section we present also the computational indices and scores for SVD identified from the post-processing of the numerical results obtained with *Model S*. In particular, we first define the computational hemodynamic indices and associated scores identified with *Model S* (Section 7.3.1) and then we present their results in terms of discriminating power between DEG and NODEG patients (Section 7.3.2).

7.3.1. Definition of hemodynamic and synthetic scores (*Model S*)

Analogously to what was done for *Model R*, we perform a post-processing of the numerical results obtained with *Model S*, based on the phase-average velocity field, to identify indices that discriminate between DEG and NODEG patients.

In what follows we introduce four hemodynamic indices, based on the quantities of interest defined in Section 6.1, identified with *Model S*. In particular, we consider:

- $A^{WSS}(t)$, i.e. the area of the aortic wall where the WSS magnitude is greater than the threshold of 5 Pa . This threshold identifies regions of high WSS , not necessarily pathological. Notice that instantaneous WSS magnitude typically ranges from 1 to 7 [Pa] in straight vessels of the arterial system [68]. High values of WSS can be associated with changes in the endothelial cell behavior, potentially exacerbating inflammation [77];

- $V_Q^\%(t)$, i.e. the fraction of volume where Q is greater than a selected threshold [246] of 50000 $H\text{z}^2$. This threshold is chosen to properly isolate vortical structures. The proposed volume fraction gives a measure of flow disturbance inside the considered domain. Disturbed flow has a well-proven impact on vascular endothelial cells and contributes to the pathophysiology of clinical conditions such as in-stent re-stenosis as well as aortic valve calcification [52];
- $avgTAWSS$, i.e. the average-in-space of the diastolic $TAWSS(\mathbf{x}; [T_S, T])$ on the aortic face of the bioprosthetic leaflets. Notice that low shear stresses on the aortic side of the aortic valve can enhance the permeability of the endothelial cell barrier with respect to small molecules [211]. In particular, we consider only the diastolic period because the deposition of material on the leaflets mainly occurs during the diastolic phase;
- $avgOSI$, i.e. the average-in-space $OSI(\mathbf{x}; [0, T])$ on the aortic face of the bioprosthetic leaflets. Oscillatory shear stresses on the aortic side of the valve promote inflammation and calcification [192].

In order to discriminate between DEG and NODEG patients, we assign a score related to each hemodynamic index. In particular, indicating with the bar average values over time, we consider the scalar quantities $\overline{AWSS}$, $\overline{V_Q^\%}$, $avgTAWSS$, $avgOSI$.

In order to clearly separate between patients with and without SVD at long-term follow-up exam (DEG vs NODEG), also for *Model S* we define a global synthetic score, which combines the proposed hemodynamic scores, so that it includes multiple hemodynamic features that may influence the degeneration of TAVI valves.

In order to be combined, the hemodynamic scores have to first be normalized. Thanks to increased number of patients analyzed with *Model S* with respect to *Model R*, we split the study population (14 patients) into a normalization set (12 patients) and a blind set (2 patients: DEG7 and NODEG7), we compute the first (Ψ_1) and third (Ψ_3) quartiles of each score in the normalization set and we linearly project the interval $[\Psi_1 - 1.5 * IQR, \Psi_3 + 1.5 * IQR]$ into the interval $[-1, 1]$, where $IQR = \Psi_3 - \Psi_1$ is the inter-quartile range.

The global synthetic score $SV D_{score}^S$ of *Model S* reads:

$$SV D_{score}^S = \frac{1}{2} \left(mean \left\{ \overline{AWSS}_N, \overline{V_Q^\%}_N, -avgTAWSS_N, avgOSI_N \right\} \right) + \frac{1}{2} \left(max \left\{ \overline{AWSS}_N, \overline{V_Q^\%}_N, -avgTAWSS_N, avgOSI_N \right\} \right). \quad (7.1a)$$

where the subscript N identifies the hemodynamic normalized score and the opposite of $avgTAWSS_N$ is considered in order to associate low values of this hemodynamic score to high values of the synthetic score.

7.3.2. Results of the hemodynamic and synthetic scores (*Model S*)

In Figure 7.3 we report for patient DEG3, as a representative of the study population, the spatial distribution of the hemodynamic features used to define the hemodynamic scores for *Model S* presented in Section 7.3.1.

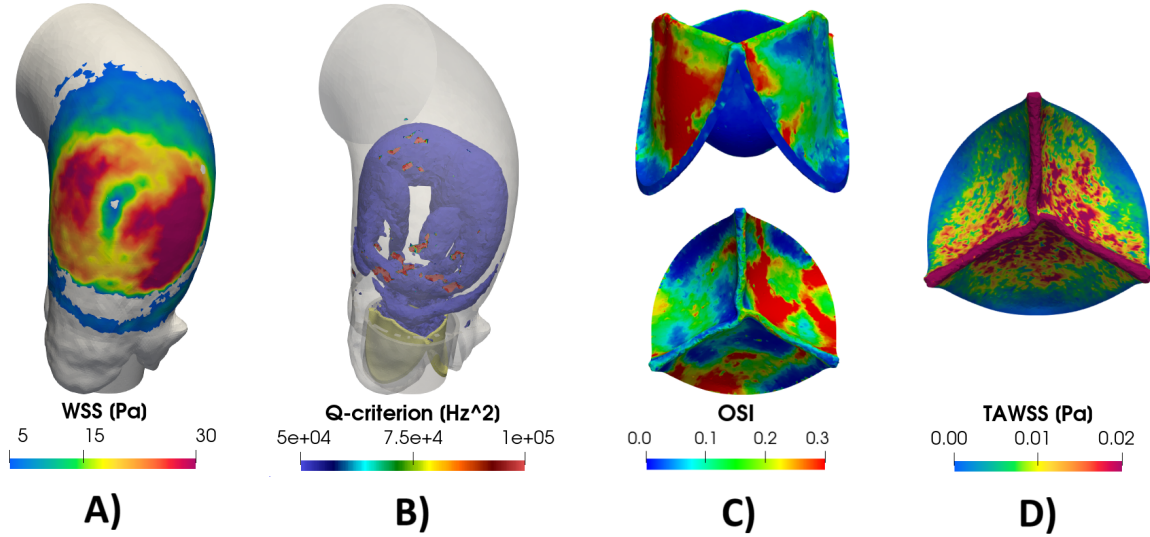


Figure 7.3: Hemodynamic features used to compute the hemodynamic scores for *Model S* (see Section 7.3.1): A) Area of the aortic wall where the WSS magnitude is greater than 5 Pa used to compute $\overline{A^{WSS}}$; B) Volume where Q-criterion is greater than 50000 Hz^2 used to compute $\overline{V_Q^{\%}}$; C) OSI on the aortic side of the leaflets during both systole and diastole used to compute $avgOSI$; D) $TAWSS$ on the aortic side of the leaflets during diastole used to compute $avgTAWSS$. Patient DEG3.

In Table 7.5 we report, for the 14 patients analyzed with *Model S*, the values of the hemodynamic scores introduced in Section 7.3.1.

In Figure 7.4 we plot using boxplots the distribution of the hemodynamic scores obtained with *Model S* in the DEG and NODEG sub-populations. In particular, each hemodynamic index shows an increased variability (wider boxes) in the DEG patients with respect to the NODEG ones, with the only exception of $avgTAWSS$ which takes low values for each DEG patient.

Table 7.5: Values of the hemodynamic scores $\overline{A^{WSS}}$, $\overline{V_Q^\%}$, $avgOSI$, and $avgTAWSS$ defined in Section 7.3.1 for the 14 patients analyzed with *Model S*.

ID	$\overline{A^{WSS}}$	$\overline{V_Q^\%}$	$avgOSI$	$avgTAWSS$
DEG1	1.48×10^{-3}	2.81×10^{-2}	1.43×10^{-1}	1.03×10^{-2}
DEG2	1.25×10^{-3}	3.68×10^{-2}	1.57×10^{-1}	1.21×10^{-2}
DEG3	1.48×10^{-3}	2.46×10^{-2}	1.61×10^{-1}	1.18×10^{-2}
DEG4	1.41×10^{-3}	1.30×10^{-2}	1.35×10^{-1}	0.98×10^{-2}
DEG5	1.16×10^{-3}	3.20×10^{-2}	1.65×10^{-1}	0.79×10^{-2}
DEG6	1.04×10^{-3}	4.18×10^{-2}	1.51×10^{-1}	0.91×10^{-2}
DEG7	0.96×10^{-3}	3.43×10^{-2}	1.94×10^{-1}	1.24×10^{-2}
NODEG1	1.20×10^{-3}	2.86×10^{-2}	1.43×10^{-1}	2.34×10^{-2}
NODEG2	0.92×10^{-3}	1.69×10^{-2}	1.31×10^{-1}	0.87×10^{-2}
NODEG3	1.30×10^{-3}	1.88×10^{-2}	1.50×10^{-1}	1.01×10^{-2}
NODEG4	1.24×10^{-3}	2.23×10^{-2}	1.33×10^{-1}	0.90×10^{-2}
NODEG5	1.00×10^{-3}	2.13×10^{-2}	1.30×10^{-1}	3.21×10^{-2}
NODEG6	1.29×10^{-3}	4.35×10^{-2}	1.29×10^{-1}	4.03×10^{-2}
NODEG7	1.27×10^{-3}	2.72×10^{-2}	1.41×10^{-1}	1.10×10^{-2}

To properly assess differences between the two sub-groups of patients (DEG vs NODEG) in terms of each individual hemodynamic score, the double-tailed Wilcoxon rank-sum test is employed: we found that $avgOSI$ is the only index showing statistically significant differences ($p = 0.007$) between DEG and NODEG patients, whereas for the other indices we have in any case $p > 0.1$. Thus, with *Model S* we were able to identify only one hemodynamic score for which DEG patients show a different statistical distribution with respect to NODEG patients, whereas three scores were identified with *Model S* (see Section 7.2.2).

Additionally, we report in Table 7.6, for both the normalization and blind sets, the values of the global SVD_{score}^S introduced in Section 7.3.1. In particular, for the normalization set DEG patients present SVD_{score}^S values greater than or equal to 0.15, whereas NODEG patients present a score lower than 0.15. Thus, this global synthetic score seems to be able to discriminate between the two sub-groups of patients and can be interpreted as likelihood of developing a premature onset of SVD. This is confirmed by the application of this score

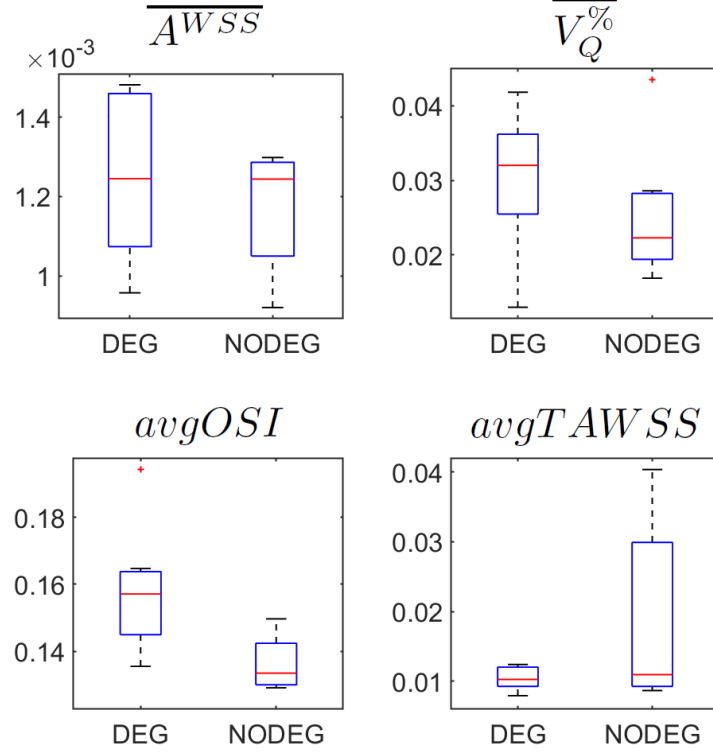


Figure 7.4: Boxplot distributions of the hemodynamic scores $\overline{A^{WSS}}$, $\overline{V_Q^{\%}}$, $avgOSI$, and $avgTAWSS$ in the DEG and NODEG sub-populations. *Model S*.

Table 7.6: For each patient in the study population we report the value of the global synthetic score $SV D_{score}^S$ defined in Section 7.3.1 Patient DEG7 and NODEG7 belong to the blind set. *Model S*.

ID	$SV D_{score}^S$	ID	$SV D_{score}^S$
DEG1	0.29	NODEG1	−0.06
DEG2	0.23	NODEG2	0.04
DEG3	0.31	NODEG3	0.11
DEG4	0.15	NODEG4	0.12
DEG5	0.27	NODEG5	−0.34
DEG6	0.30	NODEG6	0.11
DEG7	0.56	NODEG7	0.09

to two cases (DEG7 and NODEG7) not used during the normalization. Specifically, as reported in Table 7.6 we obtained $SV D_{score}^S = 0.56$ for DEG7 and $SV D_{score}^S = 0.09$ for NODEG7.

We notice that, also for *Model S*, the global synthetic score $SV D_{score}^S$ turns out to be more robust than the four individual hemodynamic scores in discriminating between DEG and NODEG patients. In particular, in the case no hemodynamic score alone is able to separate the two groups of patients.

8 | Final remarks, limitations, and future perspectives

8.1. Final Remarks

The mechanisms underlying the development of SVD in transcatheter bio-prosthetic valves are still not fully understood: multiple active processes are involved, from mechanical stresses to long-term immune rejection and atherosclerosis-like tissue remodeling [128]. Specifically, inflammatory reaction and immune response may play a crucial role in the pathogenesis of SVD, which is associated with an elevated immune cell infiltration in the bio-prosthetic leaflets [38, 255]. Clinical studies identified some risk factors related to SVD, such as small prosthesis size [109], a valve-in-valve procedure [196], young age, patient-prosthesis mismatch, larger body surface area, and smoking [236]. Also, in [175] the authors hypothesized that an accelerated flow across the implanted valve, due to a high cardiac output, could be a factor in the development of SVD. This is in agreement with the characteristics of our study population (see Table 3.2) which show that, on average, DEG patients are younger, with a larger body surface area, and with an increased cardiac output. However, the risk factors reported in Table 3.2 alone are not able to discriminate between patients with and without SVD at long-term follow-up exam (DEG vs NODEG).

In this context, computational modeling represents a powerful tool for filling the gap by identifying the conditions that may lead to a premature onset of SVD. Indeed, it provides a detailed description of post-TAVI hemodynamics, allowing for the investigation of the accelerated flow features that may influence SVD. Accordingly, in this thesis we employed both a *Simplified* and a *Realistic* CFD model to numerically simulate post-TAVI hemodynamics in patients who received a balloon-expandable Edwards SAPIEN or SAPIEN-XT 23 mm valve in order to introduce computational hemodynamic risk factors for the premature onset of SVD.

First, we notice that in our study we analyzed post-TAVI hemodynamics just after the implantation in relation to the long-term degeneration of the implanted valves. This is

based on the assumption that the hemodynamic patterns initiating the development of SVD are influential already a short time after the intervention [72], when the implanted bio-prosthetic valve is still fully functioning. This allowed us to avoid the modeling of the bio-prosthetic leaflets degeneration process.

Moreover, we focused on balloon-expandable TAVI valves with a very similar design, i.e. the Edwards SAPIEN and SAPIEN-XT 23 mm valves (referred to as Edwards SAPIEN 23 mm in the following, for simplicity). This was done since we only had at disposal clinical data related to DEG patients who received an Edwards SAPIEN 23 mm valve. Accordingly, in order to build significant hemodynamic scores discriminating between DEG and NODEG patients, we considered also for the latter group Edwards SAPIEN 23 mm cases. Let us notice that the CFD models proposed in this thesis could be easily adapted to study other balloon-expandable cylindrical valves by modifying the dimensions and wire-frame design of the stent, whereas the adaptation to study self-expandable valves is less trivial.

As for a general analysis of post-TAVI hemodynamics, the *Simplified* CFD model proved to be able to capture the main flow features resulting from the implantation of a small size balloon-expandable valve. Thus, this model represents a valid alternative in case of a lack of data needed to apply the the *Realistic* CFD model. In particular, the *Realistic* strategy to model the bio-prosthetic leaflets could be in any case considered since it does not require any specific clinical data to be employed.

On the other hand, with the *Realistic* CFD model we were able to identify computational hemodynamic indices which have a much clearer interpretation in relation to a possible SVD pathogenesis and which show much better results in terms of correlation with a premature onset of SVD (three statistically significant indices with *Model R* vs one statistically significant index with *Model R*). Therefore, the *Realistic* CFD model should be preferred for a proper assessment of SVD.

Furthermore, we notice that the clinical data needed to apply the proposed CFD models (pre-TAVI CTA scans and early post-TAVI Doppler TTE measures) are routinely acquired within the TAVI context. Since the model does not require any ad-hoc or invasive clinical measurement, our framework can be used to perform both prospective and retrospective studies, providing a detailed and personalized description of the main flow features while sparing patients from additional measurements and exams, such as invasive pressure measurements or 4D flow MRI.

Lastly, the results presented in thesis suggest that aortic hemodynamics can indeed influence the development of SVD and should thus taken into account for a proper assessment

of this pathology both in the clinical setting and in the computational research.

8.2. Limitations

We start by noticing that our mathematical and numerical model (Chapter 4) is characterized by some simplifications:

- We modeled blood as a homogeneous Newtonian fluid and the wall as rigid. This can have an influence on hemodynamic features such as the Wall Shear Stress (WSS) [150]. However, we notice that we study elderly patients which are usually characterized by a limited tissue elasticity due to stiffening and calcifications. Moreover, in large vessel like the aorta, the influence of blood cells can be neglected and the Newtonian assumption is the standard one [190];
- We did not account for the coronary branches and thus for the corresponding blood flow. This could affect blood-dynamics inside the aortic root, specially during diastole, and thus the hemodynamic indices proposed in Sections 7.2.1-7.3.1, specially LPI , $avgOSI$, and $avgTAWSS$, being computed during the diastolic phase. Notice that, considering coronary flow with a rigid aortic wall could lead to non-physiological flow patterns since the blood flowing to the coronaries is thought to come from the relaxation of the aortic root wall following its systolic expansion [1]. In any case, we believe that the inclusion of the coronary flow should have a common effect on the hemodynamic quantities among patients;
- We provided an implicit representation of the bio-prosthetic leaflets with the RIIS method. This allowed us to capture the main flow features, such as the opening/closure dynamics, with *Model R*, and a realistic opening area. However, a Fluid-Structure Interaction (FSI) approach should be able to represent complex features, such as leaflets fluttering, and results in a more accurate computation of the stresses on the leaflets, thus could be considered in future studies;
- We discretized the continuous Navier-Stokes problem by considering linear finite elements for both the velocity and the pressure fields with a BDF1 linear time-stepping scheme. This choice could lead to an excessive numerical dissipation and the effect of employing higher-order finite elements with higher-order explicit, implicit, or multi-step time-stepping methods should be investigated in future studies.

These simplifications significantly reduced the computational cost of the numerical simulations to make our model suitable to analyze a great number of patients in a timely manner, in view of a potential clinical translation. Additionally, in this study we are inter-

ested in comparing numerical results in different patients rather than obtaining optimally accurate results for each patient. Since a fair comparison between patients is guaranteed by the adoption of the same assumptions, then we accept these simplifications.

Additionally, *Model S* is subject to the following limitations that have been partially or totally overcome by *Model R*:

- Neglecting the wire-frame design of the stent. This is accurate only on the stent's ventricular side, due to the presence of the inner fabric. This limitation could potentially have an impact on secondary diastolic flows which may pass in between the stent's struct. Thus, we provided a wire-frame design for the aortic side of the stent in *Model R*;
- Including patient-specific information concerning only the mean flow rate (i.e. the cardiac output) in the inlet boundary condition. This approach has been refined in *Model R* by considering a personalized temporal trend for the flow rate given by the velocity time signal at the center of the LVOT;
- Considering an idealized model mimicking the native aortic leaflets for the bio-prosthetic leaflets. The geometry of the leaflets in open configuration could have an impact on aortic hemodynamics. Thus, in *Model R* we consider a model which is still idealized, but mimics the SAPIEN valve leaflets studied in this thesis.

Finally, this study is subject to some further main limitations:

- We focused on a single balloon-expandable TAVI valve type, the Edwards SAPIEN 23 mm (Section 3.1). Therefore, the results of our study, particularly the proposed SVD_{score}^* , cannot be generalized to different valves with different dimensions and designs, such as self-expandable valves. This is a consequence of the clinical data at disposal, related only to DEG patients who received an Edwards SAPIEN 23 mm valve. For coherence we considered also NODEG patients with an Edwards SAPIEN 23 mm to try to isolate the effect of hemodynamics on the development of SVD. Indeed, different valve designs can influence valve deterioration due, for example, to the different distribution of mechanical stresses [217] and the different material properties of the leaflets [122]. Future studies should focus on different valve designs to investigate if the biomechanical drivers of SVD identified here are still relevant.
- We virtually inserted the bio-prosthetic valve in the aortic geometries assuming a perfect implantation, with the stent obtaining its nominal circular cross-section and being perfectly sealed to the aortic annulus (Section 3.3.2). On the other hand, the numerical simulation of the valve implantation using a structural Finite Ele-

ment Analysis would allow to obtain the deformation of the stent shape due to a non-uniform bio-prosthetic valve expansion in a native calcified valve and to capture paravalvular leakage (PVL). This would influence the post-TAVI hemodynamic patterns in the aortic root and possibly would improve the quantitative agreement with the maximum blood velocity measurements, thus it should be considered in future studies. However, we justify this simplification since balloon-expandable valves are expected to achieve an almost cylindrical shape after implantation [139], as shown from the post-TAVI CTA scans reconstructions in Figure 3.6, and since we are mainly interested in studying SVD rather than other complications related to the TAVI procedure;

- We performed only a qualitative validation, based on looking at the reconstructed geometries, of the virtual stent implantation (see Figure 3.6). A more quantitative analysis based on the mapping of the post-TAVI aortic geometry onto the pre-TAVI aortic geometry will be required in future studies to strengthen our approach;
- We derived a flow rate time-profile starting from PW Doppler TTE data, which provide the temporal evolution of the blood velocity magnitude at the center of the LVOT (Section 3.5). In order to pass from a velocity measure, i.e. the velocity time-integral, to a flow measure, i.e. the cardiac output, in the clinical practice the velocity field in the LVOT is assumed to be uniform in space. In particular, to mitigate the effects of this a priori assumption, in this work we account for the same 15% overestimation of the flow rate in all the patients. Alternatively, one could derive a flow rate profile from the time-derivative of the left ventricular volume obtained from 3D echocardiography [120] or prescribe completely patient-specific inlet conditions by exploiting 4D-Flow MRI [221]. In this case no a priori assumption on the spatial skewness of the velocity field is needed, thus potentially improving the accuracy of the resulting flow rate profile. Nonetheless, these data were not available for this retrospective study.
- The significance of our findings is limited by the sample size of our study population. This is because collecting a greater number of data related to degenerated cases with available follow-up is difficult due to the relative young age of TAVI, the limited life expectancy of its recipients, and the high dispersion of patients after the implant. Nonetheless, enlarging the study population is crucial to move toward clinical relevance.

8.3. Future Perspectives

The main outcomes of this thesis are the development of personalized CFD models for the numerical simulation of post-TAVI aortic hemodynamics, and the definition of computational hemodynamic-based scores able to identify, in the early post-TAVI scenario, patients who will experience a premature onset of Structural Valve Deterioration (SVD).

The presented CFD models showcase the ability of computational modeling to provide a detailed description of aortic hemodynamics in presence of an aortic bio-prosthetic valve. This could potentially be exploited to perform a more complete assessment of the bio-prosthesis performance. Specifically, the computational models could be used for a more accurate computation of standard clinical metrics, e.g. the transvalvular pressure gradient which is commonly computed using a simplified Bernoulli equation, or for the computation of quantities that can be hardly measured in the clinics, e.g. the WSS and its derived indices. Furthermore, our CFD models can be adapted to study other types of bio-prosthetic valves, such as self-expandable TAVI valves and surgically implanted valves, in order to investigate their hemodynamic properties. This can be useful for a patient-specific selection of the bio-prosthetic valve to be implanted based on its expected hemodynamic performance.

As for the computational scores, a possible future development is their application in a wider population to perform retrospective/prospective in-silico clinical trials in order to move toward a clinical translation. Additionally, similar approaches can be employed by studying different types of bio-prosthetic valves to investigate if aortic hemodynamics may play a role in the development of SVD in those cases.

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Conflict of interest

The author has no relevant financial or non-financial interests to disclose.

Ethics approval

The study was approved from the Institutional Review Board of Centro Cardiologico Monzino on August 3rd, 2020 and registered with number R.1262/20-CCM 1326. Informed consent was obtained from all patients.

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List of Acronyms

LV	Left Ventricle
LVOT	Left Ventricular Outflow Tract
ECM	ExtraCellular Matrix
VICs	Valve Interstitial Cells
VECs	Valve Endothelial Cells
STJ	SinoTubular Junction
CAVD	Calcific Aortic Valve Disease
TTE	Transthoracic Echocardiography
TEE	Transesophageal Echocardiography
ICE	Intracardiac Echocardiography
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
CW	Continuous Wave
PW	Pulsed Wave
MHV	Mechanical Heart Valves
BHV	Biological Heart Valves
SVD	Structural Valve Deterioration
SAVR	Surgical Aortic Valve Replacement
TAVI	Transcatheter Aortic Valve Implantation
THV	Transcatheter Heart Valves
BSA	Body Surface Area
FEM	Finite Element Method
FEA	Finite Element Analysis
FSI	Fluid-Structure Interaction
CFD	Computational Fluid Dynamics
CTA	Computed Tomography Angiography
WSS	Wall Shear Stress
NS	Navier-Stokes
LES	Large Eddy Simulation

