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Mathematical Characterization and Hemodynamic Assessment of Coro- nary Microvascular Dysfunction Using a Cardiac Perfusion Model

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Abstract

Coronary Microvascular Dysfunction (CMD) is increasingly recognized as a fundamental driver of ischemic heart disease, yet its in vivo assessment remains challenging due to the microscopic scale of the vessels and the complex biophysical interactions regulating Myocardial Blood Flow (MBF). This thesis aims to mathematically characterize CMD through a multiphysics and multiscale computational framework. To capture the effects of cardiac contraction on the microvasculature, a fully-coupled 0D-3D electromechanical model is integrated with a Navier-Stokes-Darcy perfusion model, employing a compliant multi-compartment Darcy formulation. Structural microvascular alterations typical of CMD, including capillary rarefaction and distal lumen narrowing, were simulated by modulating specific network parameters. The framework was first evaluated on an idealized bifurcation geometry for sensitivity analysis and subsequently applied to a realistic 3D left heart geometry perfusing the biventricular myocardium. Numerical simulations successfully reproduced physiological coronary hemodynamics, notably the diastolic dominance driven by cyclic intramyocardial compression. Under simulated pathological conditions, the model accurately captured key hemodynamic markers of microvascular impairment: severe reduction in conductive capacity, targeted subendocardial ischemia, reduced MBF, the emergence of systolic retrograde flow, and a Coronary Flow Reserve (CFR) below the physiological threshold. This computational framework provides a promising in silico approach for investigating microcirculatory diseases, laying a valuable foundation to support the non-invasive assessment of complex coronary and microvascular hemodynamics.

Keywords: Coronary Microvascular Dysfunction (CMD); Cardiac Perfusion; Computational Hemodynamics; Darcy Model; Myocardial Ischemia

Abstract in lingua italiana

La disfunzione del microcircolo coronarico (CMD) è sempre più riconosciuta come una causa primaria della cardiopatia ischemica, ma la sua valutazione in vivo rimane complessa a causa della scala microscopica dei vasi coinvolti. Questa tesi si pone l'obiettivo di caratterizzare matematicamente la CMD attraverso un framework computazionale multifisica e multiscale. Per catturare gli effetti della contrazione cardiaca sul microcircolo, un modello elettromeccanico 0D-3D completamente accoppiato è stato integrato con un modello di perfusione Navier-Stokes-Darcy, impiegando una formulazione Darcy multicompartimentale compliant. Le alterazioni strutturali tipiche della CMD, come la rarefazione capillare e la riduzione del lume distale, sono state simulate modulando parametri specifici della rete. Il framework è stato inizialmente testato su una biforcazione idealizzata per un'analisi di sensibilità e successivamente applicato a una geometria 3D realistica del cuore sinistro con perfusione del miocardio biventricolare. Le simulazioni numeriche hanno riprodotto fedelmente l'emodinamica coronarica fisiologica, in particolare la dominanza diastolica indotta dalla compressione intramiocardica ciclica. In condizioni patologiche, il modello ha catturato con successo marcatori clinici chiave della compromissione microvascolare: drastica riduzione della capacità conduttiva, ischemia subendocardica, diminuzione del flusso sanguigno miocardico (MBF), comparsa di flusso retrogrado sistolico e una riserva di flusso coronarico (CFR) inferiore alla soglia fisiologica. Il modello proposto offre un promettente approccio in silico per lo studio delle patologie del microcircolo, ponendo delle valide basi metodologiche per supportare la valutazione non invasiva della complessa emodinamica coronarica e microvascolare.

Parole chiave: Disfunzione del Microcircolo Coronarico (CMD); Perfusione Cardiaca; Emodinamica Computazionale; Modello di Darcy; Ischemia Miocardica

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Myocardial infarction and myocardial ischemia have traditionally been considered 'large vessel' diseases, primarily caused by atherosclerosis and obstructive atherothrombotic events in epicardial coronary arteries. However, more than 40% of patients with angina or myocardial ischemia present no signs of obstructive coronary artery disease [12, 48]. Consequently, impairment of the coronary microcirculation has been increasingly recognized as a fundamental driver of ischemic heart disease. The spectrum of structural and functional alterations within the coronary microcirculation that lead to an inadequate coronary blood supply is denoted with the term Coronary Microvascular Dysfunction (CMD). This condition is responsible for angina and myocardial ischemia not only in patients with Ischemia and No Obstructive Coronary Arteries (INOCA) or Myocardial Infarction with No Obstructive Coronary Arteries (MINOCA), but it also plays a crucial role in a wide spectrum of cardiovascular diseases, including cardiomyopathies, Takotsubo syndrome, and Heart Failure (HF), in particular Heart Failure with Preserved Ejection Fraction (HFpEF) [12, 38, 41].

Despite its clinical relevance, the *in vivo* assessment of CMD remains challenging due to the microscopic scale of the vessels involved and the complex interplay of metabolic, endothelial, and mechanical factors regulating myocardial blood flow. In this context, advanced mathematical modeling provides a powerful, non-invasive tool to investigate the underlying biophysical and hemodynamic mechanisms of the disease.

The primary objective of this thesis is to mathematically characterize CMD by capturing the complex variety of phenomena underlying a microcirculatory defect. To achieve this, we integrate the multiscale and multiphysics cardiac perfusion model proposed in [63] with the compliant, multi-compartment Darcy model for microcirculation developed in [39]. The resulting framework encompasses electrophysiology, active and passive solid mechanics, hemodynamics, valve dynamics, and perfusion. Specifically, a fully-coupled 0D-3D electromechanical model is employed to drive a fully-coupled Navier-Stokes-Darcy perfusion model.

The proposed CMD modeling strategy is first developed and tested on an idealized bifurcation geometry to isolate and analyze the effects of microvascular alterations, such as vascular rarefaction and lumen reduction. Subsequently, the model is applied to a realistic 3D left heart geometry perfusing the biventricular myocardium. The validity of the framework is assessed by comparing the simulated Myocardial Blood Flow (MBF), the endocardial-to-epicardial perfusion ratios, and the Coronary Flow Reserve (CFR) against established clinical ranges from the literature.

The thesis is organized as follows. Chapter 1 provides the anatomical and physiological background of the cardiovascular system and details the mechanisms of CMD. Chapter 2 introduces the mathematical formulation of the core models utilized. Chapter 3 details

the numerical methods and spatial-temporal discretization strategies adopted. Finally, Chapter 4 presents and discusses the results of the numerical simulations on both idealized and realistic geometries.

1 | Heart and Cardiovascular System

The cardiovascular system is the ensemble of arteries, veins and capillaries whose role is to ensure systemic perfusion and cellular homeostasis maintenance with continuous supply of oxygen and nutrients. It can be seen as a closed hydraulic system with the heart at its center, acting as two rhythmic and dynamic pumps. The heart is a muscular organ which from a functional and physiological viewpoint can be considered as the union of two distinct parts: the right heart, at the basis of pulmonary circulation, and the left heart, which regulates systemic circulation. This dichotomy is due to the fact that, although both circulation systems are characterized by the same volume of blood per unit time, they operate in two very different regimes. Systemic circulation is a high-pressure system, required to overcome the resistance exerted by peripheral arterioles. Conversely, pulmonary circulation maintains high blood flow at low intravascular arterial pressure, which is also reflected in vessels structure, since pulmonary arteries have thinner walls with many fewer vascular smooth muscle cells if compared to systemic arteries [54]. In this chapter we will focus on functional and morphologic anatomy of the left heart and coronary circulation as the main parts involved in cardiac perfusion. We then discuss the phases of cardiac cycle and their effect on perfusion (Section 1.2). To conclude, passing through a description of epicardial coronary circulation in Section 1.3, we detail cardiac microcirculation and its pathological conditions (Sections 1.4 and 1.5).

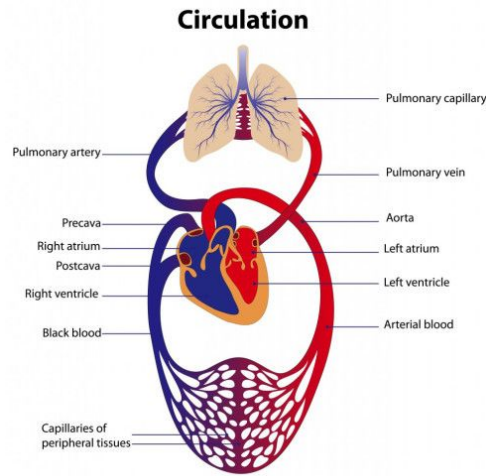


Figure 1.1: Schematic representation of cardiovascular circulation (image taken from [33]).

1.1. The Left Heart

The left heart has the primary role of sustaining systemic perfusion and, due to the need to generate high pressure gradients to overcome peripheral vascular resistance, its morphology is adapted to this aim, from the helical orientation of myocardial ventricular fibers to the aortic load-bearing capacity. At the same time, coronary circulation has to perfuse myocardial tissue, overcoming the obstacle represented by systolic compressive forces that limit blood flow when metabolic demand is at its peak. The left heart is composed of two chambers, the left atrium and the left ventricle, which are separated by the mitral valve. The left atrium is the most posteriorly and superiorly situated of the cardiac chambers, beginning at the pulmonary veno-atrial junctions (typically four) and terminating at the fibro-fatty tissue lane that marks the atrioventricular junction at the mitral orifice [26]. The left atrium receives oxygenated blood from the pulmonary veins and acts as a reservoir during ventricular systolic phase, as a conduit during early diastole and as an active pump in late diastolic phase [27].

Blood flow from the left atrium to the left ventricle is regulated by the mitral valve, which is a complex and dynamic apparatus composed of the annulus, valve leaflets, chordae tendineae, and papillary muscles.

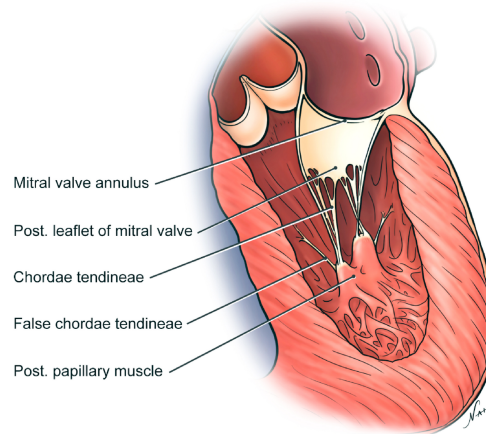


Figure 1.2: An overview on mitral valve apparatus (image taken from [60]).

These components have to let blood transition during the diastolic filling phase, where a moderate pressure gradient develops between atrium and ventricle, and must resist the strong pressure generated in the ventricle due to compressive forces. During this systolic phase the papillary muscles (PM) contract simultaneously with the left ventricular wall. This contraction pulls the PM towards the apex, counteracting the upward force of the leaflets and avoiding their eversion into the atrium [17].

Normal left ventricle geometry has been conceptualized as a prolate ellipsoid shape with its long-axis directed from apex to base [50]. It comprises an inlet, apical trabecular, and an outlet portion although these portions do not have discrete anatomical borders. The left ventricular wall is thickest near the cardiac base (around 12-15 mm) and thins to 1-2 mm at the apex [25]. For describing the global arrangement, most studies and computational models have depicted left ventricular myocardial architecture as a transmural continuum between two helical fiber geometries, where right-handed helical geometry in the subendocardial region gradually changes into left-handed geometry in the subepi-cardial region, resulting in an energetically efficient arrangement [50]. This architecture allows the ventricle to generate enough force to increase the pressure from 5-10 mmHg up to 120 mmHg during systole and generate a sufficient pressure gradient to pump blood towards the systemic circulation.

The bridge between the left ventricle and the ascending aorta (and systemic circulation) is represented by the aortic valve which has the function of channeling large volume of fluids, maintaining laminar flow, minimal resistance, and least possible tissue stress and damage. The aortic valve presents a trileaflet design, which represents the optimal solution for low resistance valve opening [10]. Together, this highly specialized architecture of the left atrium, mitral apparatus, left ventricle, and aortic valve ensures efficient blood ejection. The rhythmic alternation of contraction and relaxation of these struc-

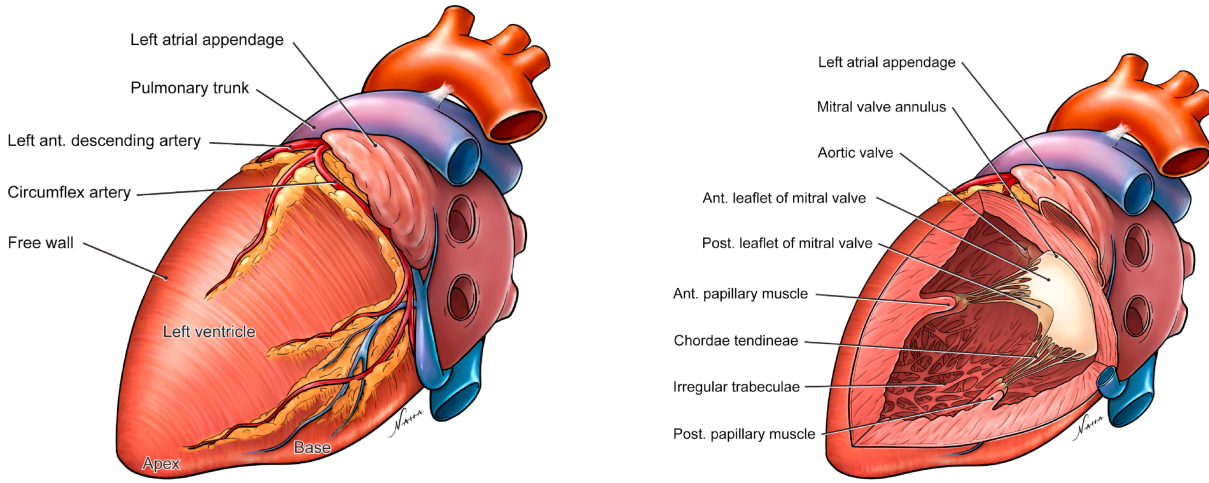


Figure 1.3: Left ventricle components (image taken from [60]).

tures is what governs the pressure gradients necessary for systemic perfusion and sets the mechanical basis for the cardiac cycle.

1.2. Cardiac Cycle

The complex sequence of mechanical and electrical events that allows the left heart to fulfill its role is known as the cardiac cycle. Understanding the different phases that characterize this cycle is not only essential to describe cardiac pump function, but it is also fundamental to understand the processes underlying myocardial perfusion, as coronary flow is heavily influenced by the compressive forces generated by the myocardium during these stages.

We present the phases of the cardiac cycle in the order reported in Figure 1.4 considering the left heart only, as for the right heart we observe analogous phases for the corresponding components. The end of ejection is marked by the closure of the aortic valve and the consequent dicrotic notch, determined by flow inversion due to depletion of the blood momentum and the negative pressure gradient developed between the ventricle and the ascending aorta [22]. Diastole begins with the isovolumetric relaxation phase; the mitral valve is still closed, and the ventricle is an isolated chamber undergoing a vertical pressure drop with constant volume. As the ventricular pressure goes below the atrial pressure, the mitral valve opens, allowing the blood contained in the atrium to flow into the ventricle due to the pressure gradient and driven by muscle relaxation that thins the myocardium and moves the ventricular base upward. This phase is denoted as ventricular passive filling. At the end of the diastolic phase, the atrium undergoes an active contraction that develops a positive pressure wave (a-wave) that pushes the residual blood into

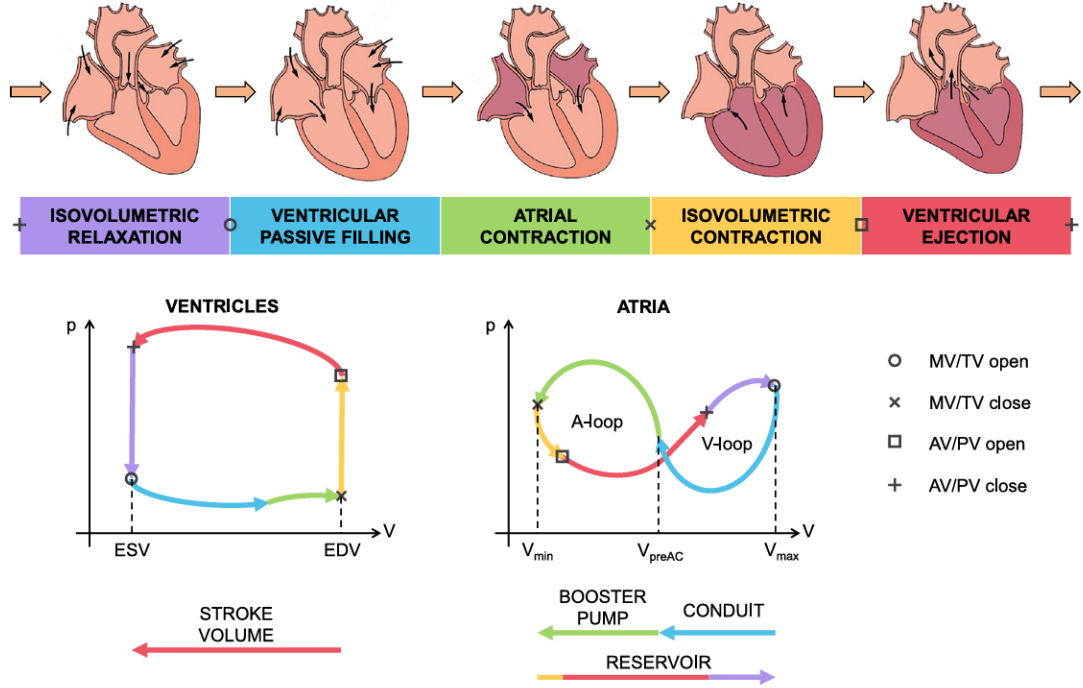


Figure 1.4: Five phases of the cardiac cycle and representation of ventricular and atrial P-V loops (image taken from [19]).

the ventricle (atrial kick) [31]. Then, active ventricular contraction begins, leading to a rapid increase in ventricular pressure and to atrioventricular valve closure. As the left ventricular pressure exceeds the value in the ascending aorta, the aortic valve opens and the ventricular ejection phase starts.

As shown in Figure 1.4, ventricular and atrial pressure-volume curves, used to measure the work done during the cycle, are very different. Ventricles present a square-shaped curve, in which we can distinguish the isovolumetric phases, separated by the ejection and filling phases. The atrial curve is instead eight-shaped and can be divided into A-loop, dominated by atrial contraction and relaxation, and V-loop, dominated by the effect of the ventricles on the atria [19].

As mentioned above, these phases have primary importance in perfusion, since the forces developed by myocardial muscle, in particular in left ventricle myocardium, exert a compressive action on microcirculation, leading to a predominantly diastolic flow and pulsatile metabolic supply.

1.3. Epicardial Coronary Circulation

To sustain the high metabolic demand required by the continuous mechanical work of the cardiac cycle, the heart relies on its own dedicated vascular network. The epicardial coronary circulation is responsible for delivering oxygenated blood to the myocardium. From two of the three aortic sinuses of Valsalva originate the two main coronary arteries. The right coronary artery (RCA) originates from the right sinus of Valsalva and enters directly the posterior atrioventricular groove, descending anteriorly and inferiorly to the right border of the heart. RCA branches primarily supply the right side of the heart, but also extend to part of the left atrium, a posterior region of the left ventricle, and the posterior third of the interventricular septum [34, 47]. The left main coronary artery (LMCA) originates from the left sinus of Valsalva and bifurcates into the left circumflex coronary artery (LCx) and the left anterior descending artery (LAD). An anatomically relevant feature is the LAD's behavior at the apex, known as the wraparound phenomenon. Indeed, the left descending artery courses the anterior atrioventricular groove and does not terminate at the apex but curves around it, allowing the perfusion of the very apex and part of the posterior atrioventricular groove [23]. There is variability among population in the architecture of coronary arteries branches: about 70-80% of individuals have a right dominant circulation, meaning that the posterior descending artery (PDA) originates from the RCA, in 5-10% of the population the PDA rises from the LCx, denoting left dominance, and 10-20% of cases present codominant circulation [30]. In most cases the dominant branch also provides blood supply to the sinoatrial and atrioventricular nodes, with some exceptions [23].

At rest, normal coronary blood flow averages approximately 225 to 250 mL/min, which accounts for about 5% of the total cardiac output. Following the epicardial arterial distribution and the subsequent capillary exchange, deoxygenated blood is collected by the cardiac venous system. The majority of left ventricular venous return drains into the great cardiac vein, which empties into the coronary sinus and ultimately into the right atrium. Right ventricular venous drainage occurs primarily via the anterior cardiac veins directly into the right atrium.

Coronary arteries follow primarily an epicardial course, acting as conductance vessels with low resistance. Then, smaller branches penetrate perpendicularly into the myocardium and give rise to the microcirculation, which we discuss in Section 1.4.

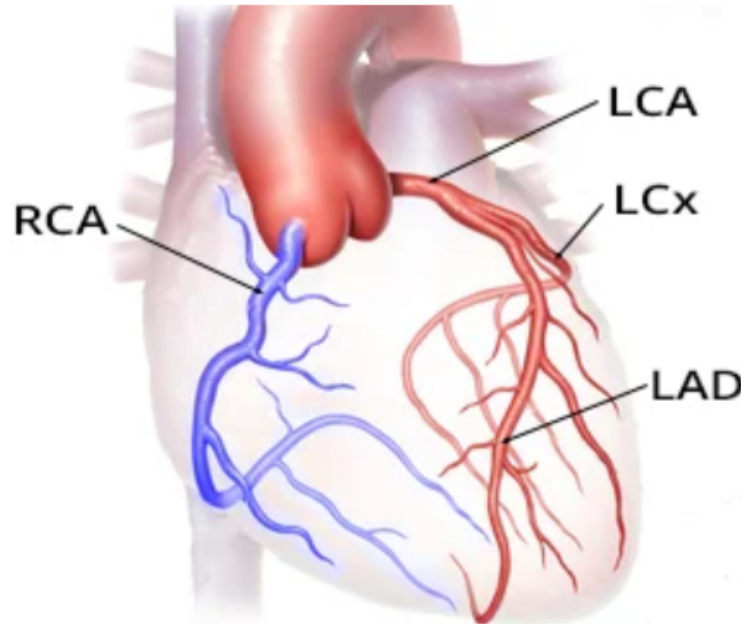


Figure 1.5: Visual representation of main epicardial coronary arteries (image taken from [15]).

1.4. Cardiac Microcirculation

The human heart is one of the most demanding organs in terms of oxygen and nutrients and to meet this need it relies on a vascular network composed of several types of vessels that can be classified by size into *macrocirculation* (the epicardial arteries described above, vessels with diameter $> 500 \mu\text{m}$) and *microcirculation* [16]. Within the latter, we can recognize the small arteries (or pre-arterioles), the arterioles, the capillaries, and the venules. This complex network has the fundamental role of regulating myocardial blood flow (MBF), which is the amount of blood per unit of mass reaching the capillaries every minute. At rest, the myocardium extracts approximately 70–80% of the oxygen delivered by coronary blood flow. This fact implies that an increase in demand must be met by an increase in MBF, and this is generally achieved by a reduction in vascular resistance. In a healthy heart, this increase can amount up to 4-5 times the resting flow [5].

The constriction and dilation of microvessels is achieved by a tightly regulated equilibrium between a variety of vasoactive mechanisms, including metabolic, endothelial, neurohumoral, and mechanical factors. The dominant mechanism in distal arterioles is metabolic regulation: elevated cardiac work produces metabolites (H^+ , K^+ , CO_2 , adeno-

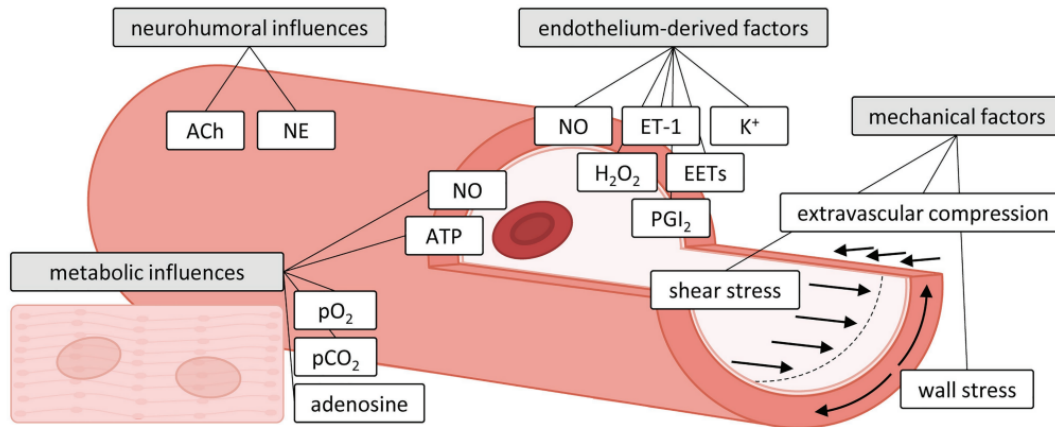


Figure 1.6: Different factors underlying vascular diameter regulation (image taken from [5]).

sine), which induce direct vasodilation. The endothelium acts as a shear stress sensor. In response to increased flow, endothelium releases vasodilators such as nitric oxide (NO), prostaglandins (PGI₂) and epoxyeicosatrienoic acids (EETs). Neural stimulation also affects tone via an interaction between direct effects on vascular smooth muscle cells and stimulation of NO release from the endothelium. In addition to these mechanisms, the vascular wall also modulates the tone in response to forces depending on intramural pressure. However, these regulation mechanisms do not act equally across the entire microvasculature, as vessels of different compartments exhibit significant differences from one another.

Small arteries are the largest vessels among microvascular tree, with a diameter between 500 and 100 μm . These vessels are the junction between epicardial coronary arteries and microcirculation and are responsible for almost 25% of the total coronary artery resistance.

Arterioles have a cross-sectional diameter between 100 and 10 μm and represent the intramyocardial component of microcirculation that plays a central role in vascular tone regulation, accounting for more than 50% of total resistance and responsible for matching the myocardial blood supply with oxygen consumption [38]. These vessels present a non uniform morphology: while the tunica media of proximal and mid-segments is composed of different layers of vascular smooth muscle cells (VSMCs) (Figure 1.7), the tunica media of the terminal portion is restricted to a few layers of VSMCs [16, 58]. In this section of the arterial tree the regulation of blood flow is strictly related to the intraluminal pressure difference: the arterioles contract during the systolic phase when the extraluminal pressure increases, leading to a strong blood flow reduction, and dilate during the diastolic phase when the myocardial muscle is relaxed. The terminal branches of the arterial tree are

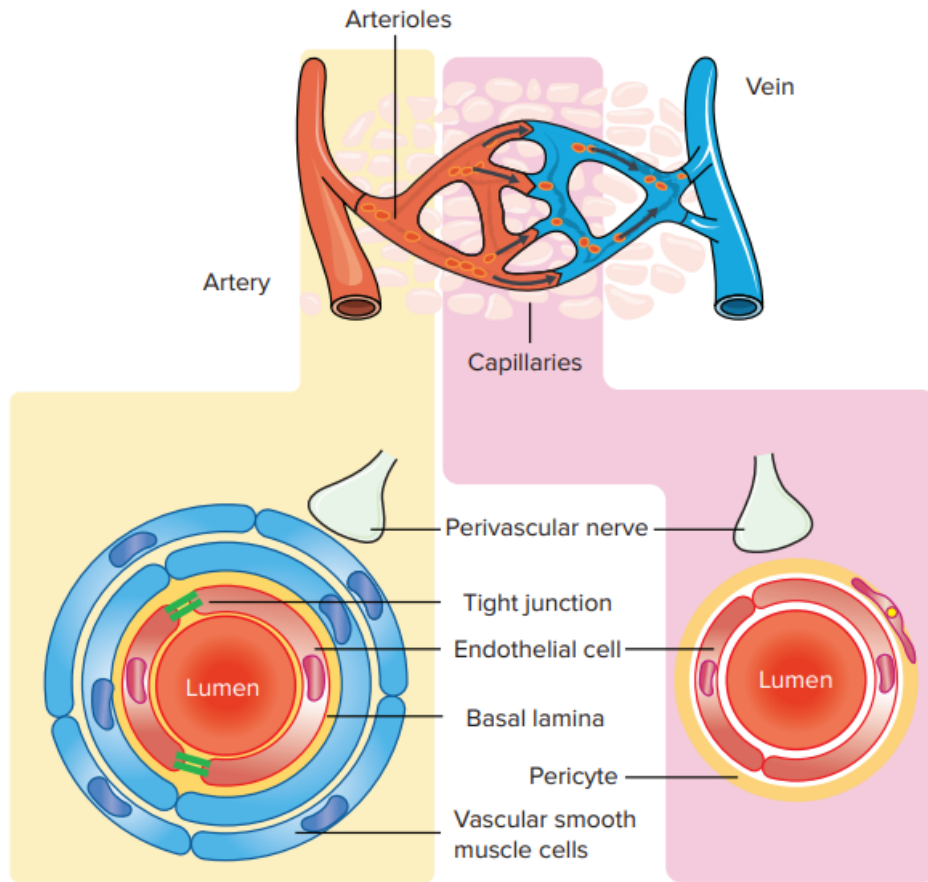


Figure 1.7: Arterioles and capillaries sectional structure (image taken from [20]).

capillaries, microscopic vessels with an average diameter of $5.7 \mu\text{m}$ in charge of nutrients and oxygen exchange given their large surface area and high permeability [45]. Their walls are composed mainly of endothelial cells without any layer of vascular smooth muscle cells, and are surrounded by small contractile cells called pericytes, which are essential for angiogenesis, endothelial regulation, and regional blood flow. Capillary density presents a gradient from the endocardium (where it is higher due to the increased oxygen demand) to the epicardium. This higher density of capillary volume in the subendocardium allows greater diastolic flow in this region compared to subepicardial flow, which compensates for the fact that in the subendocardium systolic flow is dramatically low due to the strong compressive forces [53].

1.5. Coronary Microvascular Dysfunction

Coronary Microvascular Dysfunction (CMD) can be defined as the subset of disorders that affect the structure and function of coronary microcirculation leading to inadequate

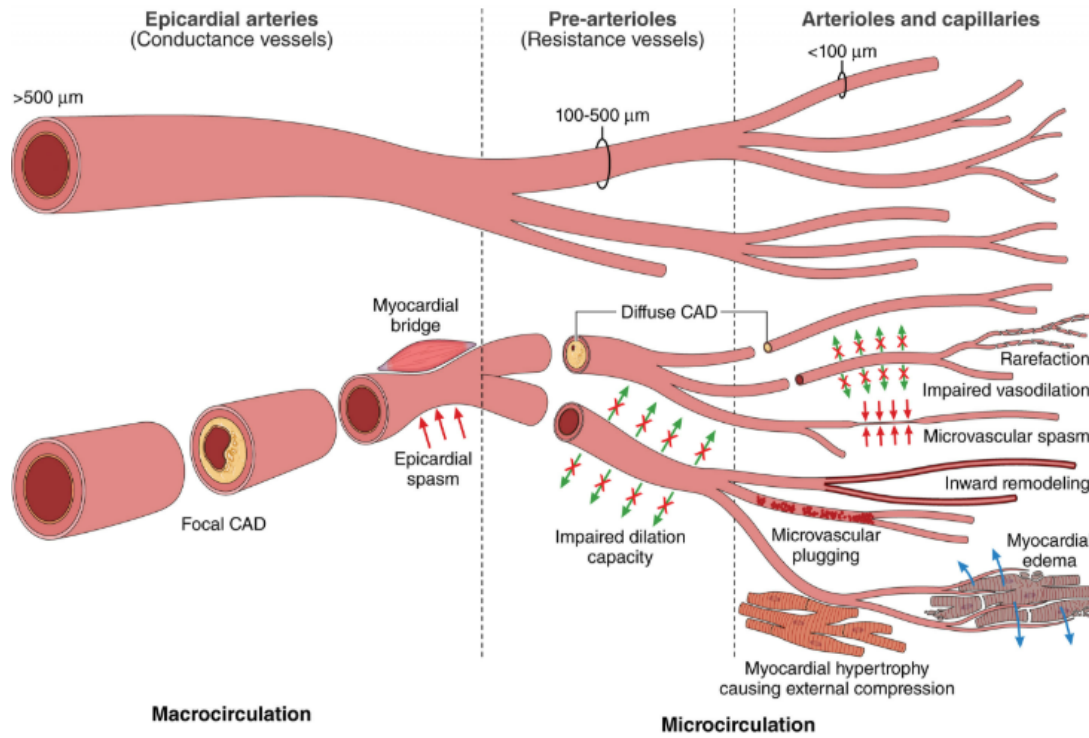


Figure 1.8: Microcirculation hierarchical organization and microvascular pathology spectrum (image taken from [51]).

coronary blood supply. The mechanisms underlying this pathology involve the combination of structural (anatomical remodeling) and functional (impaired vasomotor tone) alterations that compromise the ability of coronary microcirculation to increase blood flow in response to elevated myocardial oxygen demand (Figure 1.8). Structural CMD endotypes are more often linked to higher likelihood of acute coronary syndromes and higher mortality. In contrast, functional CMD is more commonly associated with an increased risk of hospitalizations secondary to recurrent episodes of angina [48].

1.5.1. Functional CMD

Functional etiologies of CMD include impaired relaxation, or in the case of microvascular spasm, transient vasoconstriction of the microcirculatory arterioles. The mechanisms underlying this condition can be classified as either endothelium-dependent or endothelium-independent. Endothelial dysfunction is often related to reduced production and/or enhanced degradation of nitric oxide (NO), a vasoactive factor produced by endothelial cells that promotes vascular relaxation [12, 51, 57]. Diminished endothelial NO synthase (eNOS) activity, coupled with increased reactive oxygen species (ROS) production, disrupts the balance between vasodilators and vasoconstrictors (such as endothelin-1

(ET-1) or angiotensin II), compromising the microvascular ability to meet increased blood demands.

Additional endothelium-dependent contributors to CMD may include oxidative stress and mitochondrial dysfunction, which trigger excessive ROS production and result in increased oxidative stress and decreased autophagy with consequent endothelial cell damage. Furthermore, autonomic nervous system imbalance, characterized by sympathetic overactivation and reduced parasympathetic tone, leads to impaired microvascular reactivity [14].

While endothelial dysfunctions explain impaired vasodilation, microvascular spasm requires an alteration of VSMC contractility. Vascular smooth muscle cell hyperactivity is considered one of the main substrates for spasm. The contraction and relaxation of these cells is regulated by myosin light chain (MLC) kinase and MLC phosphatase. Rho, a small guanosine triphosphate, is involved in the GTP-enhanced Ca^{2+} sensitivity of VSMC contraction and regulates MLC phosphorylation through its target Rho-kinase. An active form of Rho-kinase enhances MLC phosphorylation and induces VSMC contraction. Recent studies on the role of Rho/Rho-kinase (ROCK) pathway suggest that its inhibition may represent a novel therapeutic target of spastic microvasculature [36].

1.5.2. Structural CMD

Structural CMD represents the state in which chronic functional alterations or primary pathological processes induced an anatomic modification of the microvasculature, with consequent elevation in minimal vascular resistance and inability to meet increased flow demand, even during maximal pharmacological vasodilation (hyperemia).

There are several types of structural alterations that can affect different tracts of the vascular tree. A possible condition resulting from the chronic variation of hemodynamic forces is vascular remodeling, that can be classified into eutrophic, hypotrophic or hypertrophic, depending on whether the cross-sectional area of the vascular wall is preserved, decreases, or increases, respectively. In particular, an inward hypertrophic remodeling consists of tunica media thickening that invades the vascular lumen, reducing its diameter and increasing the wall-to-lumen ratio. Another important structural alteration is capillary rarefaction, which consists of a loss in capillary density. Alterations in capillary density, especially in the subendocardium, have great impact on local myocardial functions. Factors contributing to capillary rarefaction include removal of angiogenic stimuli or generation of anti-angiogenic substances, flow discontinuation, disruption of endothelial-pericyte association and endothelial dysfunction [5]. Finally, collagen and extracellular matter deposition around arterioles impedes their proper vasodilation, defining

a condition called perivascular fibrosis. A key mechanism that leads to fibrosis is the endothelial-to-mesenchymal transition (EndMT) which has a double effect: endothelial cells transformed into fibroblasts leave the luminal protective layer, leading to capillary rarefaction, and their migration into the interstitial space and collagen production contribute to fibrosis. This interplay between structural and functional alterations is not unique, but indeed they often coexist and reinforce each other. Reduced NO production by endothelial cells promotes collagen deposition and EndMT, exacerbating microvascular rarefaction. Structural alterations affect WSS-mediated activation of endothelial nitric oxide synthase (eNOS) sustaining microvascular hyper-resistance and worsening functional impairment [59].

1.5.3. Methods of Assessing CMD

The coronary microvasculature can be evaluated through both invasive and non-invasive techniques.

Non-invasive techniques can only assess the vasodilator capacity of the microcirculation and provide an estimate of myocardial blood flow, while endothelium-dependent dysfunctions can only be assessed through invasive provocation testing. Non-invasive techniques mostly rely on MBF and Myocardial Perfusion Reserve (MPR) analysis. The former can be evaluated at rest and at peak hyperemia using Positron Emission Tomography (PET), while the latter can be assessed using Cardiac Magnetic Resonance imaging (CMR) by measuring the changes in the intensity of myocardial signals between peak hyperemia and rest. However, using non-invasive techniques, the diagnosis of CMD should be made only after the exclusion of obstructive CAD using computed tomography coronary angiography or invasive coronary angiography [12, 45].

Invasive techniques then allow measuring Coronary Flow Reserve (CFR) and index of microvascular resistance (IMR) to evaluate vasodilatory response, and to assess microvascular hypercontractive response through intracoronary provocation testing. CFR is defined as the ratio between adenosine-induced hyperemic blood flow and resting blood flow:

$$\text{CFR} = \frac{\text{MBF}_{\text{hyperemia}}}{\text{MBF}_{\text{rest}}} \quad (1.1)$$

and represents a surrogate marker for vasodilatory capacity with normal values considered to be greater than a cut-off value between 2.0 and 2.5. IMR is a microcirculation-specific parameter, obtained using thermodilution and computed as the product of pressure distal to the catheter and mean transit time of cold saline flush at hyperemia. Values > 25 are considered to be a marker for structural damages such as rarefaction, remodeling, and fibrosis [45, 48]. As mentioned above, microvascular spasm must be evaluated through

intracoronary provocation test with acetylcholine (Ach). This is a proven safe procedure in which escalating doses of Ach, up to 200 mcg, are injected into the left descending artery (LAD). Healthy endothelium responds by releasing NO to counteract the vasoconstrictor action of Ach, while dysfunctional endothelium, which cannot release enough NO, encounters vasoconstriction. In this case, the patient will demonstrate ischemic electrocardiographic changes along with reproduction of typical symptoms (angina) without angiographic evidence of epicardial vasoconstriction [35, 45, 48].

2 | Mathematical Models

Cardiac perfusion is the process that ensures the supply of oxygen and nutrients to the myocardium through coronary circulation. To model this process, we employ a mathematical framework incorporating all relevant physics involved: a fully-coupled 0D-3D electromechanical model triggers a fully-coupled Navier-Stokes-Darcy perfusion model. As computational domain, we consider a realistic cardiac geometry provided by the Zygote solid 3D heart model [28]: an anatomical CAD model representing an average healthy human heart reconstructed from high-resolution CT scan data. Section 2.1 introduces the core models for electromechanics, together with a 0D closed-loop model for circulation. The fluid dynamics problem, including the modeling description of muscle contraction and valvular dynamics effects on the flow, is addressed in Section 2.2. Subsequently, Section 2.3 describes the multi-compartment Darcy problem used to model myocardial perfusion. The coupling conditions between the different models are detailed in Section 2.4, while in Section 2.5 we present the modeling choices adopted to simulate CMD pathology.

2.1. Electromechanics

Numerical simulations of electromechanical activities of the heart are becoming the cornerstone of computational cardiology, due to the fact that the coupling between electrical and mechanical processes is at the basis of cardiac function. To describe the several physical processes involved, such as electrophysiology, biochemistry and mechanics, we consider the model presented in [19, 44]. This is a 0D hemodynamic model of the whole cardiovascular system, coupled with a 3D-electromechanical model to form a closed loop 3D-0D circulation model, which is capable of describing the interplay at different spatial and temporal scales of the processes mentioned above, ranging from nanometers and nanoseconds to centimeters and seconds.

We set this problem in the left heart solid domain represented in Figure 2.1. This stress-free reference configuration we denote as $\hat{\Omega}^s$ has to be recovered from medical imaging through the algorithm reported in [44]. This procedure is needed because geometries acquired in vivo through medical imaging present residual internal stresses and are loaded by internal pressures. The procedure consists in virtually deflating the cardiac chambers



Figure 2.1: Left heart solid computational domain in reference configuration.

and recovering the reference configuration $\hat{\Omega}^s$. Then, to initialize the numerical simulation, the cardiac chambers are inflated by applying the correspondent end diastolic pressures, obtaining an initial displacement field.

2.1.1. Fiber Generation

To simulate cardiac electromechanical activity we have first to define the muscular fiber architecture, since a cardiac tissue is organized in sheets of fibers which determine a preferential direction of the electrical signal propagation. This is done relying on the *Laplace-Dirichlet Rule Based Method* [4, 40]. The first procedure consists of computing the intramural distance ϕ going from epicardium to endocardium, and different internal distances ψ_i computed from Laplace boundary value problems which are used to discriminate the atrium from the ventricle and to represent different atrial and ventricular distances. Heart distances gradients are then combined to define at every point $\hat{\mathbf{x}} \in \hat{\Omega}^s$ a local orthonormal basis $[\mathbf{f}_0, \mathbf{s}_0, \mathbf{n}_0]$ accounting for the anisotropic properties of the cardiac tissue, where $\mathbf{f}_0$ is the fiber direction, $\mathbf{n}_0$ is the sheet-normal direction, $\mathbf{s}_0$ is the sheet direction.

2.1.2. Electrophysiology ($\mathcal{E}$) – ($\mathcal{J}$)

The electrophysiological model is obtained by coupling the monodomain equation, which is a diffusion-reaction PDE that models the evolution of the transmembrane potential at the macroscale, with the ten Tusscher-Panfilov ionic model (TTP06)[55], that describes ionic activity and fluxes across the cell membrane at the microscale. The domain of interest of electrophysiology is the left ventricle solid domain, which we denote as $\hat{\Omega}_{LV}^s$. As done in [8, 63], we treat the left atrium as electrically passive, which is a reasonable simplification for our purpose since the active mechanics of the atrium has a considerable impact on the ventricular flow only during the filling phase, with an effect on cardiac perfusion that can be considered negligible. Introducing the parameters χ_m and C_m that represent the area of the cell membrane per tissue volume and the membrane capacitance, respectively, the monodomain equation for the transmembrane potential ν , equipped with homogeneous Neumann boundary condition and increased with the mechano-electric feedbacks, reads:

$$(\mathcal{E}) \begin{cases} J\chi_m \left[C_m \frac{\partial \nu}{\partial t} + \mathcal{I}_{\text{ion}}(\nu, \mathbf{w}, \mathbf{z}) \right] - \nabla \cdot (J\mathbf{F}^{-1} \mathbf{D}_M \mathbf{F}^{-T} \nabla \nu) \\ \quad \quad \quad = J\chi_m \mathcal{I}_{\text{app}}(t) & \text{in } \hat{\Omega}_{LV}^s \times (0, T], \\ (J\mathbf{F}^{-1} \mathbf{D}_M \mathbf{F}^{-T} \nabla \nu) \cdot \mathbf{N} = 0 & \text{on } \partial \hat{\Omega}_{LV}^s \times (0, T), \end{cases} \quad (2.1)$$

with $\nu = \nu_0$ in $\hat{\Omega}_{LV}^s$ at time $t = 0$. The diffusion term $\nabla \cdot (J\mathbf{F}^{-1} \mathbf{D}_M \mathbf{F}^{-T} \nabla \nu)$ involves different quantities defined as follows: $\mathbf{D}_M$ is the diffusion tensor in deformed configuration, whose formulation is:

$$\mathbf{D}_M = \sigma_l \frac{\mathbf{F}\mathbf{f}_0 \otimes \mathbf{F}\mathbf{f}_0}{\|\mathbf{F}\mathbf{f}_0\|} + \sigma_t \frac{\mathbf{F}\mathbf{s}_0 \otimes \mathbf{F}\mathbf{s}_0}{\|\mathbf{F}\mathbf{s}_0\|} + \sigma_n \frac{\mathbf{F}\mathbf{n}_0 \otimes \mathbf{F}\mathbf{n}_0}{\|\mathbf{F}\mathbf{n}_0\|} \quad (2.2)$$

where $\sigma_l, \sigma_t, \sigma_n$ are the longitudinal, transversal and normal conductivities. $\mathbf{F} = \mathbf{I} + \nabla \mathbf{d}$ is the deformation tensor and $J = \det(\mathbf{F})$ the deformation Jacobian. The applied current $\mathcal{I}_{\text{app}}$ surrogates the effect of the Purkinje network by triggering the action potential in precise sites in the myocardium. We impose this current on three points $\hat{\mathbf{x}}_{\text{app}}^0, \hat{\mathbf{x}}_{\text{app}}^1, \hat{\mathbf{x}}_{\text{app}}^2$ on the ventricular endocardium considering the following analytical expression:

$$\mathcal{I}_{\text{app}}(\hat{\mathbf{x}}, t) = \begin{cases} \sum_{i=0}^2 A_{\text{app}} \exp \left\{ - \left(\frac{\|\hat{\mathbf{x}} - \hat{\mathbf{x}}_{\text{app}}^i\|}{\sigma_{\text{app}}} \right)^2 \right\} & \text{if } t \in (0, T_{\text{app}}], \\ 0 & \text{if } t > T_{\text{app}}. \end{cases} \quad (2.3)$$

To describe the evolution of the vector of gating variables $\mathbf{w}$ and the vector of ionic concentrations of the different species involved $\mathbf{z}$, together with the ionic current $\mathcal{I}_{ion}$, the ten Tusscher-Panfilov ionic model adopted reads:

$$(\mathcal{I}) \begin{cases} \frac{\partial \mathbf{w}}{\partial t} - \mathbf{H}(\nu, \mathbf{w}) = 0, \\ \frac{\partial \mathbf{z}}{\partial t} - \mathbf{G}(\nu, \mathbf{w}, \mathbf{z}) = 0, \end{cases} \quad (2.4)$$

in $\hat{\Omega}_{LV}^s \times (0, T]$, with $\mathbf{w} = \mathbf{w}_0$ and $\mathbf{z} = \mathbf{z}_0$ in $\hat{\Omega}_{LV}^s$ at $t = 0$. $\mathbf{H}$ and $\mathbf{G}$ are two nonlinear operators that encapsulate the transition rates of the ion channel gates and the intracellular ionic transients, respectively. The temporal evolution of these microscale states is driven by the local macroscopic potential ν , which in turn is updated by the resulting ionic current $\mathcal{I}_{ion}$, establishing a two-way coupling.

2.1.3. Force Generation Model ($\mathcal{A}$)

To accurately represent the generation of active forces in the cardiac tissue, we adopt the *RDQ20* model presented in [42], which is biophysically detailed, meaning that the different subcellular mechanisms by which cardiomyocytes generate an active force in response to variations of calcium concentration are explicitly represented. In particular, this model explicitly represents the end-to-end interactions of tropomyosin and the attachment-detachment mechanism of crossbridges. These explicit formulations are responsible for reproducing the macroscopic force-velocity relationship and the fiber-stretch and fiber-stretch-rate feedbacks. As this model features more than 2000 variables, it is surrogated by an ANN-based reduced order model with just two internal variables [43]. The formulation of the active force generation model reads:

$$(\mathcal{A}) \left\{ \frac{\partial \mathbf{s}}{\partial t} = \mathbf{A} \left(\mathbf{s}, w_{Ca}, \text{SL}, \frac{\partial(\text{SL})}{\partial t} \right) \right. \quad \text{in } \hat{\Omega}_{LV}^s \times (0, T], \quad (2.5)$$

with $\mathbf{s} = \mathbf{s}_0$ in $\hat{\Omega}_{LV}^s$ at $t = 0$.

The active tension T_a is derived as a nonlinear function K of the local sarcomere length SL and the microscopic state vector $\mathbf{s}$. In this formulation, the microscale crossbridge stiffness a_{XB} acts as a scaling factor, linking the force generated at the microscopic level to the macroscopic tension. We then express this relation for every point $\hat{\mathbf{x}} \in \hat{\Omega}_{LV}^s$ as follows:

$$T_a(\mathbf{s}, \text{SL}) = a_{XB} K(\mathbf{s}, \text{SL}) \quad (2.6)$$

2.1.4. Active and Passive Mechanics ($\mathcal{M}$)

To describe the cardiac mechanics we have first to introduce the Piola-Kirchhoff stress tensor which embeds the active and passive mechanical properties of the tissue:

$$\mathbf{P}(\mathbf{d}^s, T_a) = \frac{\partial \mathcal{W}(\mathbf{F})}{\partial \mathbf{F}} + T_a \frac{\mathbf{F} \mathbf{f}_0 \otimes \mathbf{f}_0}{\sqrt{\mathcal{I}_{4f}}}. \quad (2.7)$$

The passive part of the Piola-Kirchhoff stress tensor $\frac{\partial \mathcal{W}(\mathbf{F})}{\partial \mathbf{F}}$ is obtained considering the Guccione strain energy density function $\mathcal{W}(\mathbf{F}) = \frac{C}{2}(e^Q - 1)$, with

$$Q = b_{ff}E_{ff}^2 + b_{ss}E_{ss}^2 + b_{nn}E_{nn}^2 + b_{fs}(E_{fs}^2 + E_{sf}^2) + b_{fn}(E_{fn}^2 + E_{nf}^2) + b_{sn}(E_{sn}^2 + E_{ns}^2), \quad (2.8)$$

where E_{ab} are the entries of the Green-Lagrange strain energy tensor $\mathbf{E} = \frac{1}{2}(\mathbf{C} - \mathbf{I})$, with $\mathbf{C} = \mathbf{F}^T \mathbf{F}$. Moreover, a weakly incompressible constraint is introduced considering a further term $\mathcal{W}_{vol}(J) = \frac{B}{2}(J - 1) \log(J)$, convex in J with $J = 1$ global minimum, that penalizes large variations of volume. The term B represents the bulk modulus [44]. The terms appearing in the active part of the tensor are $\mathcal{I}_{4f} = \mathbf{F} \mathbf{f}_0 \cdot \mathbf{F} \mathbf{f}_0$, which is a measure of the tissue stretch along the fiber direction, and the active tension T_a obtained by the RDQ20 force generation model.

The displacement of the heart wall is modeled in a Lagrangian framework with the elastodynamics equation:

$$(\mathcal{M}) \begin{cases} \rho_s \frac{\partial^2 \mathbf{d}^s}{\partial t^2} - \nabla \cdot \mathbf{P}(\mathbf{d}^s, T_a(\mathbf{s}, \text{SL})) = 0 & \text{in } \hat{\Omega}^s \times (0, T] \\ \mathbf{d}^s = \mathbf{d}_0 & \text{in } \hat{\Omega}^s \times \{0\}, \end{cases} \quad (2.9)$$

and the resulting vector $\mathbf{d}^s$ defines the following Lagrangian map:

$$\mathcal{L}^s(\hat{\mathbf{x}}, t) = \hat{\mathbf{x}} + \mathbf{d}^s(\hat{\mathbf{x}}, t) \quad \forall \hat{\mathbf{x}} \in \hat{\Omega}^s, \quad \forall t \in (0, T].$$

In order to impose the boundary conditions, we consider the partition of the boundary $\partial \hat{\Omega}^s = \hat{\Gamma}^{epi} \cup \hat{\Gamma}^{endo} \cup \hat{\Gamma}^{rings}$. The valvular and pulmonary veins rings are assumed to be fixed, then we impose a homogeneous Dirichlet boundary condition:

$$\mathbf{d}^s = \mathbf{0} \quad \text{on } \hat{\Gamma}_{PV}^{rings} \cup \hat{\Gamma}_V^{rings} \times (0, T], \quad (2.10)$$

while on the ascending aortic ring is set a homogeneous Neumann boundary condition:

$$\mathbf{P}\mathbf{N} = \mathbf{0} \quad \text{on } \hat{\Gamma}_{AA}^{rings} \times (0, T]. \quad (2.11)$$

On the ventricular and atrial chamber walls, as well as on the ascending aorta endothelium, we impose the effect of blood pressure, modeled by a closed 0D circulation model, through a Neumann boundary condition:

$$\mathbf{P}\mathbf{N} = -p_i(t)J\mathbf{F}^{-T}\mathbf{N} \quad \text{on } \hat{\Gamma}_i^{endo} \times (0, T], \quad (2.12)$$

with $i \in \{LV, LA, AA\}$. In the end, to model the interaction with the surrounding organs, we impose on the epicardial surface a generalized Robin boundary condition that surrogates the presence of the pericardial sac and the epicardial adipose tissue:

$$\mathbf{P}\mathbf{N} = -\mathbf{K}^{epi}\mathbf{d}^s - \mathbf{C}^{epi}\frac{\partial \mathbf{d}^s}{\partial t} \quad \text{on } \hat{\Gamma}^{epi} \times (0, T], \quad (2.13)$$

where $\mathbf{K}^{epi} = K_{\perp}^{epi}(\mathbf{N} \otimes \mathbf{N}) + K_{\parallel}^{epi}(\mathbf{I} - \mathbf{N} \otimes \mathbf{N})$ and $\mathbf{C}^{epi} = C_{\perp}^{epi}(\mathbf{N} \otimes \mathbf{N}) + C_{\parallel}^{epi}(\mathbf{I} - \mathbf{N} \otimes \mathbf{N})$, denoting with $K_{\perp}^{epi}$ and $K_{\parallel}^{epi}$ the stiffness, and $C_{\perp}^{epi}$ and $C_{\parallel}^{epi}$ the viscosity of the epicardial tissue in normal and tangential directions.

2.1.5. 0D Circulation Model ($\mathcal{C}$)

In order to account for the fluid dynamics feedback on the electromechanical model, we couple the latter with a 0D closed-loop circulation model, which provides the internal pressures imposed in the Neumann boundary condition (2.12). As presented in [44], the core idea of the lumped parameter circulation model is to represent the systemic and pulmonary circulations as Resistive-Inductance-Capacitance (RLC) circuits, the valves as non-ideal diodes, and the heart chambers as elastance elements. From the full circulation model we remove the compartments that have a 3D description, that are left atrium, left

ventricle, mitral valve and ascending aorta. The resulting circulation problem reads:

$$\left\{ \begin{array}{l} \frac{dV_{RA}(t)}{dt} = Q_{VEN}^{SYS}(t) - Q_{TV}(t), \\ \frac{dV_{RV}(t)}{dt} = Q_{TV}(t) - Q_{PV}(t), \\ C_{AR}^{SYS} \frac{dp_{AR}^{SYS}(t)}{dt} = Q_{AV}(t) - Q_{AR}^{SYS}(t), \\ C_{VEN}^{SYS} \frac{dp_{VEN}^{SYS}(t)}{dt} = Q_{AR}^{SYS}(t) - Q_{VEN}^{SYS}(t), \\ C_{AR}^{PUL} \frac{dp_{AR}^{PUL}(t)}{dt} = Q_{PV}(t) - Q_{AR}^{PUL}(t), \\ C_{VEN}^{PUL} \frac{dp_{VEN}^{PUL}(t)}{dt} = Q_{AR}^{PUL}(t) - Q_{VEN}^{PUL}(t), \\ \frac{L_{AR}^{SYS}}{R_{AR}^{SYS}} \frac{dQ_{AR}^{SYS}(t)}{dt} = -Q_{AR}^{SYS}(t) - \frac{p_{VEN}^{SYS}(t) - p_{AR}^{SYS}(t)}{R_{AR}^{SYS}}, \\ \frac{L_{VEN}^{SYS}}{R_{VEN}^{SYS}} \frac{dQ_{VEN}^{SYS}(t)}{dt} = -Q_{VEN}^{SYS}(t) - \frac{p_{RA}(t) - p_{VEN}^{SYS}(t)}{R_{VEN}^{SYS}}, \\ \frac{L_{AR}^{PUL}}{R_{AR}^{PUL}} \frac{dQ_{AR}^{PUL}(t)}{dt} = -Q_{AR}^{PUL}(t) - \frac{p_{VEN}^{PUL}(t) - p_{AR}^{PUL}(t)}{R_{AR}^{PUL}}, \end{array} \right. \quad (2.14)$$

with

$$\left\{ \begin{array}{l} p_{RV}(t) = p_{EX}(t) + E_{RV}(t)(V_{RV}(t) - V_{0,RV}), \\ p_{RA}(t) = p_{EX}(t) + E_{RA}(t)(V_{RA}(t) - V_{0,RA}), \\ Q_{PV}(t) = \frac{p_{RV}(t) - p_{AR}^{PUL}(t)}{R_{PV}(p_{RV}(t), p_{AR}^{PUL}(t))}, \\ Q_{TV}(t) = \frac{p_{RA}(t) - p_{RV}(t)}{R_{TV}(p_{RA}(t), p_{RV}(t))} \end{array} \right. \quad (2.15)$$

where $p_{EX}(t) = 0$ is the external pressure, $E_{RA}(t)$ and $E_{RV}(t)$ are elastances of right atrium and ventricle [8, 44].

The systems of equations (2.14) and (2.15) can be summarized in the following compact notation:

$$(\mathcal{C}) \left\{ \frac{d\mathbf{c}(t)}{dt} = \tilde{\mathbf{D}}(t, \mathbf{c}(t), p_{LV}(t), p_{LA}(t), p_{AA}(t)), \right. \quad (2.16)$$

for $t \in (0, T]$, with $\mathbf{c}(0) = \mathbf{c}_0$.

The circulation model is coupled with 3D electromechanics by imposing continuity between the cavity volumes ($\mathcal{V}$): $V_i^{0D} = V_i(\mathbf{d}^s(t))$ for $i \in \{LA, LV\}$ [63].

2.2. Fluid dynamics

To model fluid dynamics in the time dependent domain Ω^f , we employ a 3D Navier-Stokes model in an *arbitrary Lagrangian-Eulerian* (ALE) framework with *Resistive Immersed Implicit Surface* (RIIS) method for the description of atrial and mitral valves.

The fluid dynamics problem is solved on the current configuration of the fluid domain Ω^f , which is obtained from the reference domain $\hat{\Omega}^f$ by the following ALE map:

$$\mathcal{L}^f(\hat{\mathbf{x}}, t) = \hat{\mathbf{x}} + \mathbf{d}^f(\hat{\mathbf{x}}, t) \quad \forall \hat{\mathbf{x}} \in \hat{\Omega}^f, \quad \forall t \in (0, T].$$

The displacement field $\mathbf{d}^f$ is the solution of a Laplace equation in the reference configuration, imposing the displacement field obtained by electromechanics and projected onto the endocardium as Dirichlet boundary condition on the heart walls. The coronaries are kept static imposing homogeneous Dirichlet BC, coherently with the choice to maintain fixed the biventricular walls in the perfusion problem. The formulation of the resulting Laplace problem reads:

$$\begin{cases} -\Delta \mathbf{d}^f = 0 & \text{in } \hat{\Omega}^f \times [0, T], \\ \mathbf{d}^f = 0 & \text{on } \Gamma_c^f \times [0, T], \\ \mathbf{d}^f = \mathbf{d}^s|_{\Gamma_w^f} & \text{on } \Gamma_w^f \times [0, T], \end{cases} \quad (2.17)$$

where we denoted as Γ_w^f the left heart walls and with Γ_c^f the coronaries surface.

We define the ALE velocity as the time derivative of $\mathbf{d}^f$, pushed forward to the current configuration:

$$\mathbf{u}_{\text{ALE}}(\mathbf{x}, t) = \frac{\partial \mathbf{d}^f(\mathcal{L}^{-1}(\mathbf{x}, t))}{\partial t}. \quad (2.18)$$

To model the effects on the blood of the cardiac valves we adopt the RIIS method presented in [18]. It consists of modeling valves as implicit surfaces $\Sigma_k, k \in \{\text{MV}, \text{AV}\}$ described by a signed distance function $\Phi_k : \Omega^f \times [0, T] \rightarrow \mathbb{R}$ that, in their closed configuration, exert a resistance on the fluid depending on the parameters R_k and ϵ_k , representing the specific resistance coefficient of structure k and the half-thickness of the valves leaflets, respectively. This method is introduced in the model by means of a penalization term in the Navier-Stokes momentum equation, which penalizes the mismatch between the relative fluid velocity and the velocity of the valve leaflets:

$$\mathcal{R}(\mathbf{u}^f, \mathbf{u}_{\text{ALE}}) = \sum_{k \in \{\text{MV}, \text{AV}\}} \frac{R_k}{\epsilon_k} \delta_{\Sigma_k, \epsilon_k}(\Phi_k)(\mathbf{u}^f - \mathbf{u}_{\text{ALE}} - \mathbf{u}_{\Sigma_k}), \quad (2.19)$$

where the term $\delta_{\Sigma_k}(\Phi_k)$ is the approximated Dirac function centered in Φ_k and $\mathbf{u}_{\Sigma_k}$ is the

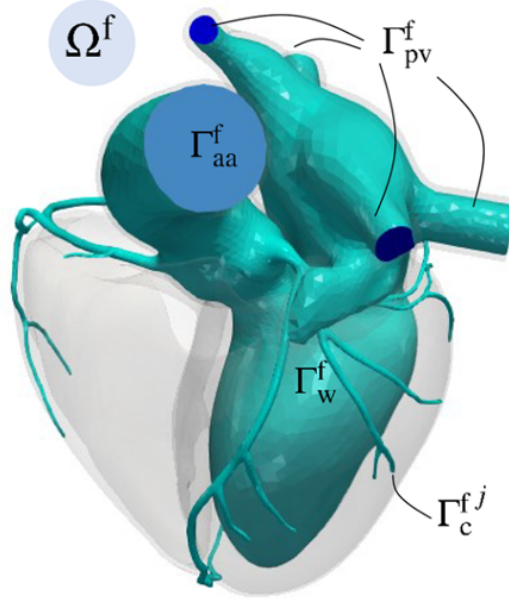


Figure 2.2: Fluid domain in current configuration (image taken from [63]).

velocity of the valve leaflets.

The evolution of blood velocity $\mathbf{u}^f(\mathbf{x}, t) : \Omega^f \times [0, T] \rightarrow \mathbb{R}^3$ and pressure $p^f : \Omega^f \times [0, T] \rightarrow \mathbb{R}$ then follows the Navier-Stokes equations for Newtonian, incompressible fluids, expressed in ALE framework and presented here in non-conservative formulation:

$$\begin{cases} \rho_f \left[\frac{\partial \mathbf{u}}{\partial t} + ((\mathbf{u}^f - \mathbf{u}_{\text{ALE}}) \cdot \nabla) \mathbf{u}^f \right] - \nabla \cdot \sigma_f(\mathbf{u}^f, p^f) + \mathcal{R}(\mathbf{u}^f, \mathbf{u}_{\text{ALE}}) = \mathbf{0} & \text{in } \Omega^f \times (0, T], \\ \nabla \cdot \mathbf{u}^f = 0 & \text{in } \Omega^f \times (0, T], \end{cases} \quad (2.20)$$

where, considering the quantities $\mu_f = 3.05 \times 10^{-3}$ kg/(ms) and $\rho_f = 1.06 \times 10^3$ kg/m³ being the blood dynamic viscosity and blood density, respectively, we have denoted as $\sigma_f(\mathbf{u}^f, p^f)$ the Cauchy stresses tensor defined by the Newtonian constitutive law $\sigma_f(\mathbf{u}^f, p^f) = -p^f I + \mu_f(\nabla \mathbf{u}^f + (\nabla \mathbf{u}^f)^T)$. We consider the following partition of the boundary $\Gamma^f = \Gamma_{pv}^f \cup \Gamma_w^f \cup \Gamma_{aa}^f \cup \Gamma_c^f$.

On the inlet surfaces denoted as Γ_{pv}^f representing the pulmonary veins we impose a Neumann boundary condition depending on the physiological pressure p^{PHYS} :

$$\sigma_f(\mathbf{u}^f, p^f) \mathbf{n} = -p^{\text{PHYS}} \mathbf{n} \quad \text{on } \Gamma_{pv}^f \times (0, T]. \quad (2.21)$$

Similarly, for the outlet surface corresponding to the ascending aorta, we impose a Neu-

mann boundary condition prescribing the systemic arterial pressure p^{SYS} , computed by the electromechanical simulation.

$$\boldsymbol{\sigma}_f(\mathbf{u}^f, p^f)\mathbf{n} = -p^{\text{SYS}}\mathbf{n} \quad \text{on } \Gamma_{\text{aa}}^f \times (0, T]. \quad (2.22)$$

At the wall Γ_w^f we consider a Dirichlet boundary condition imposing the ALE velocity

$$\mathbf{u}^f = \mathbf{u}_{\text{ALE}} \quad \text{on } \Gamma_w^f \times (0, T], \quad (2.23)$$

and for the surface Γ_c^f representing the union of J coronary outlets ($\Gamma_c^f = \bigcup_{j=1}^J \Gamma_{c,k}^f$), a null tangential traction condition is applied:

$$\mu(\nabla \mathbf{u}^f + (\nabla \mathbf{u}^f)^T)\mathbf{n} \cdot \boldsymbol{\tau} = 0 \quad \text{on } \Gamma_c^f \times (0, T], \quad (2.24)$$

together with the coupling condition reported in (2.40). To finally close the problem, a homogeneous initial condition is imposed: $\mathbf{u}^f(\mathbf{x}, 0) = \mathbf{u}_0^f(\mathbf{x}) \equiv \mathbf{0} \ \forall \ \mathbf{x} \in \Omega^f$.

2.3. Perfusion

For the perfusion problem we consider a non-deformable domain Ω^P , representing the biventricular myocardium which we treat as a porous medium.

The microvasculature includes vessels of different scales, ranging from 500 μm of small arteries to 4 μm of capillaries. This separation of spatial scales leads to a hierarchical subdivision of vessels into different compartments, while the small size of the vessels considered require us to simulate the blood flow in the myocardium as the flow through a porous medium [13]. The compartments are structured as follows: small arteries (compartment 1, $d \in (100, 500)\mu\text{m}$), arterioles (compartment 2, $d \in (8, 100)\mu\text{m}$) and capillaries (compartment 3, $d \in (4, 8)\mu\text{m}$).

As presented by Pelagi et al. in [39], we adopt a compliant three-compartments Darcy model. This choice reflects the compartmental subdivision described above and allows accounting for the effects on the flow of the cyclic stress exerted by the myocardium during the different phases of the cardiac cycle.

The strong formulation of the problem reads:

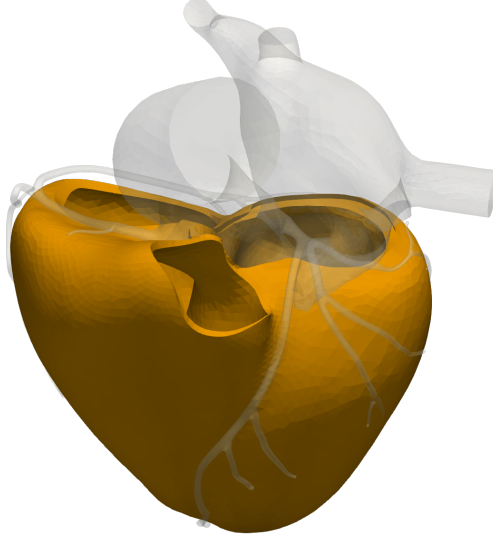


Figure 2.3: Biventricular geometry for perfusion problem.

$$\begin{cases} -\nabla \cdot (K_i \nabla p_i) + \frac{\partial \phi_i}{\partial t} + \sum_{j=1}^3 \beta_{ij}(p_i - p_j) = \theta_i & \text{in } \Omega^P \times (0, T], \\ \phi_i = f(p_i, P_{im}) & \text{in } \Omega^P \times (0, T], \\ \frac{\partial p_i}{\partial \mathbf{n}} = 0 & \text{on } \partial\Omega^P \times (0, T], \end{cases} \quad (2.25)$$

with $i = 1, 2, 3$. For each compartment i , the terms involved are the unknown blood pressure p_i , permeability K_i , and mass exchange coefficients $\beta_{ij} \geq 0$, $j = 1, 2, 3$. To enforce mass conservation among compartments it is necessary that the β -coefficients respect the condition $\beta_{ij} = \beta_{ji}$ for $i, j = 1, 2, 3$ and $\beta_{ij} \neq 0$ only when i and j refer to adjacent compartments.

θ_i is the mass sink/source term. It is set to zero for the second compartment, since here vessels exchange flow only with the vessels of the adjacent compartments. In the first compartment θ_1 is provided by the epicardial blood dynamics and is defined by the relation:

$$\theta_1 = \sum_{k=1}^N \frac{\chi^k}{|\Omega^k|} \int_{\Gamma^k} \mathbf{u}_C \cdot \mathbf{n} d\gamma, \quad \text{with } \chi^k = \begin{cases} 1 & \text{if } x \in \Omega^k, \\ 0 & \text{if } x \notin \Omega^k, \end{cases} \quad (2.26)$$

where N is the number of coronary outlets, the term $\int_{\Gamma^k} \mathbf{u}_C \cdot \mathbf{n}$ is the flow through the coronary outlet Γ^k and χ^k is the characteristic function which ensures the one-to-one

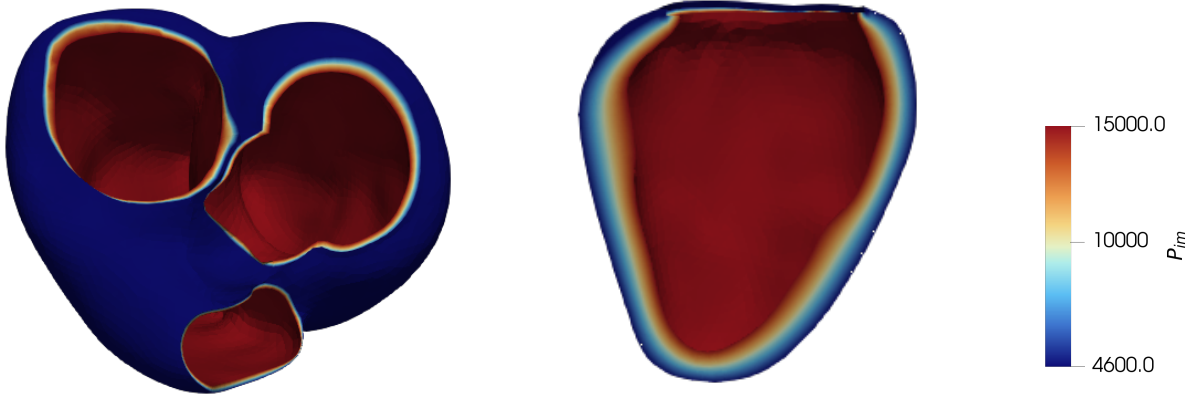


Figure 2.4: Transmural modulation of intramyocardial pressure

correspondence between each perfusion region and the respective coronary outlet. θ_3 is the sink term that accounts for the venous return as follows:

$$\theta_3 = -\gamma(p_3 - p_{ra}), \quad (2.27)$$

where γ is the conductance of the whole coronary venous circulation and p_{ra} is the pressure in the right atrium. The source term θ_1 and the sink term θ_3 respect the compatibility condition:

$$\int_{\Omega^P} (\theta_1 + \theta_3) d\mathbf{x} = 0 \quad (2.28)$$

The compliance term $\frac{\partial \phi_i}{\partial t}$ introduced in [39] representing the time derivative of i^{th} -compartment's porosity allows the effect of myocardial contraction on myocardial blood flow to be taken into account. The porosity ϕ_i is modeled through a suitable function f_i depending on compartment pressure p_i and intramyocardial pressure P_{im} , obtained from the 3D-0D electromechanical problem by linearly scaling the left ventricle pressure $P_{LV}(t)$:

$$P_{im} = \begin{cases} 0.9P_{LV} & \text{on } \partial\Omega_{endo}^P \\ 0.3P_{LV} & \text{on } \partial\Omega_{epi}^P \end{cases} \quad (2.29)$$

Introducing the quantities N_i as the total number of vessels in compartment i , L_i as the average vessel length, and A_i as the average cross section, and considering the definition of porosity as the ratio between the fluid volume and the total volume occupied by a compartment, the following relation is obtained:

$$\phi_i = \frac{V_{f,i}}{V} = \frac{N_i L_i A_i}{V} = (nL)_i A_i \quad \text{for } i = 1, 2, 3. \quad (2.30)$$

The term $(nL)_i$ is denoted as the vessel *length density*. Assuming the contraction has no effect on the length density and that the vessel cross section depends on the transmural pressure difference $(p_i - P_{im})$:

$$\frac{\partial \phi_i}{\partial t} = (nL)_i \frac{\partial A_i}{\partial (p_i - P_{im})} \frac{\partial (p_i - P_{im})}{\partial t} \quad \text{for } i = 1, 2, 3. \quad (2.31)$$

Finally denoting as $C_i = \frac{\partial A_i}{\partial (p_i - P_{im})}$ the i^{th} -compartment vessels *distensibility* and substituting (2.31) in (2.25), the final formulation of the compliant Darcy model is:

$$\begin{cases} -\nabla \cdot (K_i \nabla p_i) + (nL)_i C_i \frac{\partial (p_i - P_{im})}{\partial t} + \sum_{j=1}^3 \beta_{ij} (p_i - p_j) = \theta_i & \text{in } \Omega^P \times (0, T], \\ \frac{\partial p_i}{\partial \mathbf{n}} = 0 & \text{on } \partial \Omega^P \times (0, T]. \end{cases} \quad (2.32)$$

The parameters K_i , C_i and β_{ij} depend on the transmural pressure difference $(p_i - P_{im})$, since they are strictly related to the average vessels pore section A_i . In particular, for each compartment the cross-sectional area A_i is defined by a constitutive relation as follows:

- **Compartment 1:** This compartment includes the small arteries, vessels considered as rigid, hence with a constant cross-sectional area $A_1 = a_1 \text{ mm}^2$ (note that this implies $C_1 = 0$).
- **Compartment 2:** Arterioles are the most distensible part of the coronary tree, the constitutive relation is here reported in its general form, keeping the coefficients undetermined, as a logarithmic function in the case $(p_2 - P_{im}) \geq 0$ and extended in the negative region through a sigmoidal function:

$$A_2 = \begin{cases} a_2^- + \frac{b_2^-}{1 + e^{c_2^-(p_2 - P_{im}) + d_2^-}} [\text{mm}^2] & \text{if } p_2 - P_{im} < 0 \end{cases} \quad (2.33a)$$

$$\begin{cases} a_2^+ \ln(b_2^+(p_2 - P_{im}) + c_2^+) + d_2^+ [\text{mm}^2] & \text{if } p_2 - P_{im} \geq 0 \end{cases} \quad (2.33b)$$

- **Compartment 3:** The expression for the constitutive law of capillaries is as follows:

$$A_3 = a_3 + \frac{b_3}{1 + e^{c_3(p_3 - P_{im}) + d_3}} [\text{mm}^2] \quad (2.34)$$

To conclude we define the parameters for permeabilities and inter-compartment conductances, K_i and β_{ij} .

Permeability is considered directly proportional to porosity and is computed by the following formula:

$$K_i = \frac{\kappa}{\mu} \phi_i = \frac{\kappa}{\mu} (nL)_i A_i \quad (2.35)$$

where κ denotes the specific permeability of the fluid/matrix system and μ the blood dynamic viscosity.

For the parameters β_{ij} the definition is based on the hypothesis of considering each vessel as a Poiseuille-like resistor with conductance:

$$\beta_{vessel,i} = \frac{A_i^2}{8\pi\mu L_i} \quad (2.36)$$

and extending this formula to the whole compartment by assuming the total conductance of the compartment as directly proportional to both the vessel conductance $\beta_{vessel,i}$ and the vessel density n_i :

$$\beta_i = \delta_i^* n_i \beta_{vessel,i} = \delta_i (nL)_i A_i^2 \quad (2.37)$$

where the coefficient δ_i^* accounts for the specific morphometry of the network. The inter-compartment conductance β_{ij} is finally obtained:

$$\beta_{ij} = \frac{\delta_i (nL)_i A_i^2 + \delta_j (nL)_j A_j^2}{2} \quad (2.38)$$

2.4. Coupling Conditions

Following the description of the individual physical models, we conclude by defining the coupling conditions that relate the various processes.

To couple the electromechanical model with the hemodynamics a one-way kinematic coupling condition has to be imposed:

$$\mathbf{u}^f = \dot{\mathbf{d}}^s \text{ on } \Gamma_w \times (0, T] \quad (2.39)$$

where in Γ_w we include the atrial and ventricular endocardium and the ascending aorta endothelium.

The conditions for the fully-coupled Navier-Stokes-Darcy problem read:

$$\begin{aligned} -p^f + \mu(\nabla \mathbf{u}^f + (\nabla \mathbf{u}^f)^T) \mathbf{n} \cdot \mathbf{n} &= -\frac{1}{|\Omega^{pk}|} \int_{\Omega^{pk}} p_1^p d\mathbf{x} - \frac{1}{\alpha_k} \int_{\Gamma_c^{f,k}} \mathbf{u}^f \cdot \mathbf{n} d\gamma \quad \text{on } \Gamma_c^{f,k}, \\ \theta_1(\mathbf{x}) &= \sum_{k=1}^N \frac{\chi_{\Omega^{pk}}(\mathbf{x})}{|\Omega^{pk}|} \int_{\Gamma_c^{f,k}} \mathbf{u}^f \cdot \mathbf{n} d\gamma \quad \text{in } \Omega^P. \end{aligned} \quad (2.40)$$

2.5. Modeling the CMD

In the scenario of a dysfunctional microvascular system, the affected parameters are related to vascular resistances and inter-compartmental exchanges. Distal vascular lumens and network density appear significantly reduced due to perivascular fibrosis and vascular wall thickening, leading to impaired vasodilation in the diastolic phase. As a consequence, to properly model this pathology we modify the constitutive laws for the lumen cross-sections in the second and third compartments (Equations (2.33), (2.34)), as well as the vessel length densities $(nL)_2$ and $(nL)_3$ to simulate a condition of vascular rarefaction. The effects of this condition on the myocardium are generally diffuse, with a gradient of severity that goes from the endocardium to the epicardium, while in cases of microvascular obstruction following an acute myocardial infarction, the site of the pathology is concentrated in the specific area of the infarct core.

Since our goal is to model the quantitative effects of a pathological condition, we develop our analysis on the Darcy parameters of a specific region. In particular, we analyze the effects on capillary flow of a reduction in the vessels' ability to dilate by modulating the amplitude of the corresponding constitutive curves. We then evaluate the effects of a reduction in arteriolar and capillary length density, and subsequently the combined effect of both parameters. To account for the physiological transmural variation in capillary density [52, 53], we imposed a linear gradient on the length density parameters $(nL)_i$, $i = 2, 3$, setting them 15 – 20% lower in the subepicardium compared to the subendocardium. This allowed us to reproduce the experimental endocardial-to-epicardial perfusion ratio, which ranges from 1.2 ± 0.06 under rest conditions to 1.05 ± 0.08 during stress [3]. Other studies report a more consistent decrease of this ratio under stress conditions, individuating a range of [0.95-1.00] in basal slices, [0.90-0.94] in mid slices and [1.00-1.06] in apical slices, which are, however, higher values compared to those predicted by our model without applying a length density scaling [29].

Mathematically, this physiological baseline is achieved by applying a transmural scaling factor L_d to the uniform length densities, obtained by solving the following Laplace problem:

$$\begin{cases} -\Delta L_d = 0 & \text{in } \Omega^P, \\ L_d = 1 & \text{on } \partial\Omega_{endo}^P, \\ L_d = 0.8 & \text{on } \partial\Omega_{epi}^P, \\ \frac{\partial L_d}{\partial \mathbf{n}} = 0 & \text{on } \partial\Omega_{rings}^P. \end{cases} \quad (2.41)$$

The baseline length density is therefore defined as $(nL)_i^{base} = L_d \cdot (nL)_i$. Moreover, this choice sets a framework to account for the transmural severity gradient of CMD in the

model and makes the model more physiologically accurate, since a reversed flow ratio, obtained with the actual model, is considered a hallmark of pathological conditions [41].

To define the baseline vascular cross-sectional area in each compartment, we adopted the parameters calibrated by Pelagi et al. [39], representing a physiological hyperemic state:

$$a_1 = 0.0700; \quad (2.42)$$

$$a_2^- = 0.0030, \quad b_2^- = 0.0050, \quad c_2^- = -3.020 \times 10^{-4}, \quad d_2^- = 0; \quad (2.43)$$

$$a_2^+ = 0.0011, \quad b_2^+ = 1.200, \quad c_2^+ = 3500, \quad d_2^+ = -0.0033; \quad (2.44)$$

$$a_3 = 1.000 \times 10^{-5}, \quad b_3 = 2.400 \times 10^{-5}, \quad c_3 = -3.000 \times 10^{-4}, \quad d_3 = -0.500. \quad (2.45)$$

We preserved the small arteries rigidity hypothesis, keeping the value of their cross-sectional area fixed, assuming that structural alterations in the myocardium have little effect on this compartment.

As mentioned above, arterioles are the main regulators of myocardial blood supply, with a strong ability to contract and dilate to meet oxygen demand. These vessels, together with capillaries, are more affected by excessive external compression, with a consequent wall thickening causing a large reduction in their sectional lumen. As reported by Collet et al. [11], patients with CMD exhibit a reduction of $\approx 40\%$ in lumen area with respect to controls. To rigorously model this lumen restriction, we introduce the scaling coefficients $\psi_2, \psi_3 \in (0, 1)$ to directly reduce the amplitude of the constitutive curves. The pathological average cross-sectional areas for the second and third compartments, denoted as A_2^{CMD} and A_3^{CMD} , are respectively formulated as:

$$A_2^{CMD}(p_2, P_{im}) = \begin{cases} a_2^- + \frac{\psi_2 b_2^-}{1 + e^{c_2^-(p_2 - P_{im} + d_2^-)}} & \text{if } p_2 - P_{im} < 0, \\ (\psi_2 a_2^+) \ln(b_2^+(p_2 - P_{im}) + c_2^+) + d_2^{+'} & \text{if } p_2 - P_{im} \geq 0, \end{cases} \quad (2.46)$$

and

$$A_3^{CMD}(p_3, P_{im}) = a_3 + \frac{\psi_3 b_3}{1 + e^{c_3(p_3 - P_{im}) + d_3}}. \quad (2.47)$$

The choice of parameters allows us to obtain a coherent reduction in the average cross-sectional area in the typical $p_2 - P_{im}$ diastolic ranges (between 25-45 mmHg), with a slightly smaller decrease in the systolic phase. For the third compartment, we target an intramural pressure difference range of 10-20 mmHg. As a consequence, the subendocardial flow, which is almost totally diastolic, is more penalized. The remaining parameters of Eq. (2.46) are adapted to ensure C^1 continuity of the constitutive curve. In particular, we suitably modulate the parameter d_2^+ .

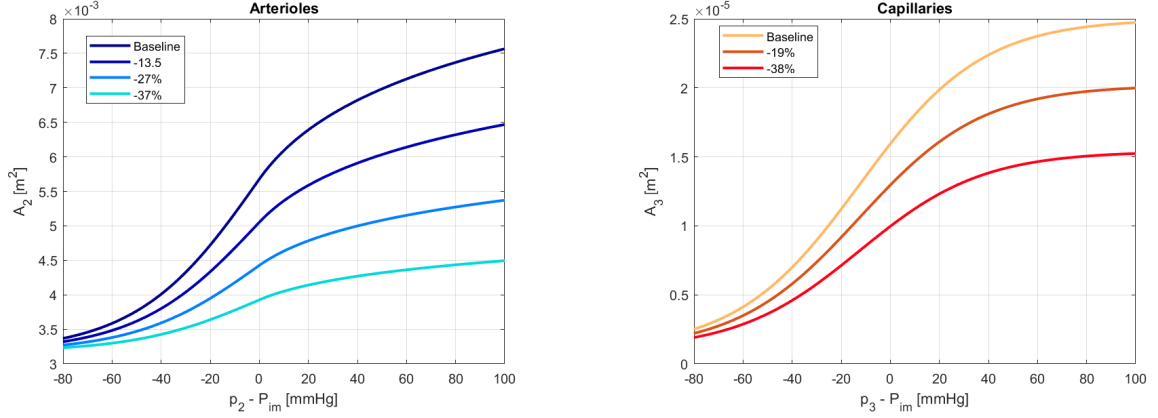


Figure 2.5: Constitutive curves representing the average cross-sectional areas A_2 (arterioles, left) and A_3 (capillaries, right) as functions of the transmural pressure differences $p_2 - P_{im}$ and $p_3 - P_{im}$, respectively. The images illustrate the progressive reduction in lumen amplitude under varying degrees of CMD severity. Legend percentages correspond to lumen area reductions evaluated at $p_2 - P_{im} = 40$ mmHg and $p_3 - P_{im} = 20$ mmHg.

Another structural alteration in CMD cases is microvascular rarefaction [12]. Clinical observations from recent studies, detecting nailfold capillaroscopy abnormalities in patients with ANOCA (Angina with No Obstructive Coronary Arteries) [46] and reduced density in patients with severe CAD [9], led to an estimated decrease of 15 – 30% in baseline vessel length density parameters $(nL)_2$ and $(nL)_3$ within the pathological region. The stronger impact in the subendocardium, considered more prone to develop interstitial fibrosis with consequent microvascular collapse, is modeled by reducing the endo/epi length density gradient. Instead of using the baseline physiological factor L_d , we define a pathological transmural scaling factor L_d^{CMD} obtained by solving the following dedicated boundary value problem:

$$\begin{cases} -\Delta L_d^{CMD} = 0 & \text{in } \Omega^P, \\ L_d^{CMD} = 1 - \delta_{CMD} & \text{on } \partial\Omega_{endo}^P, \\ L_d^{CMD} = 0.8 & \text{on } \partial\Omega_{epi}^P, \\ \frac{\partial L_d^{CMD}}{\partial \mathbf{n}} = 0 & \text{on } \partial\Omega_{rings}^P, \end{cases} \quad (2.48)$$

where $\delta_{CMD} \in [0.15, 0.30]$ dictates the severity of the endocardial density rarefaction. The pathological length densities are therefore explicitly computed as $(nL)_i^{CMD} = L_d^{CMD} \cdot (nL)_i$ for $i = 2, 3$.

These modified state variables (A_i^{CMD}) and $(nL)_i^{CMD}$ substitute their baseline coun-

terparts directly into the governing equations of the compliant Darcy model (Eq. (2.32)). Specifically, they alter the spatial diffusion by updating the compartment permeabilities K_i (defined in Eq. (2.35), being linearly proportional to both $(nL)_i$ and A_i), and they modify the mass exchange by re-evaluating the inter-compartment conductances β_{ij} (Eq. (2.38), linearly dependent on $(nL)_i, (nL)_j$ and quadratically related to A_i, A_j). This rigorous modeling choice describes in a biophysically accurate manner the mechanisms underlying coronary microvascular pathology, directly acting on the parameters that determine the resistance due to microvasculature. This has a direct impact on myocardial blood flow, which is computed as in [13]:

$$\text{MBF} = \beta_{23}(p_2 - p_3) \cdot 60 \cdot 100 \text{ mL/min}/100 \text{ mL}. \quad (2.49)$$

3 | Numerical Methods

In this chapter, we present the numerical methods and approximations adopted to solve the coupled problem. The entire problem is solved in a segregated procedure, with a one-way coupling between electromechanics and hemodynamics. First, the fully-coupled 0D-3D electromechanics problem is solved; then, the resulting displacement field is projected onto the fluid dynamics computational mesh to solve the fully-coupled Navier-Stokes-Darcy problem. Reflecting this staggered strategy, we divide the presentation of the numerical methods into two main sections: Section 3.1 details the temporal and spatial discretization adopted for electromechanics, while Section 3.2 addresses the numerical schemes for the fluid dynamics and perfusion problems.

3.1. Electromechanics

3.1.1. Time Discretization

For the time advancement of the core models, we employ the Implicit Euler method. To optimize the balance between numerical stability and computational efficiency, this time integration is combined with Implicit-Explicit (IMEX) schemes. This choice is made to balance the severe timestep restrictions (CFL conditions) of fully explicit methods with the high computational cost of fully implicit methods. The IMEX strategy overcomes these limitations by treating stiff or linear terms implicitly to guarantee unconditional stability, while handling non-linear fast dynamics explicitly to avoid costly non-linear iterations. The mechanical problem ($\mathcal{M}$) instead requires a fully implicit scheme to handle the highly nonlinear terms of the strain energy function $\mathcal{W}$. We combine this approach with a staggered strategy based on the Godunov splitting scheme, in order to coherently introduce a first order error for both operator splitting and temporal discretization [19, 44].

We split the time interval $(0, T)$ into N subintervals $[t^n, t^{n+1})$ with timestep Δt such that $t^n = n\Delta t$ for $n = 0, \dots, N$, denoting the approximation of the generic solution u at time t^n as $u(t^n) \approx u^n$.

Electrophysiology is characterized by faster dynamics compared to the other models, necessitating a smaller timestep for its solution to capture fast variations. We split each

subinterval $[t^n, t^{n+1})$ into N_{sub} smaller subintervals with timestep $\tau = \frac{\Delta t}{N_{\text{sub}}}$. Given the solution at time t^n , we set $\nu_0^{n+1} = \nu^n$, $\mathbf{w}_0^{n+1} = \mathbf{w}^n$ and $\mathbf{z}_0^{n+1} = \mathbf{z}^n$, and for $i = 0, \dots, N_{\text{sub}} - 1$ we solve:

$$(\mathcal{J}_{\text{IMEX}}) \begin{cases} \frac{1}{\tau} \mathbf{w}_{i+1}^{n+1} = \frac{1}{\tau} \mathbf{w}_i^{n+1} + \mathbf{H}(\nu_i^{n+1}, \mathbf{w}_i^{n+1}) & \text{in } \hat{\Omega}_{\text{LV}}^s, \\ \frac{1}{\tau} \mathbf{z}_{i+1}^{n+1} = \frac{1}{\tau} \mathbf{z}_i^{n+1} + \mathbf{G}(\nu_i^{n+1}, \mathbf{w}_i^{n+1}, \mathbf{z}_i^{n+1}) & \text{in } \hat{\Omega}_{\text{LV}}^s, \end{cases} \quad (3.1)$$

where we adopt an IMEX scheme featuring an explicit treatment of the ionic concentrations and an implicit treatment of the gating variables [8, 44].

We then solve the monodomain equation treating the diffusion term implicitly and the reaction term explicitly; thus, for every time interval $[t^n, t^{n+1})$, for $i = 0, \dots, N_{\text{sub}} - 1$ we look for ν_{i+1}^{n+1} such that:

$$(\mathcal{E}_{\text{IMEX}}) \begin{cases} J^n \chi_m C_m \frac{\nu_{i+1}^{n+1} - \nu_i^{n+1}}{\tau} - \nabla \cdot (J^n (\mathbf{F}^n)^{-1} \mathbf{D}_M (\mathbf{F}^n)^{-T} \nabla \nu_{i+1}^{n+1}) \\ \quad + J^n \chi_m I_{\text{ion}}(\nu_i^{n+1}, \mathbf{w}_{i+1}^{n+1}, \mathbf{z}_{i+1}^{n+1}) = J^n \chi_m I_{\text{app}}(\hat{\mathbf{x}}, t^n + (i+1)\tau) & \text{in } \hat{\Omega}_{\text{LV}}^s, \\ (J^n (\mathbf{F}^n)^{-1} \mathbf{D}_M (\mathbf{F}^n)^{-T} \nabla \nu_{i+1}^{n+1}) \cdot \mathbf{N} = 0 & \text{on } \partial \hat{\Omega}_{\text{LV}}^s. \end{cases} \quad (3.2)$$

Once the solution of the electrophysiology problem is obtained at each substep with Conjugate Gradient method (CG), we set $\nu^{n+1} = \nu_{N_{\text{sub}}}^{n+1}$, $\mathbf{w}^{n+1} = \mathbf{w}_{N_{\text{sub}}}^{n+1}$, $\mathbf{z}^{n+1} = \mathbf{z}_{N_{\text{sub}}}^{n+1}$, and update the active force generation as follows:

$$\frac{\mathbf{s}^{n+1} - \mathbf{s}^n}{\Delta t} = \mathbf{A} \left(\mathbf{s}^n, [Ca^{2+}]^{n+1}, \text{SL}^n, \frac{\text{SL}^n - \text{SL}^{n-1}}{\Delta t} \right), \quad (3.3)$$

for $n = 0, \dots, N - 1$.

The update of the 0D circulation state vector $\mathbf{c}^{n+1}$ is done using a first-order IMEX method. We split the differential operator of the lumped-parameter network into an implicit part $\tilde{\mathbf{D}}_{\text{I}}$ and an explicit part $\tilde{\mathbf{D}}_{\text{E}}$. The time advancement reads: given $\mathbf{c}^n$ for $n = 0, \dots, N - 1$, find $\mathbf{c}^{n+1}$ such that:

$$\begin{aligned} \mathbf{c}^{n+1} = \mathbf{c}^n &+ \Delta t \tilde{\mathbf{D}}_{\text{I}}(t^{n+1}, \mathbf{c}^{n+1}, p_{\text{LV}}^{n+1}, p_{\text{LA}}^{n+1}, p_{\text{AA}}^{n+1}) \\ &+ \Delta t \tilde{\mathbf{D}}_{\text{E}}(t^n, \mathbf{c}^n, p_{\text{LV}}^{n+1}, p_{\text{LA}}^{n+1}, p_{\text{AA}}^{n+1}). \end{aligned} \quad (3.4)$$

3.1.2. Space Discretization

Despite the multiscale nature of the cardiac electromechanics problem, which typically requires different spatial resolutions for the fast electrical dynamics and the slower tissue deformation, in this work we employ a single tetrahedral mesh $\mathcal{T}_h^s$ for all the core models defined on the solid computational domain $\hat{\Omega}^s$. We adopt the Galerkin Finite Element (FE) method with continuous FEs of order 1 ($\mathbb{P}_1$), thus introducing the following finite-dimensional space:

$$\mathcal{X}_h^1 = \{v_h \in C^0(\bar{\Omega}^s) : v_h|_K \in \mathbb{P}_1(K) \quad \forall K \in \mathcal{T}_h^s\}, \quad (3.5)$$

where K is an element of the mesh considered.

Let $\{\phi_m\}_{m=1}^{N_{\text{dof}}}$ be the standard nodal basis functions for the space $\mathcal{X}_h^1$, with $N_{\text{dof}} = \dim(\mathcal{X}_h^1)$. We consider the FE approximation of a generic scalar variable u as $u_h^n(\hat{\mathbf{x}}) = \sum_{j=1}^{N_{\text{dof}}} u_{h,j}^n \phi_j(\hat{\mathbf{x}})$. Analogously, we denote by $\underline{\mathbf{u}}_h^n$ the algebraic vector collecting the degrees of freedom (DOFs) $u_{h,j}^n$ of this variable at time t^n .

For vector-valued fields, such as the displacement $\mathbf{d}(t)$, we use the vector space $[\mathcal{X}_h^1]^3$ spanned by the basis functions ϕ_m , denoting its fully-discrete FE approximation by $\mathbf{d}_h^n$ and its vector of DOFs by $\underline{\mathbf{d}}_h^n$. Analogously, we denote by $\underline{\mathbf{w}}_h^n$ and $\underline{\mathbf{z}}_h^n$ the algebraic vectors of the gating and concentration variables, respectively.

With this spatial discretization, the solution of $(\mathcal{J}_{\text{IMEX}}) - (\mathcal{E}_{\text{IMEX}})$ reads: for $n = 0, \dots, N-1$, given $\underline{\mathbf{w}}_{0,h}^{n+1} = \underline{\mathbf{w}}_h^n$, $\underline{\mathbf{z}}_{0,h}^{n+1} = \underline{\mathbf{z}}_h^n$, $\underline{\boldsymbol{\nu}}_{0,h}^{n+1} = \underline{\boldsymbol{\nu}}_h^n$, for $i = 0, \dots, N_{\text{sub}} - 1$, we find $\underline{\mathbf{w}}_{i+1,h}^{n+1}$, $\underline{\mathbf{z}}_{i+1,h}^{n+1}$ by solving the following system:

$$\begin{cases} \frac{1}{\tau} \underline{\mathbf{w}}_{i+1,h}^{n+1} = \frac{1}{\tau} \underline{\mathbf{w}}_{i,h}^{n+1} + \bar{\mathbf{H}}(\underline{\boldsymbol{\nu}}_{i,h}^{n+1}, \underline{\mathbf{w}}_{i+1,h}^{n+1}), \\ \frac{1}{\tau} \underline{\mathbf{z}}_{i+1,h}^{n+1} = \frac{1}{\tau} \underline{\mathbf{z}}_{i,h}^{n+1} + \bar{\mathbf{G}}(\underline{\boldsymbol{\nu}}_{i,h}^{n+1}, \underline{\mathbf{w}}_{i,h}^{n+1}, \underline{\mathbf{z}}_{i+1,h}^{n+1}). \end{cases} \quad (3.6)$$

We then find $\underline{\boldsymbol{\nu}}_{i+1,h}^{n+1}$ by solving:

$$\begin{aligned} & \frac{1}{\tau} \mathcal{M}_{\text{ep}}^n(\underline{\boldsymbol{\nu}}_{i+1,h}^{n+1} - \underline{\boldsymbol{\nu}}_{i,h}^{n+1}) + \mathcal{K}^n(\underline{\mathbf{d}}_h^n) \underline{\boldsymbol{\nu}}_{i+1,h}^{n+1} + \mathbf{I}_{\text{ion}}(\underline{\boldsymbol{\nu}}_{i,h}^{n+1}, \underline{\mathbf{w}}_{i+1,h}^{n+1}, \underline{\mathbf{z}}_{i+1,h}^{n+1}) \\ & = \mathbf{I}_{\text{app}}(t^n + (i+1)\tau), \end{aligned} \quad (3.7)$$

where we have introduced the mass matrix $\mathcal{M}_{\text{ep}}^n$ and the stiffness matrix $\mathcal{K}^n$:

$$\begin{aligned} (\mathcal{M}_{\text{ep}}^n)_{mj} &= \int_{\hat{\Omega}^s} J_h^n \phi_j \phi_m \, d\hat{\Omega}^s, \\ \mathcal{K}_{mj}^n(\underline{\mathbf{d}}_h^n) &= \int_{\hat{\Omega}^s} (J_h^n(\mathbf{F}_h^n)^{-1} \mathbf{D}_{m,h}(\mathbf{F}_h^n)^{-T} \nabla \phi_j) \cdot \nabla \phi_m \, d\hat{\Omega}^s, \end{aligned}$$

and the vectors:

$$\begin{aligned} (\mathbf{I}_{ion}(\underline{\nu}_{i,h}^{n+1}, \underline{\mathbf{w}}_{i+1,h}^{n+1}, \underline{\mathbf{z}}_{i+1,h}^{n+1}))_m &= \int_{\hat{\Omega}^s} J_h^n \tilde{\mathcal{I}}_{ion}(\underline{\nu}_{i,h}^{n+1}, \underline{\mathbf{w}}_{i+1,h}^{n+1}, \underline{\mathbf{z}}_{i+1,h}^{n+1}) \phi_m \, d\hat{\Omega}^s, \\ (\mathbf{I}_{app})_m &= \int_{\hat{\Omega}^s} J_h^n \tilde{\mathcal{I}}_{app} \phi_m \, d\hat{\Omega}^s. \end{aligned}$$

For the efficient evaluation of the non-linear term $\mathbf{I}_{ion}$, the Ionic Current Interpolation (ICI) approach is adopted [19]. In this approach, the discrete ionic model (3.6) is solved at every vertex in the solid mesh. Then, the ionic current $\mathbf{I}_{ion}$ is evaluated at every mesh vertex, and interpolated on quadrature nodes of the mesh [8].

After N_{sub} steps of electrophysiology, the active force discrete model is solved, finding $\underline{\mathbf{s}}_h^{n+1}$ such that:

$$\underline{\mathbf{s}}_h^{n+1} = \underline{\mathbf{s}}_h^n + \Delta t \bar{\mathbf{A}} \left(\underline{\mathbf{s}}_h^n, [Ca^{2+}]_h^{n+1}, SL^n, \frac{SL^n - SL^{n-1}}{\Delta t} \right). \quad (3.8)$$

Finally, proceeding analogously, we present the full discretization of the mechanical problem. Given $\underline{\mathbf{d}}_h^n$, we find the displacement vector at the next timestep $\underline{\mathbf{d}}_h^{n+1}$ and the cavity pressures $p_{\text{LV}}^{n+1}, p_{\text{LA}}^{n+1}$ by solving the following system, for $n = 0, \dots, N-1$:

$$\left\{ \begin{aligned} &\left(\rho_s \frac{1}{\Delta t^2} \mathcal{M}_m + \frac{1}{\Delta t} \mathcal{F} + \mathcal{G} \right) \underline{\mathbf{d}}_h^{n+1} + \mathbf{S}(\underline{\mathbf{d}}_h^{n+1}, \mathbf{T}_{a,h}^{n+1}) \\ &= \rho_s \frac{2}{\Delta t^2} \mathcal{M}_m \underline{\mathbf{d}}_h^n - \rho_s \frac{1}{\Delta t^2} \mathcal{M}_m \underline{\mathbf{d}}_h^{n-1} + \frac{1}{\Delta t} \mathcal{F} \underline{\mathbf{d}}_h^n \\ &\quad + p_{\text{LV}}^{n+1} \mathbf{p}_{\text{LV}}(\underline{\mathbf{d}}_h^{n+1}) + p_{\text{LA}}^{n+1} \mathbf{p}_{\text{LA}}(\underline{\mathbf{d}}_h^{n+1}) + p_{\text{AA}}^n \mathbf{p}_{\text{AA}}(\underline{\mathbf{d}}_h^{n+1}), \\ &V_{\text{LV}}^{3D}(\underline{\mathbf{d}}_h^{n+1}) = V_{\text{LV}}^{0D}(\mathbf{c}^n), \\ &V_{\text{LA}}^{3D}(\underline{\mathbf{d}}_h^{n+1}) = V_{\text{LA}}^{0D}(\mathbf{c}^n), \end{aligned} \right. \quad (3.9)$$

where the discrete vector and matrix components are defined as follows:

$$(\mathcal{S}(\underline{\mathbf{d}}_h^{n+1}, \mathbf{T}_{a,h}^{n+1}))_m = \int_{\hat{\Omega}^s} \mathbf{P}(\underline{\mathbf{d}}_h^{n+1}, \mathbf{T}_{a,h}^{n+1}) : \nabla \phi_m \, d\hat{\Omega}^s, \quad (3.10)$$

$$\mathcal{F}_{mj} = \int_{\hat{\Gamma}^{\text{epi}}} \left[C_{\perp}^{\text{epi}}(\mathbf{N} \otimes \mathbf{N}) + C_{\parallel}^{\text{epi}}(\mathbf{I} - \mathbf{N} \otimes \mathbf{N}) \right] \phi_j \cdot \phi_m \, d\hat{\Gamma}^{\text{epi}}, \quad (3.11)$$

$$\mathcal{G}_{mj} = \int_{\hat{\Gamma}^{\text{epi}}} \left[K_{\perp}^{\text{epi}}(\mathbf{N} \otimes \mathbf{N}) + K_{\parallel}^{\text{epi}}(\mathbf{I} - \mathbf{N} \otimes \mathbf{N}) \right] \phi_j \cdot \phi_m \, d\hat{\Gamma}^{\text{epi}}, \quad (3.12)$$

$$(\mathbf{p}_k(\underline{\mathbf{d}}_h^{n+1}))_m = - \int_{\hat{\Gamma}_k^{\text{endo}}} J_h^{n+1}(\mathbf{F}_h^{n+1})^{-T} \mathbf{N} \cdot \phi_m \, d\hat{\Gamma}_k^{\text{endo}}, \quad (3.13)$$

with $k \in \{\text{LV}, \text{LA}, \text{AA}\}$, ϕ_m a generic test function for the finite dimensional space $[\mathcal{X}_h^1]^3$ and $\mathcal{M}_m$ the standard mass matrix.

We remark that the aortic pressure is taken at the time step t^n , as it is equal to the systemic arterial pressure of the circulation state vector $\mathbf{c}^n$. The formulation of Eq (3.9) typically exhibits numerical oscillations when coupled with an active force model and a circulation model. One source of instability is the fiber-stretch-rate feedback, arising from an inconsistent description of strain in Eulerian coordinates at the microscale and in Lagrangian coordinates at the macroscale. To account for this problem the following expression substitutes the Piola tensor expression in Eq. (3.10):

$$\mathbf{P} \left(\underline{\mathbf{d}}_h^{n+1}, T_{a_h}^{n+1} + K_{a_h}^{n+1} \left(\sqrt{\mathbf{F}_h^{n+1} \mathbf{f}_0 \cdot \mathbf{F}_h^{n+1} \mathbf{f}_0} - \sqrt{\mathbf{F}_h^n \mathbf{f}_0 \cdot \mathbf{F}_h^n \mathbf{f}_0} \right) \right) \quad (3.14)$$

where K_{a_h} represents the total stiffness of the attached crossbridges [19].

The second source of instability is related to the interaction between mechanics and circulation, since the staggered scheme of Eq. (3.9) is not unconditionally stable. To correct the possible resulting oscillations, the volume constraints are computed as:

$$\begin{cases} V_{\text{LV}}^{3D}(\underline{\mathbf{d}}_h^{n+1}) = V_{\text{LV}}^{0D}(\mathbf{c}^n) + \Delta t \left[Q_{\text{MV}}(p_{\text{LA}}^{n+1}, p_{\text{LV}}^{n+1}) - Q_{\text{AV}}(p_{\text{LV}}^{n+1}, p_{\text{AR}}^{\text{SYS},n}) \right], \\ V_{\text{LA}}^{3D}(\underline{\mathbf{d}}_h^{n+1}) = V_{\text{LA}}^{0D}(\mathbf{c}^n) + \Delta t \left[Q_{\text{VEN}}^{\text{PUL},n} - Q_{\text{MV}}(p_{\text{LA}}^{n+1}, p_{\text{LV}}^{n+1}) \right]. \end{cases} \quad (3.15)$$

3.2. Fluid Dynamics - Perfusion

3.2.1. Time Discretization

We proceed as seen for electromechanics: we partition the time interval $[0, T]$ into N subintervals characterized by a timestep Δt , solving the problem at discrete time instants $t^n = n\Delta t$ for $n = 0, \dots, N$. For the approximation of time derivatives, we adopt the BDF1 scheme, combined with a semi-implicit treatment of the Navier-Stokes non-linear convective term.

Thus, given the fluid domain displacement at the previous and current time steps, the ALE velocity approximation for $n = 0, \dots, N - 1$ is computed as:

$$\mathbf{u}_{\text{ALE}}^{n+1} = \frac{\mathbf{d}^{f,n+1} - \mathbf{d}^{f,n}}{\Delta t} \quad \text{in } \Omega^{f,n+1}. \quad (3.16)$$

Subsequently, the semi-discrete formulation for the Navier-Stokes equations reads: for $n = 0, \dots, N - 1$, find the fluid velocity $\mathbf{u}^{f,n+1}$ and pressure $p^{f,n+1}$ such that:

$$\begin{cases} \rho_f \left[\frac{\mathbf{u}^{f,n+1} - \mathbf{u}^{f,n}}{\Delta t} + (\mathbf{u}^* \cdot \nabla) \mathbf{u}^{f,n+1} \right] & \text{in } \Omega^{f,n+1}, \\ -\nabla \cdot \sigma_f(\mathbf{u}^{f,n+1}, p^{f,n+1}) + \mathcal{R}(\mathbf{u}^{f,n+1}, \mathbf{u}_{\text{ALE}}^{n+1}) = \mathbf{0} & \\ \nabla \cdot \mathbf{u}^{f,n+1} = 0 & \text{in } \Omega^{f,n+1}, \end{cases} \quad (3.17)$$

completed with suitable Dirichlet and Neumann boundary conditions on $\partial\Omega^{f,n+1}$, where $\mathbf{u}^* = \mathbf{u}^{f,n} - \mathbf{u}_{\text{ALE}}^{n+1}$ represents the relative velocity considering domain motion.

Similarly, the semi-discrete formulation of the Darcy problem at each timestep reads: for $n = 0, \dots, N - 1$, given p_i^n the solution in compartment i at time t^n , we look for p_i^{n+1} such that:

$$\begin{aligned} & -\nabla \cdot (K_i^n \nabla p_i^{n+1}) + (nL)_i C_i^n \left(\frac{p_i^{n+1} - p_i^n}{\Delta t} \right) \\ & = \theta_i + (nL)_i C_i^n \left(\frac{P_{im}^{n+1} - P_{im}^n}{\Delta t} \right) - \sum_{j=1}^3 \beta_{i,j} (p_i^{n+1} - p_j^{n+1}) \quad \text{in } \Omega^p, \end{aligned} \quad (3.18)$$

where the fluid velocity in the source term θ_i of the first compartment is the one evaluated at time t^{n+1} .

3.2.2. Space Discretization

We work on tetrahedral meshes for both fluid and perfusion problems and refer to the computational meshes as $\mathcal{T}_{h_f}^f$ and $\mathcal{T}_{h_p}^p$.

We introduce the following infinite-dimensional functional spaces:

$$\begin{aligned}\mathcal{V}^f &:= \{\mathbf{v} \in [H^1(\Omega^f)]^3 : \mathbf{v} = \mathbf{g} \text{ on } \Gamma_w^f\}, & \mathcal{Q}^f &:= L^2(\Omega^f) \\ \mathcal{V}^d &:= \{\hat{\mathbf{v}} \in [H^1(\hat{\Omega}^f)]^3 : \hat{\mathbf{v}} = \mathbf{d}^s \text{ on } \Gamma_w^f\}, \\ \mathcal{V}^p &:= H^1(\Omega^p).\end{aligned}$$

For the ALE lifting problem, the Galerkin formulation is expressed as: for each $n = 0, \dots, N-1$, find the displacement $\mathbf{d}_h^{f,n+1} \in \mathcal{V}_h^d$ such that:

$$(\nabla \mathbf{d}_h^{f,n+1}, \nabla \hat{\mathbf{w}}_h) = 0, \quad \forall \hat{\mathbf{w}}_h \in \mathcal{V}_{0,h}, \quad (3.19)$$

where $\mathcal{V}_h^d$ is the finite-dimensional subspace of $\mathcal{V}^d$, which we consider to be, as for the other subspaces, piecewise linear polynomials obtained as $\mathcal{V}^d \cap \mathcal{X}_h^1$, and $(\cdot, \cdot)$ denotes the standard L^2 inner product. Thus, at every timestep the discrete ALE velocity is computed as:

$$\mathbf{u}_{\text{ALE,h}}^{n+1} = \frac{\mathbf{d}_h^{f,n+1} - \mathbf{d}_h^{f,n}}{\Delta t}. \quad (3.20)$$

Since we adopt the discrete spaces $\mathbb{P}_1 - \mathbb{P}_1$ for both velocity and pressure in the Navier-Stokes equations, an *inf-sup* stabilization is needed. For this purpose, we use the VMS-LES method that assures *inf-sup* stability, allows controlling instabilities arising from advection-dominated problems, and accounts for possible transition to turbulence effects that occur in cardiac blood flow [62]. This approach consists in a multiscale direct-sum decomposition of a general functional space $\mathcal{V}$ into the coarse and fine scale subspaces: $\mathcal{V} = \mathcal{V}_h \oplus \mathcal{V}'$. In the same way, velocity and pressure are decomposed into coarse and fine scales components, where the coarse scale part is identified by the FE approximation and the fine scale one is modeled as:

$$\begin{aligned}\mathbf{u}' &\simeq -\tau_M(\mathbf{u}_h^*) \mathbf{r}_M(\mathbf{u}_h, p_h), \\ p' &\simeq -\tau_C(\mathbf{u}_h^*) \mathbf{r}_C(\mathbf{u}_h),\end{aligned}$$

where $\mathbf{r}_M$ and $\mathbf{r}_C$ are the strong residuals of the momentum and continuity equations, while τ_M and τ_C are the stabilization parameters [21].

The resulting stabilization term added in the Navier-Stokes momentum equation reads:

$$\begin{aligned}
\mathcal{S}(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}, \mathbf{u}_h^*, \mathbf{v}_h, q_h) &= \sum_{K \in \mathcal{T}_h^f} \left(\rho_f \mathbf{u}_h^* \cdot \nabla \mathbf{v}_h + \nabla q_h, \tau_M(\mathbf{u}_h^*) \mathbf{r}_M(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}) \right)_K \\
&+ \sum_{K \in \mathcal{T}_h^f} \left(\nabla \cdot \mathbf{v}_h, \tau_C(\mathbf{u}_h^*) \mathbf{r}_C(\mathbf{u}_h^{f,n+1}) \right)_K \\
&+ \sum_{K \in \mathcal{T}_h^f} \left(\rho_f \mathbf{u}_h^* \cdot (\nabla \mathbf{v}_h)^T, \tau_M(\mathbf{u}_h^{f,n+1}) \mathbf{r}_M(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}) \right)_K \\
&- \sum_{K \in \mathcal{T}_h^f} \left(\nabla \mathbf{v}_h, \tau_M(\mathbf{u}_h^*) \mathbf{r}_M(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}) \otimes \tau_M(\mathbf{u}_h^*) \mathbf{r}_M(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}) \right)_K,
\end{aligned}$$

with $\mathbf{v}_h \in \mathcal{V}_{0,h}^f$ and $q_h \in \mathcal{Q}_h^f$ being suitable test functions.

The fully discretized VMS-LES formulation of the NS-ALE-RIIS equations reads: given $\mathbf{u}_h^n$, for any $n = 0, \dots, N-1$, find $(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}) \in \mathcal{V}_h^f \times \mathcal{Q}_h^f$ such that:

$$\begin{aligned}
&\frac{1}{\Delta t} \left(\mathbf{v}_h, \rho_f \mathbf{u}_h^{f,n+1} \right)_{\Omega^{f,n+1}} + \left(\mathbf{v}_h, \rho_f (\mathbf{u}_h^* \cdot \nabla) \mathbf{u}_h^{f,n+1} \right)_{\Omega^{f,n+1}} \\
&+ \left(\nabla \mathbf{v}_h, \mu \nabla \mathbf{u}_h^{f,n+1} \right)_{\Omega^{f,n+1}} - \left(\nabla \cdot \mathbf{v}_h, p_h^{f,n+1} \right)_{\Omega^{f,n+1}} + \left(q_h, \nabla \cdot \mathbf{u}_h^{f,n+1} \right)_{\Omega^{f,n+1}} \\
&+ \left(\mathbf{v}_h, \mathcal{R}(\mathbf{u}_h^{f,n+1}, \mathbf{u}_{\text{ALE},h}^{n+1}) \right)_{\Omega^{f,n+1}} + \mathcal{S}(\mathbf{u}_h^{f,n+1}, p_h^{f,n+1}, \mathbf{u}_h^*, \mathbf{v}_h, q_h) \\
&= (\mathbf{v}_h, \mathbf{h}^{n+1})_{\Gamma_N^{n+1}} + (\mathbf{v}_h, \rho_f (\mathbf{u}_h^* \cdot \mathbf{n}) - \mathbf{u}_h^{f,n+1})_{\Gamma_N^{n+1}} + \frac{1}{\Delta t} \left(\mathbf{v}_h, \rho_f \mathbf{u}_h^{f,n} \right)_{\Omega^{f,n}},
\end{aligned}$$

for all $(\mathbf{v}_h, q_h) \in \mathcal{V}_{0,h}^f \times \mathcal{Q}_h^f$. We remark that the backflow stabilization term is also added to the formulation to account for possible instabilities at the pulmonary vein inlets and at the aortic outlet.

For the perfusion problem, the same FE discretization is applied. Considering the finite-dimensional space $\mathcal{V}_h^p = \mathcal{V}^p \cap \mathcal{X}_h^1$, we obtain the following fully discrete formulation: given $p_{i,h}^n$, for any $n = 0, \dots, N-1$, find $p_{i,h}^{n+1} \in \mathcal{V}_h^p$ such that:

$$(K_i^n \nabla p_{i,h}^{n+1}, q_h)_{\Omega^p} + \frac{(nL)_i C_i^n}{\Delta t} (p_{i,h}^{n+1} - p_{i,h}^n, q_h)_{\Omega^p} = (\theta_i, q_h)_{\Omega^p} \quad (3.21)$$

$$+ \frac{(nL)_i C_i^n}{\Delta t} (P_{im,h}^{n+1} - P_{im,h}^n, q_h)_{\Omega^p} - \sum_{j=1}^3 (\beta_{ij} (p_{i,h}^{n+1} - p_{j,h}^{n+1}), q_h)_{\Omega^p}, \quad (3.22)$$

for all test functions $q_h \in \mathcal{V}_{0,h}^p$.

4 | Numerical Simulations

In this chapter, we present the results of the numerical simulations. We begin by introducing the electromechanical simulation, which serves as the foundation for all subsequent perfusion analyses. Next, we report the results obtained from an idealized geometry, employed as a test case to analyze the effects of varying the Darcy parameters detailed in Section 2.5. Finally, we describe and discuss the results achieved using the realistic Zygote geometry.

All numerical simulations are executed using `lifex` [2], an open-source, high-performance C++ library specifically designed for the finite element solution of multiphysics, multiscale, and multidomain problems. Conceived within the framework of the iHEART project, `lifex` was developed with a primary focus on the integrated mathematical modeling of the cardiac function, making it the ideal framework for our highly coupled electromechanical and perfusion analyses.

The library leverages modern programming paradigms and is built upon the `deal.II` finite element core [1], from which it inherits advanced capabilities for mesh handling, supporting both hexahedral and tetrahedral elements, and arbitrary degree finite element approximations. To address the severe computational demand of 3D cardiac models, `lifex` is natively designed for High-Performance Computing (HPC). It exploits the Message Passing Interface (MPI) for distributed-memory parallelization and interfaces with state-of-the-art linear algebra backends, such as PETSc and Trilinos, to efficiently assemble and solve massive linear and non-linear algebraic systems. For our specific setup, the coupled problems are scaled and solved in parallel on 28 cores.

4.1. Electromechanics

An electromechanical simulation is performed to compute the pressure curves within the systemic arterial system and the left ventricle. These curves provide the necessary boundary conditions for the perfusion problem, specifically, the systemic arterial pressure is imposed as aortic outlet pressure in Eq. (2.22) and the left ventricle pressure is used to compute the intramyocardial pressure in Eq. (2.29). Furthermore, we extract the solid displacement field and project it onto the fluid domain surface by solving (2.17) to derive

the ALE velocity for the fluid dynamics simulations, computed as the displacement time derivative (Eq. (2.18)).

The computational domain consists of a triangulation of the left heart solid domain $\hat{\Omega}^s$, comprising 147,386 tetrahedra, 39,586 triangles, and 33,576 nodes (Figure 4.1), which is utilized for both electrophysiology and mechanics. It is important to note that this mesh resolution is relatively coarse to effectively capture the traveling electrical wavefront of (2.1), which requires us to compensate by artificially increasing the conductivities in (2.2) [63].

Regarding the temporal discretization, we adopt a time step $\tau = 50 \mu s$ for the electrophysiology solver (3.1)-(3.2), and $\Delta t = 1000 \mu s$ for the mechanics, activation, and circulation problems (3.9)-(3.3)-(3.4). These different time scales are visible by comparing Figure 4.3 and Figure 4.4, where it is clear that the evolution of mechanical displacement is significantly slower than the propagation of calcium concentration and action potential. The simulation runs for three consecutive heartbeats to ensure the circulation variables reach a stable limit cycle, and the solution from the final cycle is extracted for analysis. A comprehensive description of the calibration process of electromechanical simulation is provided in Appendix A.

Figure 4.2 illustrates the pressure curves we need for perfusion. Specifically, the pressure in systemic arteries is imposed as aortic boundary condition in Eq. (2.22), and the pressure in the left ventricle is used to define the intramyocardial pressure in Eq. (2.29). In Figure 4.3 we report the evolution of the displacement field used to compute the ALE velocity. While a physiological systolic contraction typically involves the ventricular base descending towards the apex, our results reflect the imposition of homogeneous Dirichlet boundary conditions on the mitral valve ring. Consequently, the most significant displacement occurs at the apex, which is compressed upwards, effectively driving the blood toward the ascending aorta.

The macroscopic pumping performance of the left ventricle (LV) aligns well with physiological human targets. During the diastolic filling phase, the LV volume (V_{LV}) progressively increases, reaching an End-Diastolic Volume (EDV) of 133.6 mL. Following isovolumetric contraction, the aortic valve opens, and the volume decreases to an End-Systolic Volume (ESV) of 63.1 mL (see Figure 4.2). These chamber volumetric variations yield a Stroke Volume (SV) of 70.6 mL and an Ejection Fraction (EF) of 52.8%, both falling within the established physiological range for a healthy adult [7, 56]. In terms of hemodynamics, the intraventricular pressure (p_{LV}) peaks during mid-systole at approximately 110.5 mmHg. The aortic pressure (p_{AA}) accurately tracks this peak during the ejection phase and exhibits a physiological exponential decay during diastole, operating within a standard normotensive range between 76.9 mmHg and 109.3 mmHg. Ultimately,

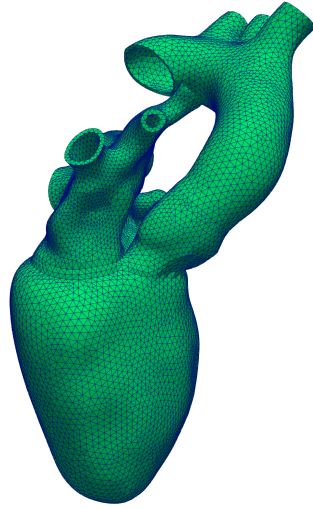


Figure 4.1: Computational mesh for electromechanics.

the temporal evolution of both the biomechanical state variables and the zero-dimensional hemodynamic indicators confirms that the full 3D electromechanical model successfully reproduces a physiological cardiac cycle.

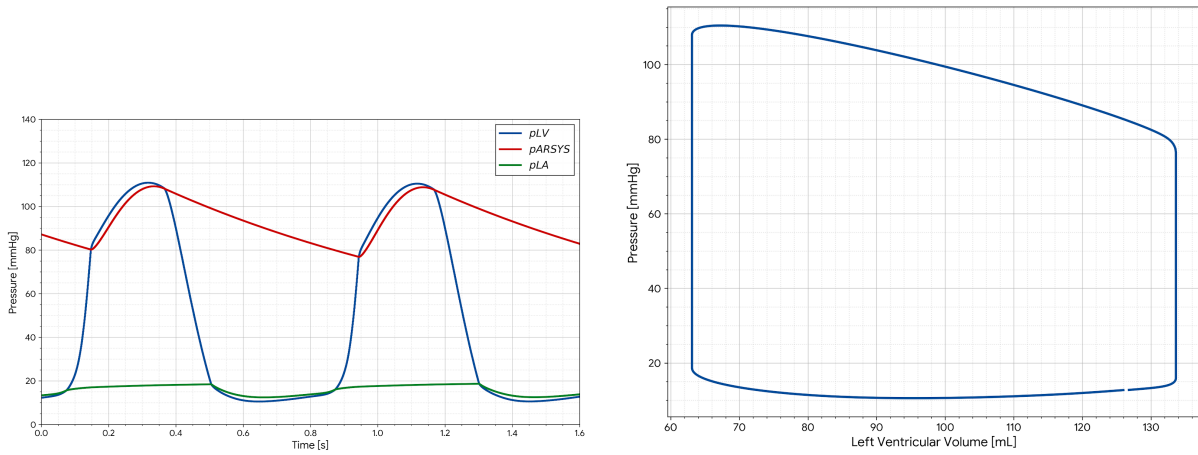


Figure 4.2: Left ventricle (p_{LV}), systemic arteries (p_{AR}^{SYS}) and atrium (p_{LA}) pressures in the last two heartbeats (left), and pressure-volume loop in left ventricle (right).

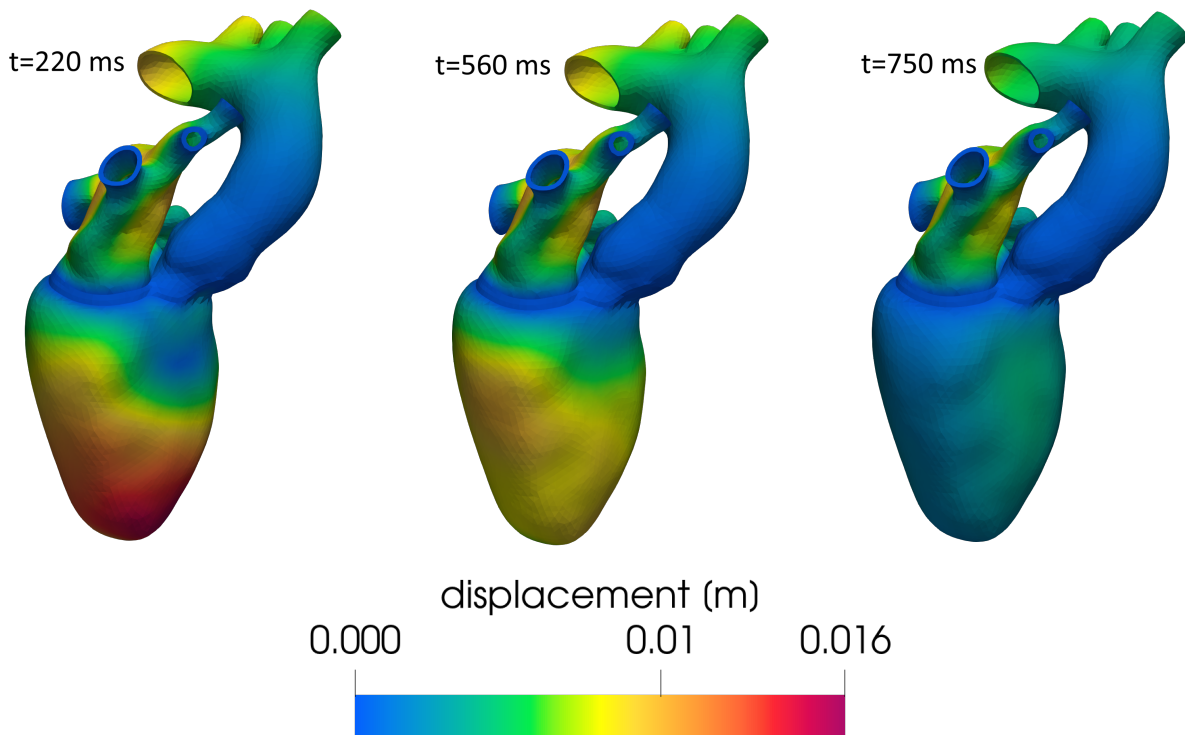


Figure 4.3: Evolution over time of displacement field

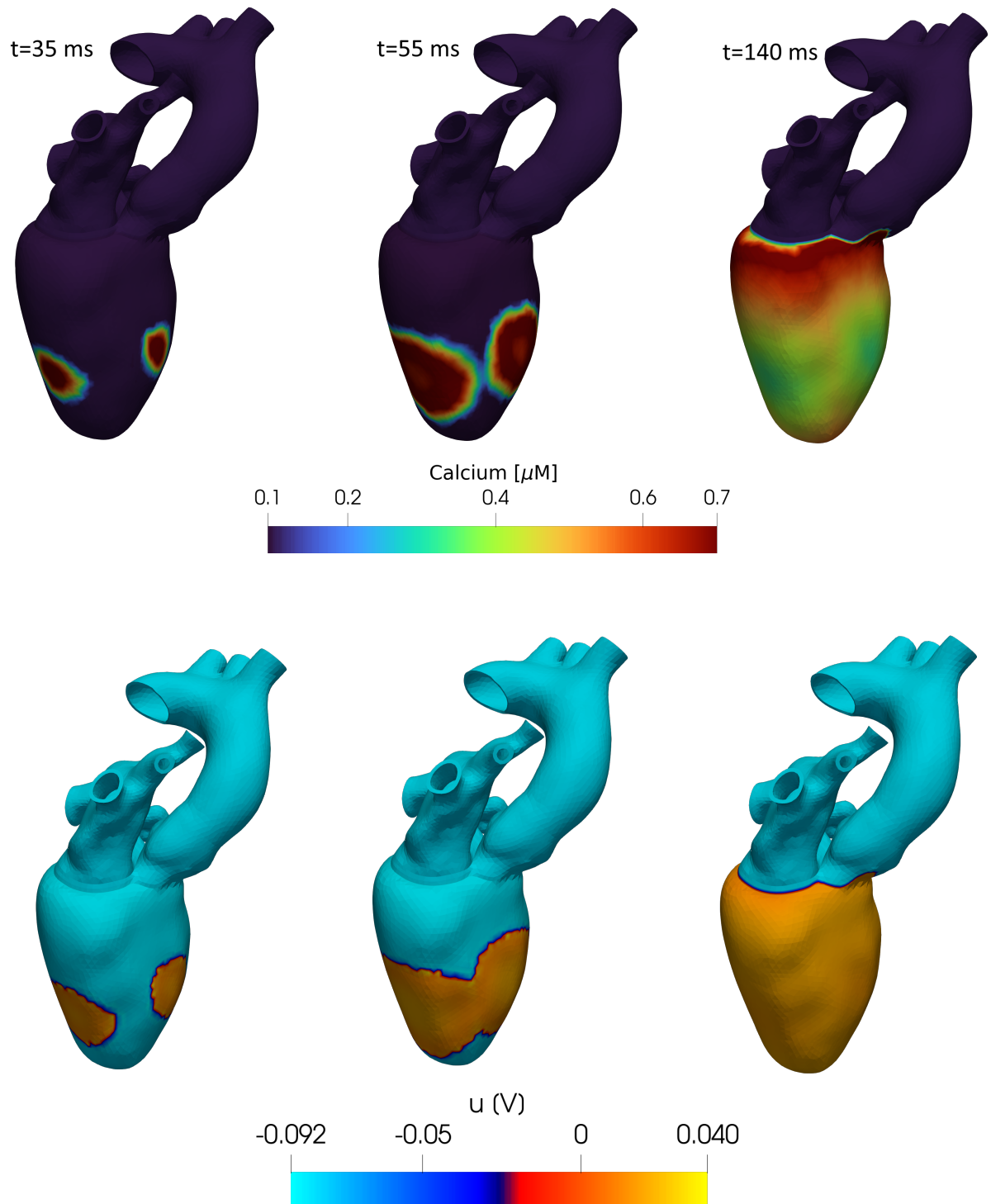


Figure 4.4: Propagation of calcium concentration (top) and action potential (bottom) in left ventricle

4.2. Idealized Geometry

We begin our analysis by presenting several tests conducted in an idealized geometry that represents two coronary branches that feed into two myocardial perfusion regions. This geometry is illustrated in Figure 4.5a. The Navier-Stokes mesh consists of 21,566 tetrahedra, 9,288 triangles, and 6,144 nodes, while the Darcy mesh comprises 50,000 hexahedra, 9,250 quadrangles, and 54,756 nodes. The inlet and outlet surfaces of the fluid domain both have a diameter of 1 mm, and the main and secondary branches are approximately 2 cm long. In this domain, the fluid dynamics problem is simplified compared to the one presented in Section 2.2. Indeed, in this geometry there are no valves, hence the RIIS term in Eq. (2.20) vanishes, as well as the ALE velocity since the domain is fixed. The resulting Navier-Stokes problem can be written as follows:

$$\begin{cases} \rho_f \left[\frac{\partial \mathbf{u}^f}{\partial t} + (\mathbf{u}^f \cdot \nabla) \mathbf{u}^f \right] - \nabla \cdot \sigma_f(\mathbf{u}^f, p^f) = \mathbf{0} & \text{in } \Omega_{\text{id}}^f \times (0, T], \\ \nabla \cdot \mathbf{u}^f = 0 & \text{in } \Omega_{\text{id}}^f \times (0, T], \end{cases} \quad (4.1)$$

with the condition defined in Eq. (2.22) imposed at the inlet section, no slip conditions on bifurcation walls, and the Robin coupling conditions defined in Eq. (2.40) at the two outlet sections.

The Darcy domain, which we denote with Ω_{id}^P , is divided into two perfusion regions (one for each coronary outlet), each with 2×2 cm faces and a depth of 1 cm, as shown in Figure 4.5b. In this domain the perfusion problem defined in Eq. (2.32) is solved, with the epicardium represented by the face where the fluid domain branches enter, and the endocardium is represented by the opposite face.

The subsequent tests were performed by keeping the parameters of the upper region fixed while varying the length densities (Eq. (2.48)) and constitutive curves (Eq. (2.46), (2.47)) of the bottom region. This approach allowed us to evaluate the effects of different modeling choices at a relatively low computational cost.

First, we detail the results of a baseline simulation, performed using the calibration presented in [39] and enriched with the transmural modulation of the length density, as defined in Eq. (2.41). As detailed above, the inlet Neumann boundary condition (2.22) was prescribed to impose the aortic pressure obtained from the last heartbeat of the electromechanical simulation.

As shown in Figure 4.6, the adopted model accurately captures the phasic nature of coronary blood flow, exhibiting strong flow during the diastolic phase and near-zero flow at the systolic peak.

An additional finding observed in this simplified test is the physiological accuracy of the

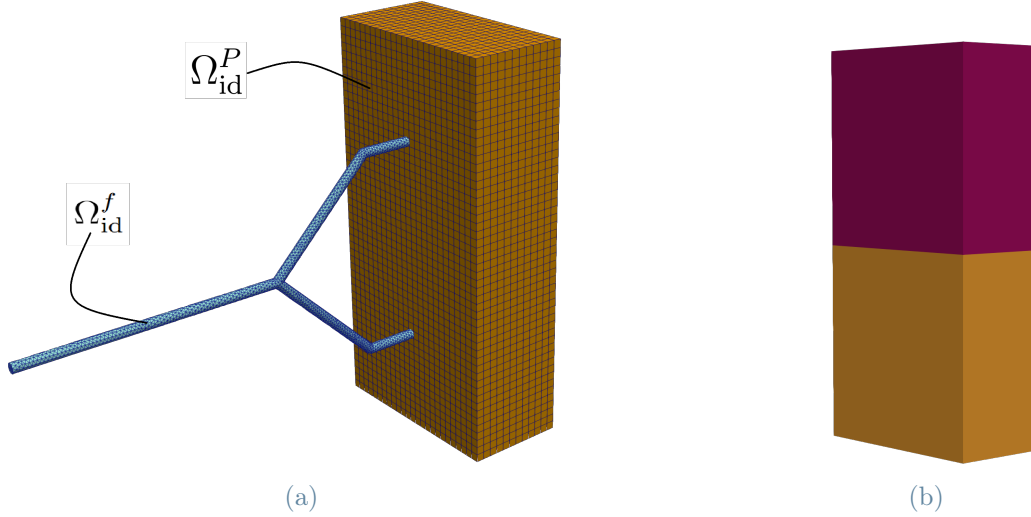


Figure 4.5: (a) Computational meshes of the idealized geometry: the Navier-Stokes mesh is shown in light blue, and the Darcy mesh in orange. (b) Subdivision of the Darcy domain into two distinct perfusion regions.

subendocardial and subepicardial Myocardial Blood Flow (MBF) trends, as reported in Figure 4.7. The subendocardial regions experience substantial oscillations in blood supply, characterized by high peaks during the diastolic phase and deep minima at the systolic peak. In contrast, the subepicardial capillary flow exhibits relatively minor variations between the diastolic and systolic phases.

We then performed a series of distinct simulations. Figure 4.8a illustrates the effects of four different endocardial factor selections for the Laplace problem (2.48). We simulated a vascular rarefaction phenomenon by progressively decreasing the subendocardial length density by up to 30%, while maintaining the 0.85 factor in the subepicardium. This led to a flow reduction predominantly during early diastole; during systole, the variation is less pronounced, as the length density also affects the compliance term defined in Eq. (2.31), resulting in a balance of opposing contributions.

A deeper decrease is observed in Figure 4.8b, where different modulations of the constitutive curves for the average areas of arterioles (Eq. (2.46)) and capillaries (Eq. (2.47)) in the pathologic region were tested. We progressively decreased the lumen area by up to 40%, which drove the average endocardial MBF below the physiological threshold, considered to be between 1.7 and 2.0 mL/min/g (corresponding to 178.5 and 210 mL/min/100 mL) [49, 57]. As expected, the severity of the pathological condition exhibits a transmural

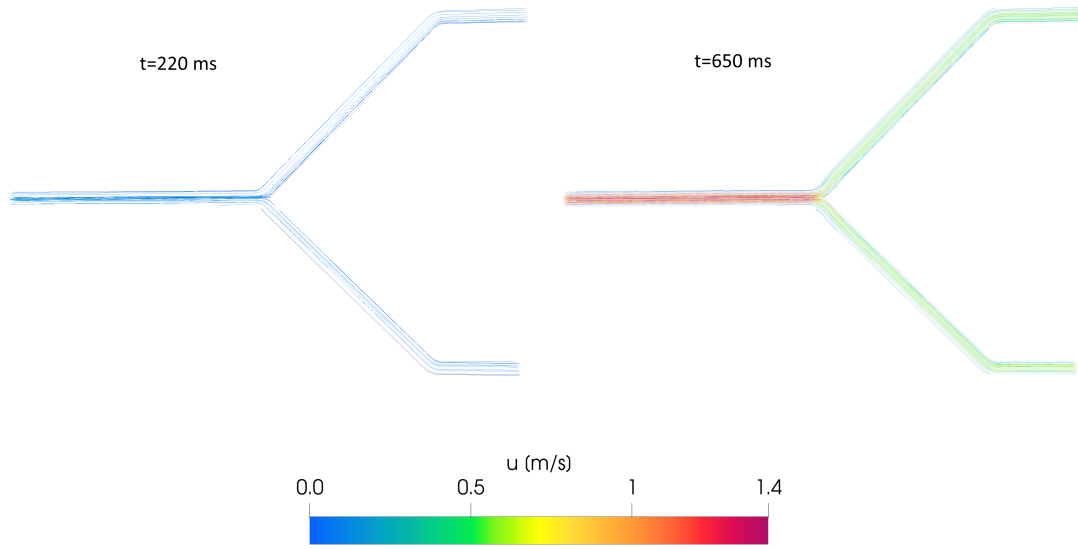
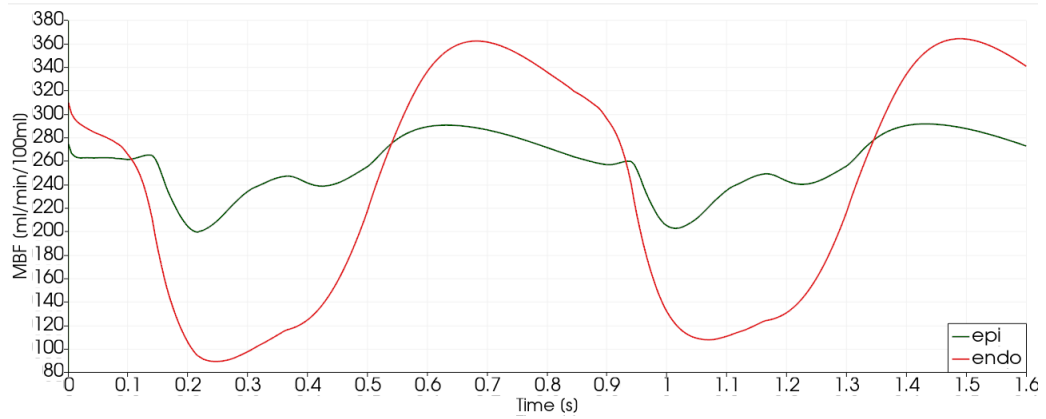
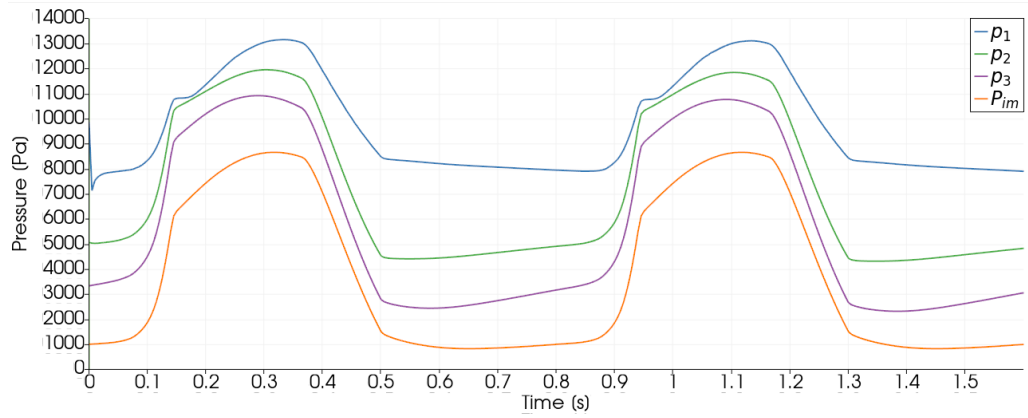


Figure 4.6: Comparison between diastolic and systolic flows in the idealized bifurcation geometry

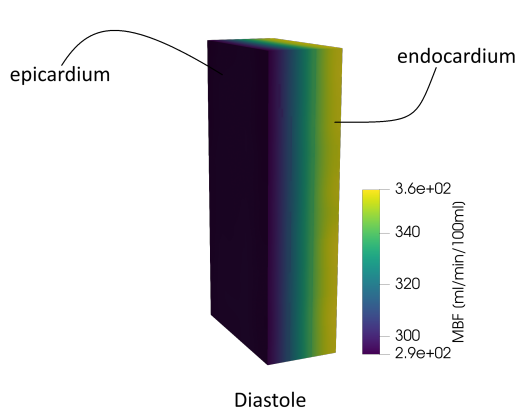
gradient, evidenced by a reduced but still physiological flow in the subepicardial region.



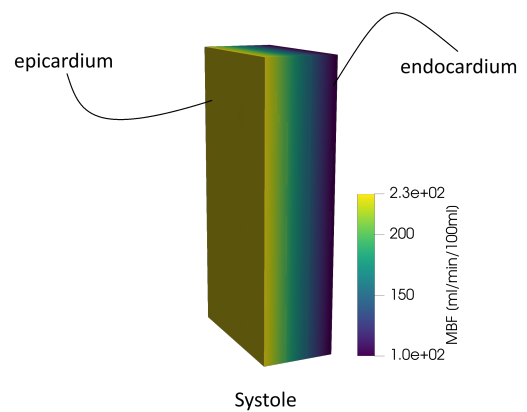
(a)



(b)



(c)



(d)

Figure 4.7: Results of baseline simulation on idealized geometry. Comparison between endocardial and epicardial MBF (a), pressures in the three Darcy compartments and intramyocardial pressure (b), diastolic MBF distribution (c), systolic MBF distribution (d).

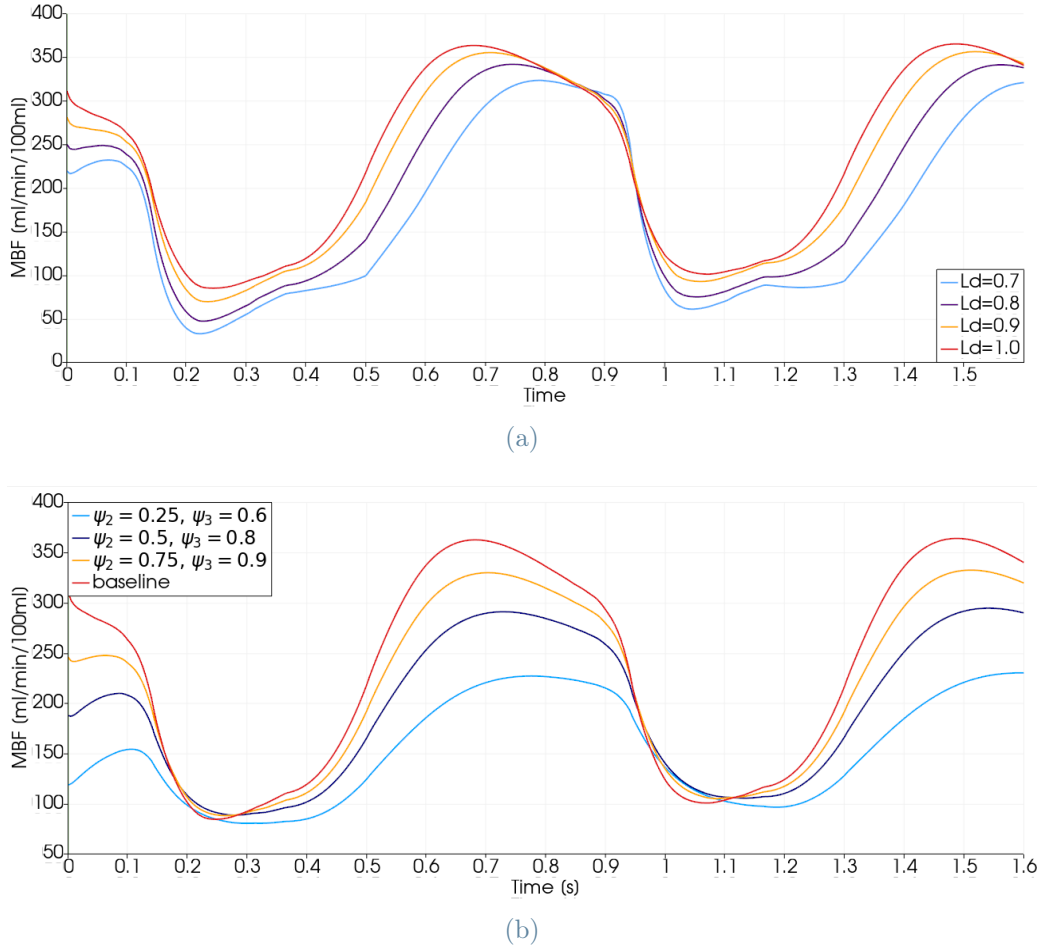


Figure 4.8: Effects on endocardial MBF of variations of length density (a) and average areas (b)

To conclude, we performed four additional tests combining the variations in both length densities and average areas. As expected, the more pronounced reduction occurs in the subendocardium where the average MBF drops from the value of 239.22 mL/min/100 mL towards 106.73 mL/min/100 mL in the worst scenario evaluated, where we set $\psi_2 = 0.25$, $\psi_3 = 0.6$ and $\delta_{CMD} = 0.3$, defining a severe pathological condition. In the midmyocardium the value observed is 147.41 mL/min/100 mL, while the subepicardium registered a drop from 260.97 mL/min/100 mL to the value of 196.78 mL/min/100 mL. These differences in flow reduction lead to a drop of the perfusion ratio from 0.92 to 0.54, suggesting a strong transmural gradient of CMD severity. An interesting phenomenon observed is the systolic flow reversal in the branch that perfuses the pathologic region (Figure 4.9), which is considered to be a hemodynamic marker of a dysfunctional microcirculation [37]. Quantitative analysis of the simulated fluid dynamics confirms this behavior at the pathologic boundary, where the flow rate transiently drops below zero during the early systolic phase. Specifically, the peak retrograde flow rate recorded is $5.06 \times 10^{-8} \text{ m}^3/\text{s}$ (approximately

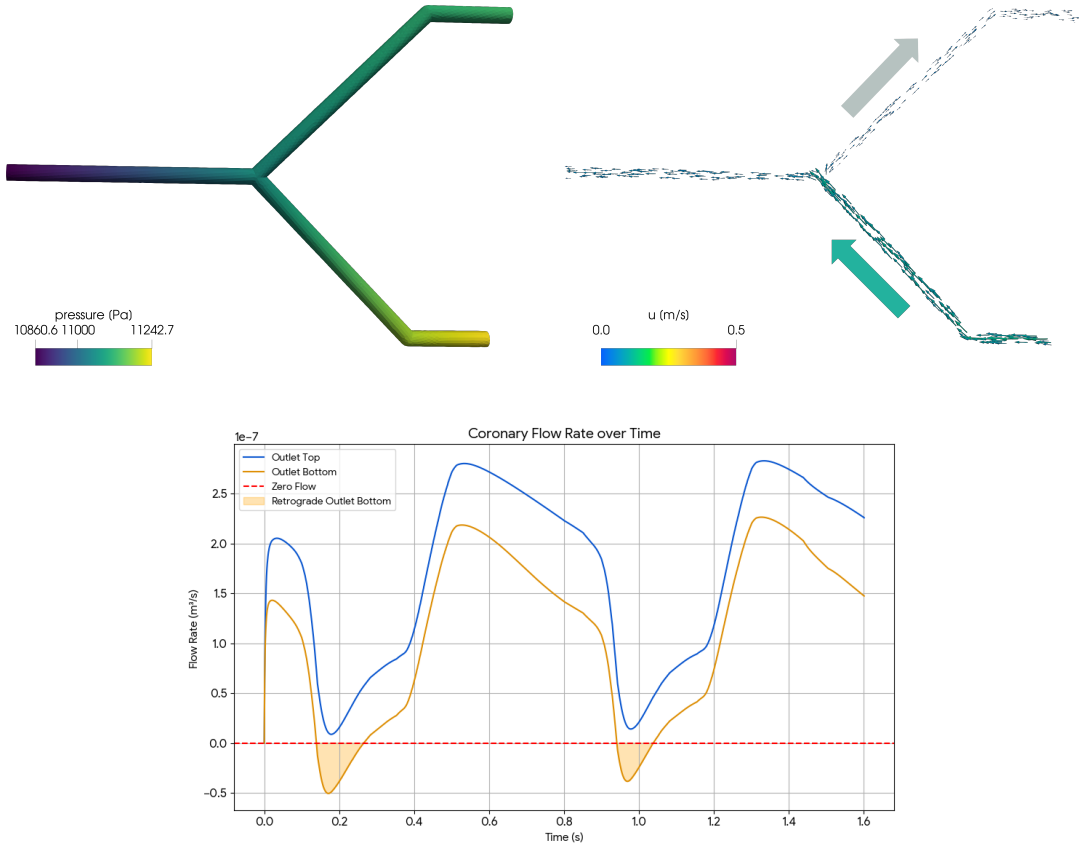


Figure 4.9: Pressure gradient inversion (top-left) and retrograde flow (top-right) due to high distal resistance in pathological region. Quantification of flow rate in the two outlets in presence of retrograde flow (bottom).

0.051 mL/s). Furthermore, the total regurgitant volume during this systolic window was calculated to be $5.92 \times 10^{-9} \text{ m}^3$ (equivalent to $\approx 5.9 \mu\text{L}$). These measurements corroborate the presence of a severe downstream microvascular resistance.

4.3. Realistic Geometry

We finally translated the observations onto the realistic human heart geometry. Both computational meshes adopted for the Navier-Stokes and Darcy problems are tetrahedral. The fluid mesh is made of 566,927 tetrahedra, 85,982 triangles, and 113,704 DOFs (Figure 4.10a), while the Darcy mesh consists of 153,587 tetrahedra, 24,358 triangles, and 30,648 nodes (Figure 4.10b).

The subdivision of the myocardium into perfusion regions is performed according to the methodology presented in [13]. This procedure assumes a one-to-one correspondence be-

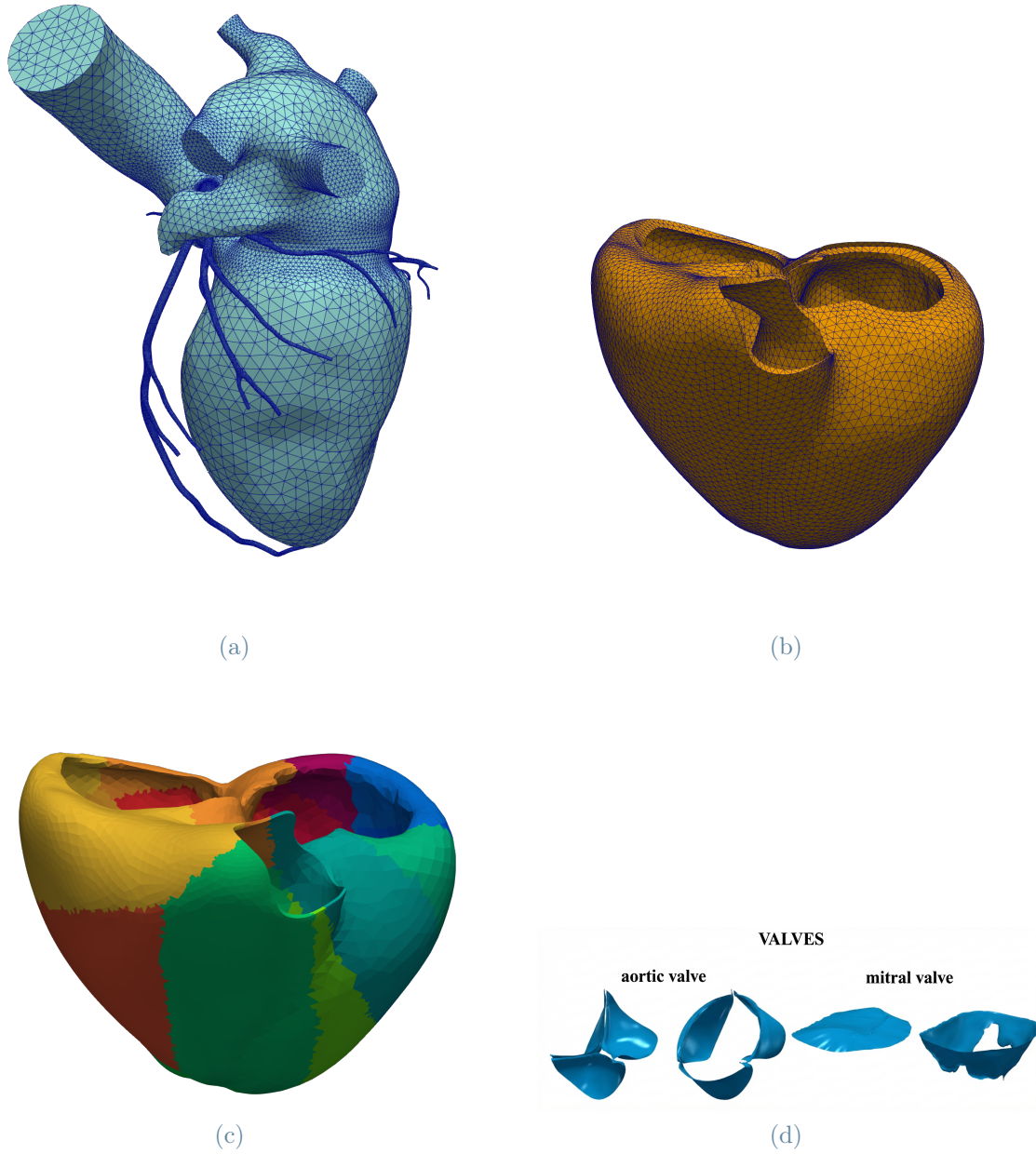


Figure 4.10: Computational meshes for fluid dynamics (a) and perfusion (b) problems, myocardial subdivision into perfusion regions (c), and aortic and mitral valves in open and closed configurations (image taken from [63]) (d).

tween perfusion regions and coronary outlets, constructing the regions such that a generic point P in the myocardium belongs to the perfusion region Ω_j^P if the epicardial outlet Γ_j is its closest section. It is necessary to clarify that the coronary reconstruction used here presents only 17 coronary outlets. This number is insufficient to accurately perfuse the entire biventricular myocardium and leads to the generation of excessively large perfusion regions, which directly affects the source term of the first Darcy compartment (Eq. (2.26)). Since our focus is to analyze the modeling choices adopted for CMD pathology, we artificially reduced the volume of the largest perfusion regions to obtain more realistic source terms. We believe that a more precise coronary reconstruction, in particular in the septal region where the lack of perfusing vessels was more evident, would be necessary to accurately reproduce realistic flows.

4.3.1. Baseline Simulation

We first perform a baseline simulation where parameters are calibrated to reproduce physiological flows. We first project the displacement field of the electromechanical simulation on the fluid domain, extracting the wall velocity and displacement at each timestep. We then synchronize the opening and closure of cardiac valves to coincide with the times where intraventricular, atrial and systemic pressures intersect each other. In particular, we impose the opening and closure of aortic valve based on the intersections between p_{LV} and p_{AR}^{SYS} , and the timings of the mitral valve are imposed on the basis of p_{LV} and p_{LA} values. For both aortic and mitral valves we adopt a specific resistance coefficient $R_k = 10^4 \text{ kg}/(\text{m} \cdot \text{s})$ and a half-thickness of the valves leaflets $\epsilon_k = 2 \cdot 10^{-3} \text{ m}$. We remark that, since the ratio $\frac{R_k}{\epsilon_k}$ influences the condition number of the linear system associated with the discretization of the fluid problem, this choice must be reasonable to avoid unnecessary increase in computational cost. The coefficients α_k for the Robin coupling condition (Eq. (2.40)) and all the parameters adopted in the Darcy model are listed in Table B.1 and Table B.2 of Appendix B, respectively.

We simulate two heartbeats of period 0.8 s, adopting a timestep of $\Delta t = 10^{-3} \text{ s}$, and considering the results of the second cycle to mitigate the effect of initial conditions.

Regarding fluid dynamics results, during the systolic phase we observe results consistent with electromechanics, with a stroke volume of 52.8% and a peak flow through the aortic valve of 575.97 mL/s. During the diastolic phase, the model accurately reproduces the ventricular filling mechanism. The flow across the mitral valve, dynamically regulated by the RIIS opening coefficient, exhibits an influx with peak flow rates reaching approximately 323.5 mL/s. The atrial filling dynamics demonstrate a consistent accumu-

lation phase characterized by a peak inflow rate of 106.5 mL/s during ventricular systole, correctly highlighting the reservoir function of the left atrium. These combined metrics, that we illustrate in Figure 4.11, confirm the structural and functional reliability of the model in describing the cyclic mass transfer from the pulmonary inlets, through the mitral apparatus, and into the ventricular chamber.

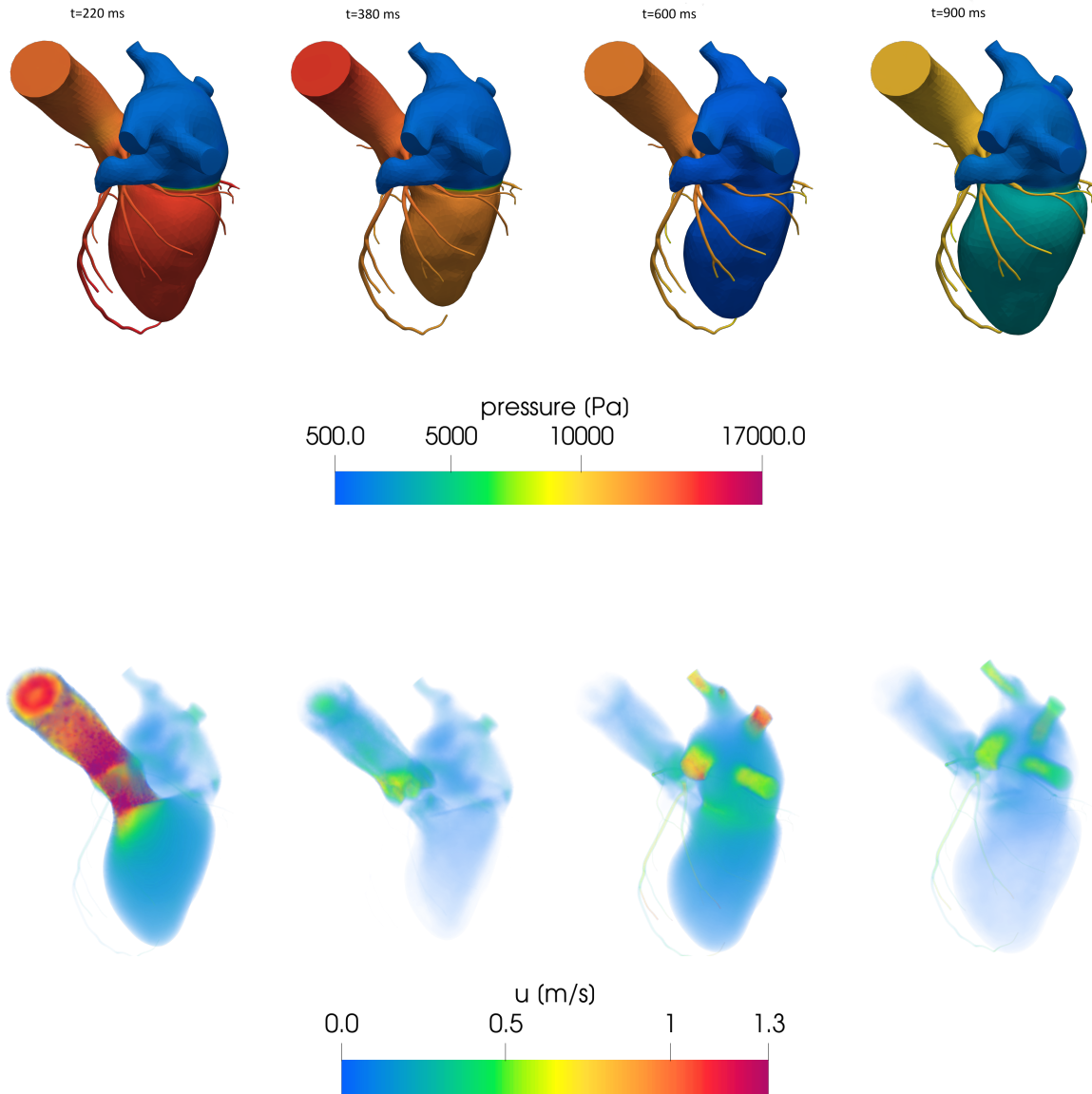


Figure 4.11: Temporal evolution of hemodynamics variables in a heartbeat, from early systole to late diastole. Top: pressure evolution. Bottom: velocity magnitude evolution

Also in this realistic geometry we observe systolic pressure inversion (visible in the left panel of Figure 4.12), driven by the rise in intramyocardial pressure (P_{im}). This mechanical compression acts on the microvasculature, drastically increasing the distal

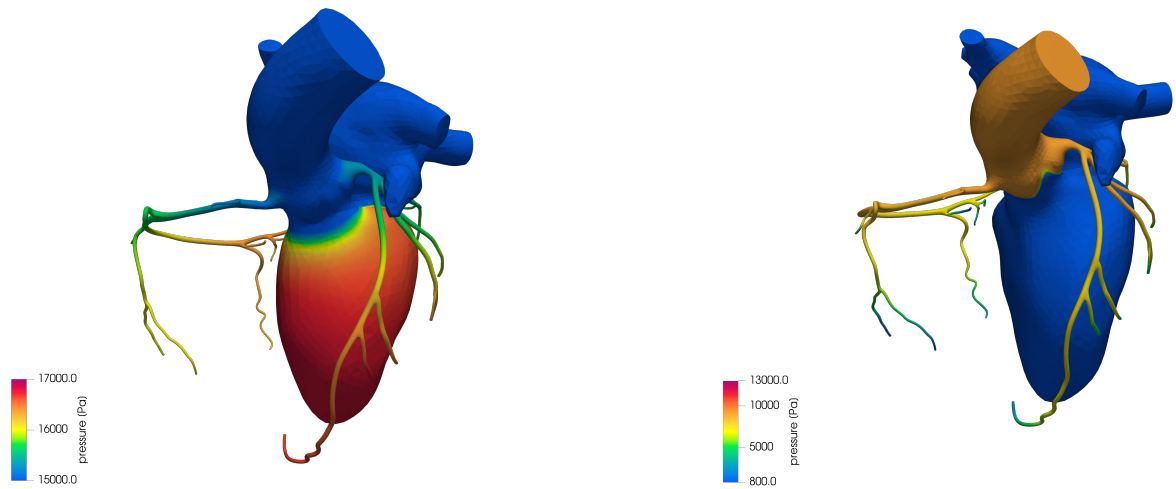


Figure 4.12: Comparison between pressure gradient in coronary arteries in systolic and diastolic phase. We remark that at the systolic time considered (left) the pressure gradient is inverted.

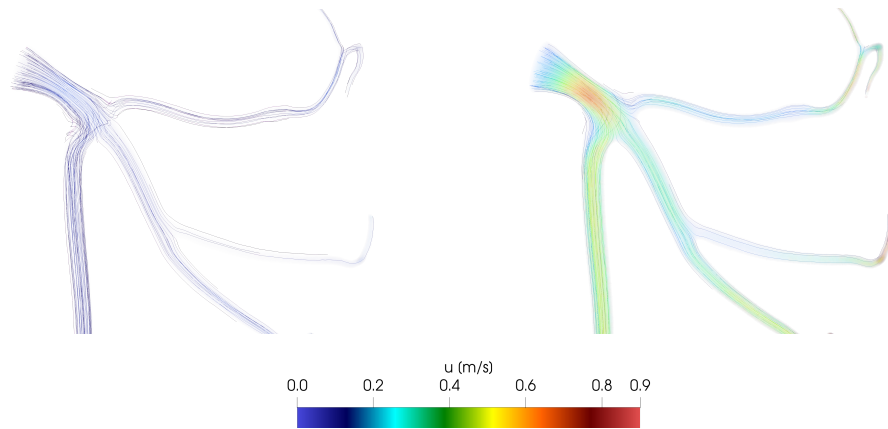


Figure 4.13: Comparison between systolic (left) and diastolic (right) flows in the left coronary artery.

resistance and causing a temporary impedance of the flow in the penetrating branches, which in this case does not result in flow reversal due to inertial forces. Conversely, during the diastolic phase (Figure 4.13, right), the relaxation of the myocardial muscle relieves this external compression. The distal resistance drops, allowing the coronary flow to reach its physiological peak and ensuring adequate perfusion of the ventricular wall.

4.3.2. Myocardial Perfusion and Microvascular Dysfunction

We now shift our focus to the microcirculatory scale to analyze the myocardial blood flow and evaluate the impact of pathological structural variations. As previously demonstrated in the idealized geometry, the compliant multicompartment Darcy model allows us to assess the transmural distribution of perfusion across the myocardial wall.

Our analysis will primarily focus on the left ventricle. Accurately modeling right ventricular perfusion would require adopting a side-specific intramyocardial pressure to account for the lower pressures developed in the right ventricle during systole.

The physiological myocardial blood flow is presented in Figure 4.14, highlighting a remarkable difference in the endocardium between diastolic and systolic MBF.

Next, we scale the average area constitutive curves of perfusion regions 6 and 7 (Figure 4.15), along with the endocardial length densities in the last two Darcy compartments, using the factors reported in Table 4.1. It is worth noting that scaling by the factor ψ_2 in Eq. (2.46) requires recalibrating the parameter d_2^+ to ensure C^1 continuity of the constitutive curve.

Tests	ψ_2	ψ_3	δ_{CMD}
Baseline	1.0	1.0	0.0
Test 1	0.75	0.875	0.1
Test 2	0.5	0.7	0.2
Test 3	0.25	0.6	0.3

Table 4.1: Values of constitutive curves scaling coefficients (ψ_2, ψ_3) and degree of capillary rarefaction δ_{CMD}

The MBF is spatially averaged within each perfusion region and temporally averaged over the last simulated heartbeat, to mitigate the influence of initial conditions. The results are reported in Figure 4.16. The average MBF in the analyzed regions begins at physiological baseline values and gradually decreases below the threshold of 170 mL/min/100 mL. Since this is a regional average, it inherently encompasses both endocardial and epicardial values. To accurately assess the severity of the pathological condition, the analysis must be stratified by myocardial layer, consistent with the approach used for the idealized geometry. We focus particularly on the endocardial layer, where pathological effects are most pronounced.

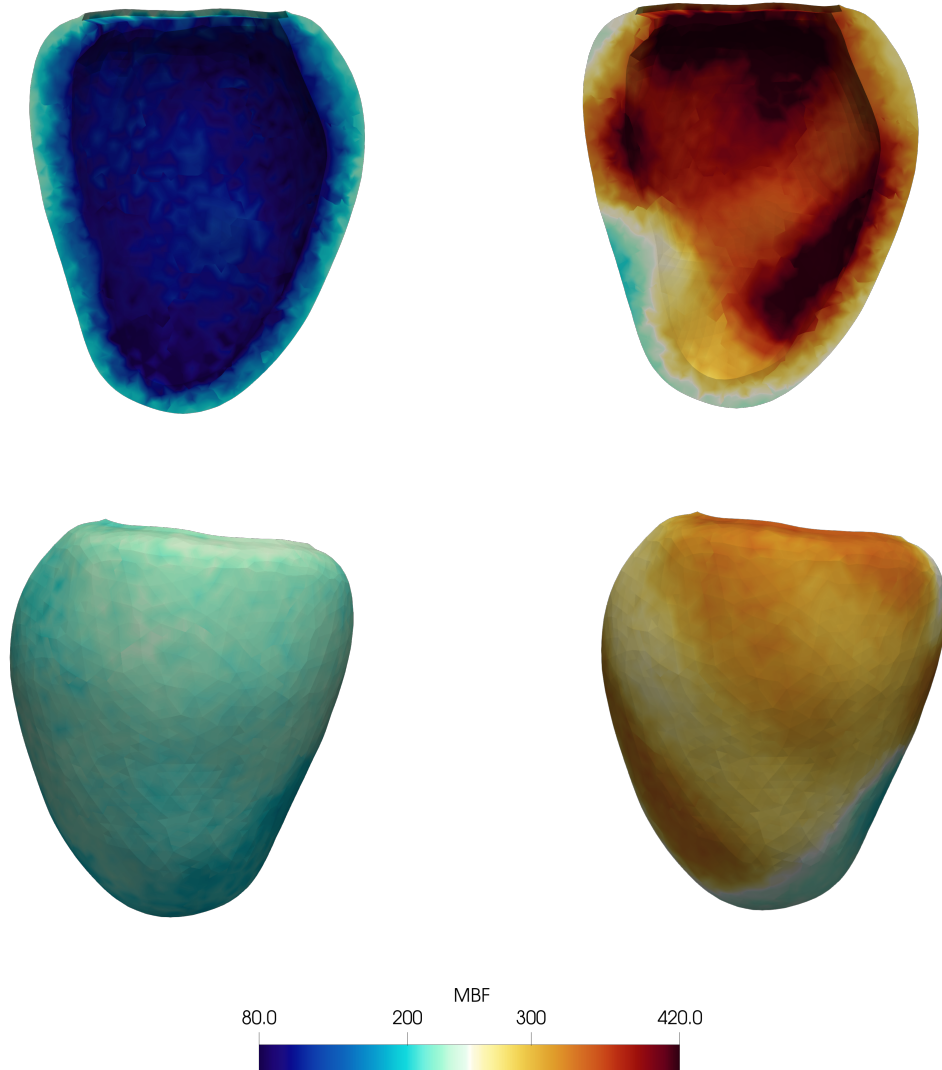


Figure 4.14: MBF in part of the left ventricle at systolic peak (left) and mid-diastole (right), in endocardium (top) and epicardium (bottom)

A fundamental biomarker for CMD assessment is the Coronary Flow Reserve (CFR), defined as the ratio between hyperemic and resting flows (Eq. (1.1)), which directly reflects the microvascular capacity to respond to increased oxygen demand. Clinical studies using PET report an average CFR of 3.74 ± 1.00 [24]. To evaluate the CFR in our tests, we estimate the resting flow by dividing the baseline endocardial MBF (computed as the temporal average over a single heartbeat at a specific probe location) by this physiological factor of 3.74. We then also compare the resulting value with literature estimates of average resting MBF, which are approximately 0.62 ± 0.13 mL/min/g (or 65.10 ± 13.65 mL/min/100 mL) [6]. A CFR value below 2.5 is considered the clinical hallmark of defective microvasculature [32, 61, 64].

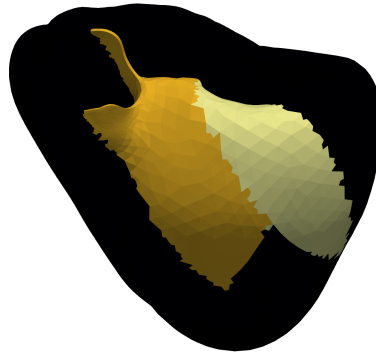


Figure 4.15: Perfusion regions 6 (left) and 7 (right).

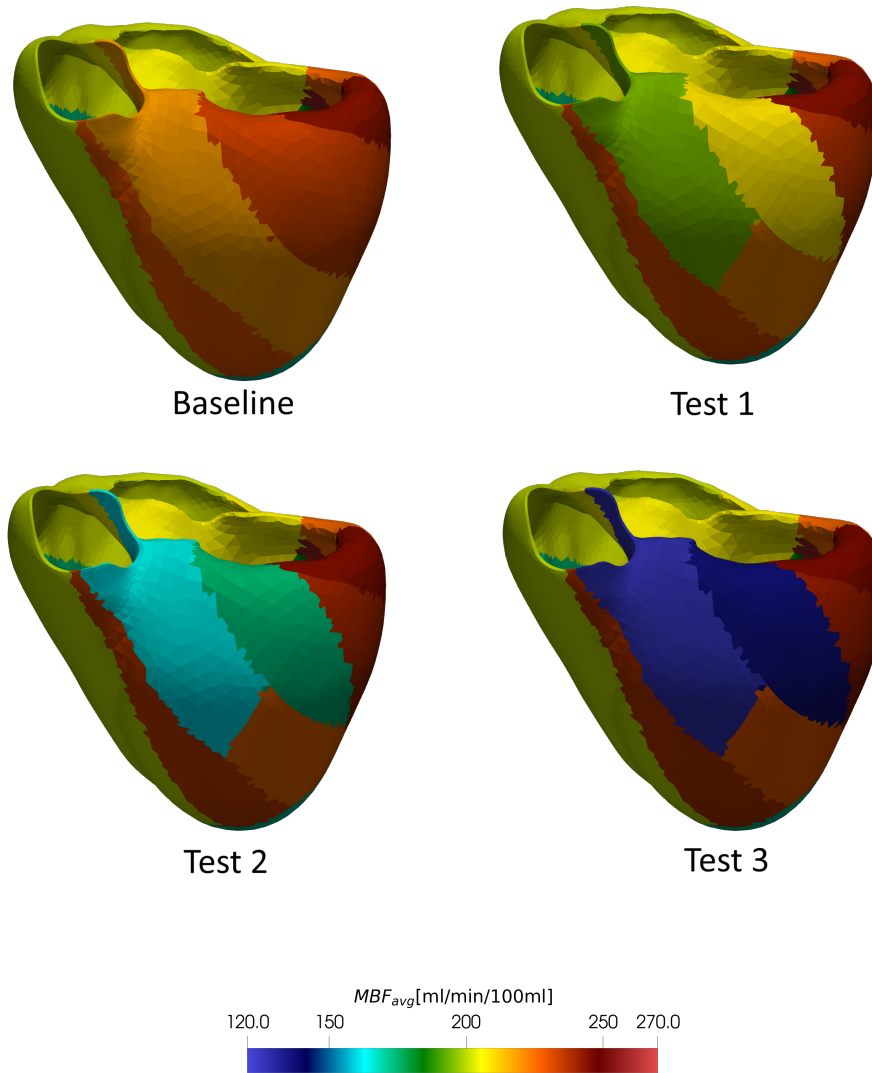


Figure 4.16: Average MBF per perfusion region in the cases considered: baseline (top-left), test 1 (top-right), test 2 (bottom-left), test 3 (bottom-right).

Region 6	$\text{MBF}_{\text{endo}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	$\text{MBF}_{\text{epi}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	PR	CFR
Baseline	224.07	240.96	0.93	3.74
Test 1	198.75	226.82	0.88	3.31
Test 2	159.14	207.05	0.77	2.65
Test 3	108.85	176.15	0.61	1.81

Table 4.2: Results in region 6.

Region 7	$\text{MBF}_{\text{endo}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	$\text{MBF}_{\text{epi}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	PR	CFR
Baseline	268.13	274.74	0.98	3.74
Test 1	225.19	259.20	0.87	3.14
Test 2	175.90	229.17	0.77	2.45
Test 3	124.54	189.86	0.65	1.73

Table 4.3: Results in region 7.

In the baseline simulation, the measured endocardial MBF was 224.07 mL/min/100 mL in region 6 and 268.13 mL/min/100 mL in region 7. The corresponding epicardial values were 240.96 mL/min/100 mL and 274.74 mL/min/100 mL, resulting in endocardial-to-epicardial perfusion ratios of 0.93 and 0.98 for regions 6 and 7, respectively. Applying the aforementioned physiological CFR factor of 3.74 to our baseline hyperemic results yields the estimated resting endocardial MBF. This calculation results in resting values of 59.91 mL/min/100 mL for region 6 and 71.69 mL/min/100 mL for region 7, consistent with the physiological range [51.45, 78.75] introduced above.

To assess the severity of pathological conditions comparing the results obtained with the biomarkers provided by clinical literature (time averaged MBF, CFR, Perfusion Ratio (PR)) we took four probe points in the myocardium, two for each perfusion region analyzed, one in the subendocardium, one in the subepicardium. We evaluated the average MBF in each probe location in the second heartbeat. The results are reported in Tables 4.2 and 4.3.

We can observe that there is a gradual drop in every analyzed biomarker as the severity of the simulated coronary microvascular dysfunction increases from Test 1 to Test 3. The reduction in Myocardial Blood Flow is not uniform across the myocardial wall. The subendocardial layer (MBF_{endo}) exhibits a significantly steeper decline compared to the subepicardial layer (MBF_{epi}), as also shown in Figure 4.17. This disproportionate impairment is clearly captured by the perfusion ratio, which drops progressively from physiological baseline values to severely ischemic values in Test 3. This result aligns per-

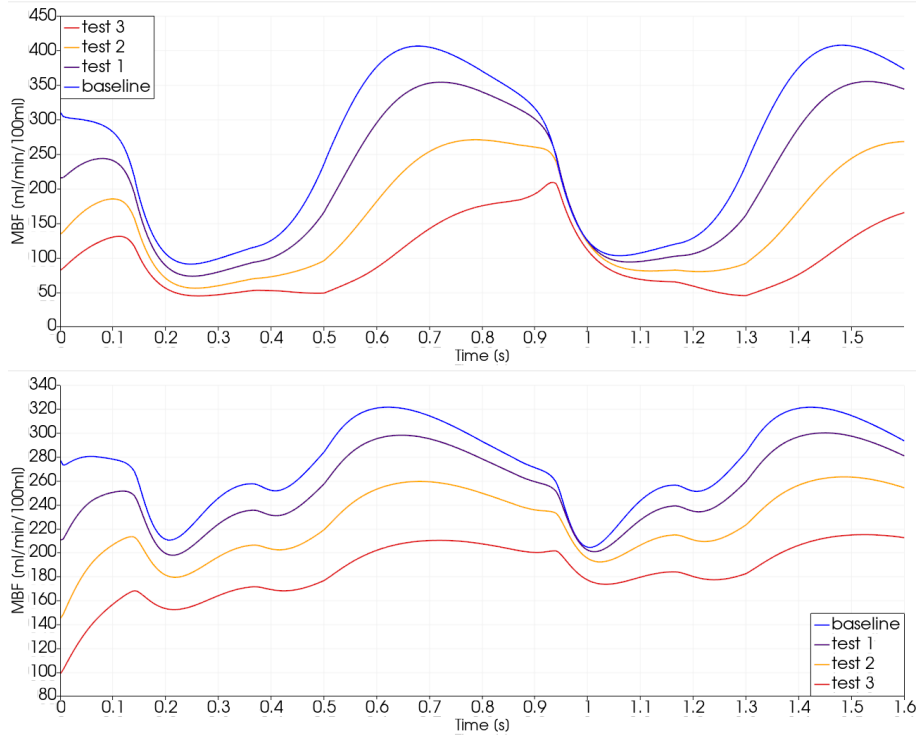


Figure 4.17: MBF over time in the different tests performed measured in probe locations of region 7: subendocardium on the left, subepicardium on the right.

fectly with the phenomenon of subendocardial vulnerability to ischemia, primarily driven by the higher compressive forces acting on the inner layers of the ventricle during the systolic phase.

Furthermore, evaluating the CFR provides a direct clinical framing of our numerical tests. Considering the threshold of 2.5 as the hallmark for microvascular disease, Test 1 represents a mild, yet non-pathological, structural alteration. Test 2 depicts a moderate-to-severe dysfunction: Region 7 already crosses the clinical threshold dropping to a pathological CFR of 2.45, while Region 6 borders it with a value of 2.65. Finally, Test 3 simulates a condition of severe microvascular rarefaction and dysfunction. In this scenario, both regions exhibit CFR values (1.81 and 1.73) well below the pathological limit, accompanied by a substantially impaired baseline-to-hyperemia flow adaptability and severe subendocardial hypoperfusion.

The severe pathological condition of test 3 is also confirmed by observing macroscopic hemodynamic results. Indeed, as observed in the idealized geometry, the strong increase in distal resistance, with consequent pressure increase and weaker flow, leads to the rise of systolic flow reversal in the branch perfusing the pathological region, as shown in Figure 4.18.

We finally discuss a sensitivity analysis of the parameters involved in the modeling of

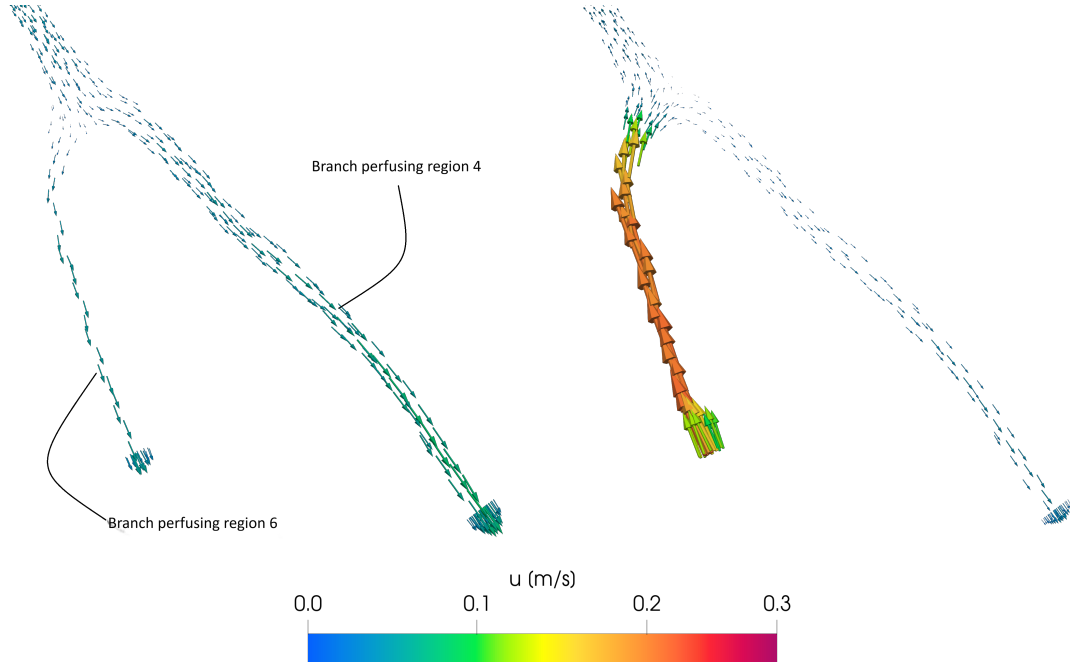


Figure 4.18: Retrograde flow in branch perfusing the pathologic region 6. Comparison between baseline simulation (left) and test 3 (right)

CMD. Regarding the effects of length density variations on MBF, we refer to the work of Pelagi et al. [39]. To analyze the impact of different modulations of the constitutive curves, we performed a series of simulations systematically varying the scaling parameter ψ_2 with length density and ψ_3 fixed to baseline values, and subsequently we varied ψ_3 keeping length density and ψ_2 fixed to baseline values. The results are reported in Table 4.4 and 4.5, respectively.

We then conducted a regression analysis to evaluate their correlation with the MBF, finding an excellent fit with the exponential trends illustrated in Figure 4.19. Specifically, this analysis was performed for both the localized MBF extracted at an endocardial probe location and the spatially averaged MBF within region 7.

We observe that a reduction in ψ_2 induces a similar decrease in both the regionally averaged MBF and the localized endocardial MBF. This uniform impairment is driven by the hydraulic bottleneck introduced in the second compartment. By drastically increasing its local resistance, the flow restriction limits blood supply to the downstream capillary bed regardless of the transmural depth. Conversely, increasing ψ_2 beyond a value of 1 yields a substantially larger increase in the regional MBF compared to the localized endocardial MBF, which could be due to the fact that diastolic flow in the endocardium is more prone to encounter a saturation phenomenon, being already particularly high in this layer. On the other hand, when reducing the capillary area (via ψ_3), the flow

ψ_2	$\text{MBF}_{\text{endo}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	$\text{MBF}_{\text{avg}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$
1.5	276.39	287.27
1.0	268.13	268.09
0.75	253.84	253.47
0.5	234.22	233.52
0.25	209.49	206.04

Table 4.4: Simulations results for different values of the parameter ψ_2 keeping length density and ψ_3 fixed to baseline values.

ψ_3	$\text{MBF}_{\text{endo}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$	$\text{MBF}_{\text{avg}} \left[\frac{\text{mL/min}}{100 \text{ mL}} \right]$
1.5	277.15	287.79
1.0	268.13	268.09
0.75	239.75	246.04
0.6	213.43	223.28
0.45	169.37	186.94

Table 4.5: Simulations results for different values of the parameter ψ_3 keeping length density and ψ_2 fixed to baseline values.

reduction is more pronounced in the endocardium. This occurs because the local response to an increased microvascular resistance in this specific compartment is a further drop in the distal diastolic pressure p_3 . This pressure reduction lowers the transmural pressure gradient, rendering the subendocardial vessels far less capable of counteracting the severe external myocardial compression during the cardiac cycle.

In summary, the proposed computational framework successfully bridges the macroscopic epicardial hemodynamics with a detailed microcirculatory representation, providing a robust tool for the investigation of CMD. By progressively altering the microvascular structural parameters within the multicompartment Darcy model, we were able to replicate the pathophysiological progression of the disease in a realistic 3D ventricular geometry. The model accurately captures the deterioration of key clinical biomarkers, highlighting the critical vulnerability of the subendocardium to ischemia, as evidenced by the steep decline in both the Perfusion Ratio and the Coronary Flow Reserve. Furthermore, the emergence of macroscopic phenomena, such as the systolic flow reversal in severely compromised regions, demonstrates the complex interplay between epicardial hemodynamics and increased microvascular resistance.

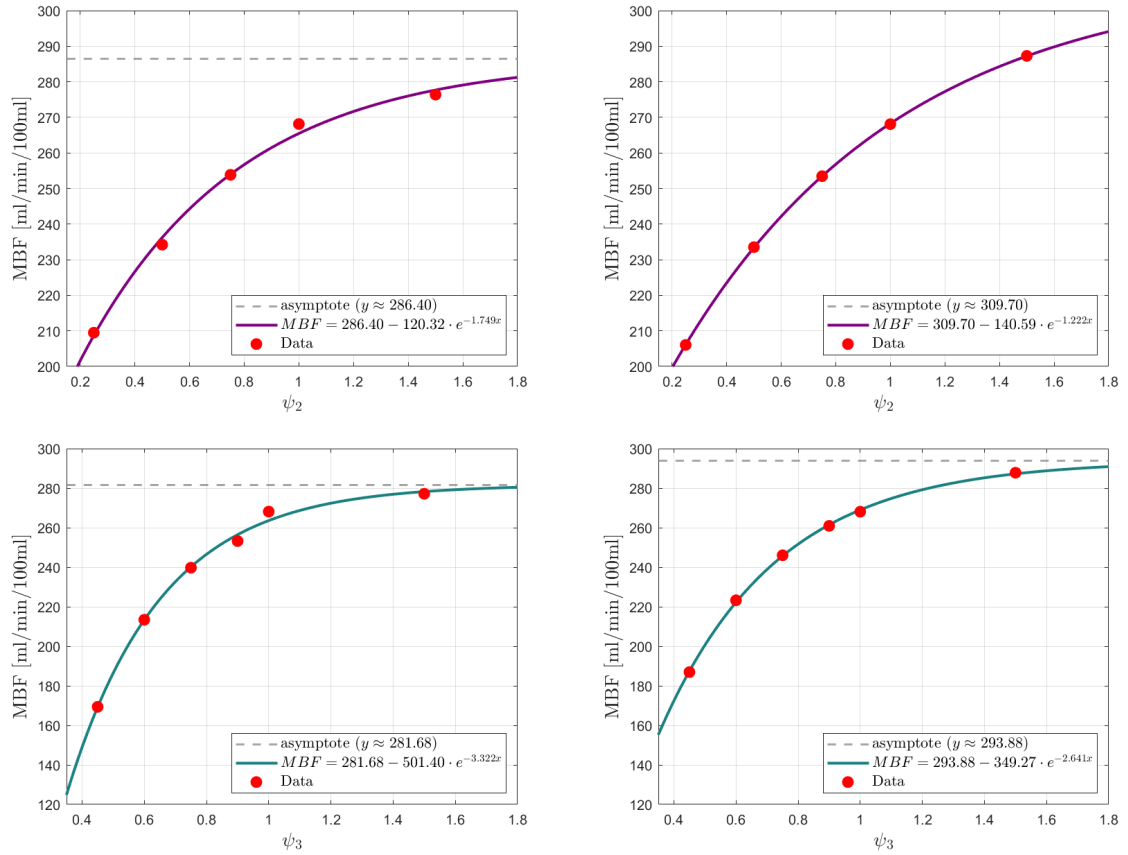


Figure 4.19: Sensitivity analysis of parameters ψ_2 (top) and ψ_3 (bottom). On the left are reported regression results regarding the MBF computed in a subendocardial probe location in region 7 and averaged in time on the second heartbeat, on the right the time-averaged MBF spatially averaged over the entire region 7. Red dots represent the simulations results obtained and reported in Table 4.4 and 4.5.

5 | Conclusions

In this thesis, we computationally investigated and provided a mathematical modeling of the structural alterations that characterize Coronary Microvascular Dysfunction.

We built upon the comprehensive cardiac multiphysics and multiscale perfusion model proposed in [63], which integrates electromechanics, fluid dynamics, and perfusion. To accurately capture the effects of cardiac contraction on the microvasculature, we replaced the previously adopted porous media formulation with the compliant multicompartment Darcy model proposed in [39]. The computational framework relied on a full coupling between electromechanics and a lumped-parameter closed-loop circulation model. This provided precise boundary conditions for the hemodynamics problem via a kinematic one-way coupling condition mapping the left heart wall displacement. Subsequently, a full coupling between the Navier-Stokes equations in an ALE framework, employing the RIIS method for valve dynamics, and the compliant multicompartment Darcy model was used to simulate cardiac perfusion.

As a first step, we performed an electromechanical simulation on a realistic left heart geometry to extract the intraventricular pressure, the systemic arterial pressure, and the wall displacement necessary to drive the Navier-Stokes-Darcy model.

Starting from data collected from clinical literature, we simulated the alterations that define a defective microcirculation by acting on specific parameters of the Darcy model. In particular, we found that the most relevant structural alterations in CMD patients are capillary rarefaction, estimated to be a loss of approximately 15 – 30% in vessel volume density [9, 46], and a reduction of up to 40% in the cross-sectional area of the distal lumen [11]. We initially addressed the physiological transmural gradient of vessel volume density, which is higher in the subendocardium [52, 53], by introducing a linear scaling of the length density parameter in the last two Darcy compartments, obtained by solving a Laplace problem. Building upon this framework, we simulated capillary rarefaction by gradually reducing the endocardial scaling factor. Finally, we modeled distal vessel lumen reduction by modulating the constitutive curves of the average cross-sectional areas in the arteriolar and capillary compartments.

To assess the effects of these alterations, we first analyzed the hemodynamics in a simplified idealized geometry, which allowed us to perform extensive sensitivity tests at a

low computational cost. Subsequently, we translated these observations to a realistic 3D geometry of the left heart and biventricular myocardium.

The numerical results demonstrated the capability of the proposed multiscale model to accurately reproduce physiological coronary hemodynamics, successfully capturing the phenomenon of diastolic dominance driven by the cyclic intramyocardial compression. Furthermore, the introduction of the pathological parameters yielded a realistic representation of CMD. The simulations confirmed that microvascular structural remodeling, specifically capillary rarefaction and lumen narrowing, drastically impairs the conductive capacity of the network. As expected, the model identified the subendocardium as the myocardial layer most vulnerable to ischemia, as reported in clinical literature [12], with the MBF dropping well below physiological thresholds under severe pathological conditions [49, 57]. Additionally, the model was able to capture complex hemodynamic markers of microvascular dysfunction, such as the emergence of systolic retrograde flow in the penetrating branches [37], a reduction in the perfusion ratio, and an estimated CFR below the physiological threshold of 2.5 [61, 64]. Overall, this computational framework proved to be a robust tool for the *in silico* investigation of microcirculatory diseases.

5.1. Limitations and Future Developments

This study presents specific limitations that should be addressed in future works. As highlighted in Section 4.3, the available coronary reconstruction featured a limited number of outlets, which was insufficient to provide a highly detailed perfusion mapping. To compensate for this anatomical truncation, we artificially reduced the volume of the largest perfusion regions to prevent the excessive dilution of the Darcy source terms. While this strategy allowed us to recover more realistic flow rates, it inherently introduces an approximation. A geometry featuring a more extensively segmented coronary tree, particularly in the septal region, would be necessary to further improve the accuracy of the local flow distribution.

Another relevant simplification is the adoption of a uniform intramyocardial pressure formulation for both the left and right ventricles. The two cardiac chambers operate under different pressure regimes. Applying the left ventricular pressure (p_{LV}) uniformly across the whole biventricular myocardium introduces an artificially high resistance in the right ventricular microvasculature, which restricts the validity of our perfusion analysis to the left heart. Developing a differentiated, chamber-specific intramyocardial pressure model stands as a primary requirement for a complete biventricular assessment.

Finally, a valuable development of this work would involve closing the loop between perfusion and electromechanics. Introducing a two-way coupling to account for the feed-

back effect of ischemia, where the lack of oxygen induced by CMD locally impairs the active force generation of the cardiac muscle, would allow for a comprehensive study of the progressive worsening of cardiac function driven by microvascular diseases.

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A

Appendix A

Physics	Parameter	Value	Unit
Electrophysiology (LV only)	σ_m^s	$2.00 \cdot 10^{-4}$	m^2/s
	σ_m^t	$1.05 \cdot 10^{-4}$	m^2/s
	σ_m^n	$0.55 \cdot 10^{-4}$	m^2/s
	A_{app}	25.71	V/s
	σ_{app}	$2.5 \cdot 10^{-3}$	m
	T_{app}	$3 \cdot 10^{-3}$	s
Active Force (LV only)	γ	30	
	k_d	0.36	
	α_{k_d}	-0.2083	
	K_{off}	10	1/s
	K_{basic}	5	1/s
	μ_{fp}^0	32.255	1/s
	μ'_{fp}	0.768	1/s
	a_{XB}	$2.5 \cdot 10^8$	Pa
Mechanics (Guccione)	ρ_s	1000	kg/m^3
	C	$8.8 \cdot 10^2$	Pa
	a_{ff}	8	
	a_{ss}	6	
	a_{nn}	3	
	a_{fs}	12	
	a_{fn}	3	
	a_{sn}	3	
	B	10^6	Pa
	K^{ep1}	$2 \cdot 10^5$	Pa/m
Boundary conditions	$K_{ }^{cp}$	$2 \cdot 10^4$	Pa/m
	$C_{\perp}^{ep1}$	$2 \cdot 10^4$	$\text{Pa} \cdot \text{s}/\text{m}$
	$C_{ }^{epi}$	$2 \cdot 10^3$	$\text{Pa} \cdot \text{s}/\text{m}$
In. conditions	Po	1333.2	Pa

Table A.1: Parameters used in the electromechanical model: electrophysiology, active force generation, and solid mechanics.

Compartment	Parameter	Value	Unit
Systemic arteries	R_{AR}^{SYS}	0.65	mmHg · s/mL
	C_{AR}^{SYS}	1.9	mL/mmHg
	L_{AR}^{SYS}	$2.7 \cdot 10^{-3}$	mmHg · s ² /mL
	R_{AR}^{SYS}	0.05	mmHg · s/mL
	$p_{AR}^{SYS}(0)$	80.0	mmHg
	$Q_{AR}^{SYS}(0)$	0.0	mL/s
Systemic veins	R_{VEN}^{SYS}	0.26	mmHg · s/mL
	C_{VEN}^{SYS}	60.0	mL/mmHg
	L_{VEN}^{SYS}	$5 \cdot 10^{-4}$	mmHg · s ² /mL
	$p_{VEN}^{SYS}(0)$	30.9	Pa
	$Q_{VEN}^{SYS}(0)$	0.0	mL/s
Pulmonary arteries	R_{AR}^{PUL}	0.05	mmHg · s/mL
	C_{AR}^{PUL}	10.0	mL/mmHg
	L_{AR}^{PUL}	$5 \cdot 10^{-4}$	mmHg · s ² /mL
	$p_{AR}^{PUL}(0)$	29.34	Pa
	$Q_{AR}^{PUL}(0)$	0.0	mL/s
Pulmonary veins	R_{VEN}^{PUL}	0.025	mmHg · s/mL
	C_{VEN}^{PUL}	38.4	mL/mmHg
	L_{VEN}^{PUL}	$2.083 \cdot 10^{-4}$	mmHg · s ² /mL
	$p_{VEN}^{PUL}(0)$	13.58	Pa
	$Q_{VEN}^{PUL}(0)$	0.0	mL/s
Right atrium	E_A	0.06	mmHg/mL
	E_B	0.07	mmHg/mL
	t_C	0.80	s
	T_C	0.17	s
	T_R	0.17	s
	$V_{RA}(0)$	64.17	mL
Right ventricle	E_A	0.55	mmHg/mL
	E_B	0.05	mmHg/mL
	t_C	0.0	s
	T_C	0.34	s
	T_R	0.15	s
	$V_{RV}(0)$	148.9	mL
Mitral valve	R_{min}	0.0075	mmHg · s/mL
	R_{max}	75006.2	mmHg · s/mL
Aortic valve	R_{min}	0.0075	mmHg · s/mL
	R_{max}	75006.2	mmHg · s/mL
Tricuspid valve	R_{min}	0.0075	mmHg · s/mL
	R_{max}	75006.2	mmHg · s/mL
Pulmonary valve	R_{min}	0.0075	mmHg · s/mL
	R_{max}	75006.2	mmHg · s/mL

Table A.2: Parameters of the circulation model for the electromechanical simulation.

B | Appendix B

Region	α [$\text{m}^3/(\text{Pa} \cdot \text{s})$]
1	$4.65 \cdot 10^{-5}$
2	$1.07 \cdot 10^{-4}$
3	$3.15 \cdot 10^{-4}$
4	$1.28 \cdot 10^{-4}$
5	$1.63 \cdot 10^{-4}$
6	$4.46 \cdot 10^{-4}$
7	$2.22 \cdot 10^{-4}$
8	$2.56 \cdot 10^{-4}$
9	$4.91 \cdot 10^{-5}$
10	$1.24 \cdot 10^{-4}$
11	$7.23 \cdot 10^{-5}$
12	$2.09 \cdot 10^{-5}$
13	$8.22 \cdot 10^{-5}$
14	$8.83 \cdot 10^{-5}$
15	$5.51 \cdot 10^{-5}$
16	$2.35 \cdot 10^{-4}$
17	$1.12 \cdot 10^{-4}$

Table B.1: Parameters used in the multicompartment Darcy model: coefficients in the Robin coupling condition (α). The parameters have been estimated in [13].

Parameter	Value [compartments]
Length density $(nL)_i$	$[0.5 ; 15 ; 8000] \text{ mm mm}^{-3}$
Specific permeability κ	$1.75 \times 10^{-10} \text{ m}^{-1}$
Morphometry factor δ_i	$[0.005 ; 0.05 ; 10] \text{ mm}^{-1} \text{ s}^{-1} \text{ Pa}^{-1}$
Veins conductance γ	$8 \times 10^{-6} \text{ s}^{-1}$
Right atrium pressure p_{ra}	2 mmHg
Blood density ρ	1063 kg m^{-3}
Blood viscosity μ	0.0035 Pa s

Table B.2: Parameters for the multicompartment Darcy model.

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