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Executive Summary of the Thesis

Mathematical Characterization and Hemodynamic Assessment of Coronary Microvascular Dysfunction Using a Cardiac Perfusion Model

Laurea Magistrale in Mathematical Engineering - Ingegneria Matematica

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1. Introduction

Coronary Microvascular Dysfunction (CMD) encompasses a set of structural and functional alterations of the coronary microcirculation, leading to an inadequate blood supply to the myocardium even in the absence of epicardial artery stenosis [1]. The clinical assessment of CMD remains challenging due to the physical impossibility of imaging the microvasculature *in vivo*. In this context, computational modeling represents a powerful non-invasive tool to investigate the underlying mechanics of coronary perfusion and the hemodynamic implications of microvascular diseases.

The main objective of this thesis is to mathematically characterize and computationally assess the hemodynamic impact of CMD, providing a biophysically based description of the structural alterations that drive microcirculatory dysfunction. To this end, we build upon a comprehensive multiphysics and multiscale cardiac perfusion model [4] that integrates electromechanics and large-vessel hemodynamics. As a key advancement, we adopt a compliant multicompartment Darcy formulation [2] to accurately capture the cyclic effects of cardiac contraction on the microvascular network, allowing for a rigorous quantitative evaluation of Myocardial Blood Flow (MBF). Finally, we assess the reliability of the proposed CMD modeling framework by comparing the *in silico* results with relevant clinical biomarkers, such as the Coronary Flow Reserve (CFR) and the endocardium-to-epicardium perfusion ratio.

2. The Multiphysics and Multiscale Model

The model adopted can be seen as two main blocks, connected by a one-way kinematic coupling condition:

Electromechanics and Circulation: A full 3D electromechanical model of the left heart is coupled with a lumped-parameter closed-loop circulation model, as proposed in [3]. This block solves for cardiac electrophysiology, active force generation, and solid mechanics, providing the fundamental boundary conditions for the hemodynamics problem: the intraventricular pressure, the systemic arterial pressure, and the myocardial wall displacement. The displacement field is then projected onto the fluid domain via a kinematic one-way coupling.

Hemodynamics and Microvascular Perfusion: The macroscale blood flow within the

epicardial coronary arteries and the ventricular chamber is governed by the Navier-Stokes equations, solved in an Arbitrary Lagrangian-Eulerian (ALE) framework to account for domain deformation. Cardiac valve dynamics are handled via the Resistive Immersed Implicit Surface (RIIS) method. The microcirculation is modeled using a compliant multicompartment Darcy formulation [2]. The myocardial tissue is treated as a poroelastic medium divided into distinct vascular compartments (small arteries, arterioles, capillaries) . This compliant formulation embeds the effect of intramyocardial pressure, allowing the model to accurately capture the cyclic mechanical compression (and consequent resistance variations) of the microvascular network during systole. Finally, the Navier-Stokes and Darcy domains are strongly coupled via Robin interface conditions, which feed the macroscale blood flow from the epicardial outlets into the corresponding perfusion regions as a localized volumetric source term.

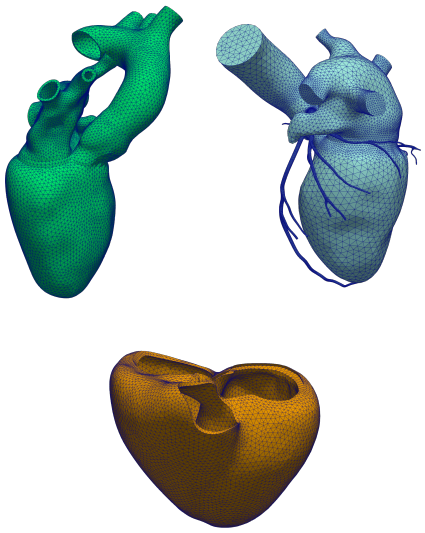

Figure 1: Computational meshes representing the electromechanics, fluid dynamics and perfusion domains.

3. Modeling Coronary Microvascular Dysfunction

A fundamental step to computationally simulate CMD is to develop its mathematical characterization, achieved by perturbing the structural parameters that govern the resistance and compliance of the Darcy microvascular compartments. Based on clinical literature, we simulated two primary manifestations of CMD: vascular rarefaction and distal lumen narrowing.

Vascular Rarefaction and Transmural Scaling: Physiologically, the myocardial microvasculature exhibits a transmural gradient, with a higher vascular volume density in the subendocardium compared to the subepicardium. To accurately reproduce this baseline distribution and obtain a realistic endocardium-to-epicardium MBF ratio, we introduced a spatial modulation for the length density parameter (L_d). This was achieved by solving a Laplace boundary value problem over the perfusion domain Ω^P:

$$\begin{cases} -\Delta L_d = 0 & \text{in } \Omega^P, \\ L_d = 1 - \delta_{CMD} & \text{on } \partial\Omega^P_{endo}, \\ L_d = 0.8 & \text{on } \partial\Omega^P_{epi}, \\ \frac{\partial L_d}{\partial \boldsymbol{n}} = 0 & \text{on } \partial\Omega^P_{rings}, \end{cases} \tag{1}$$

where $\partial\Omega^P_{endo}$, $\partial\Omega^P_{epi}$, and $\partial\Omega^P_{rings}$ denote the endocardial, epicardial, and basal ring boundaries, respectively.

This formulation encapsulates both the healthy and pathological states in a single equation. In the baseline physiological scenario, we set $\delta_{CMD} = 0$. To simulate vascular rarefaction, the parameter δ_{CMD} is introduced to dictate the severity of the endocardial capillary loss, progressively worsening the conductive capacity of the innermost layers.

Distal Lumen Narrowing: Alongside capillary rarefaction, CMD is characterized by the structural inward remodeling and wall thickening of microvessels, leading to impaired vasodilation, particularly during the diastolic phase. We modeled this pathological lumen restriction by directly modulating the constitutive curves that govern the average cross-sectional areas of the arteriolar (A_2) and capillary (A_3) compartments, as illustrated in Figure 2.

Specifically, we introduced the scaling coefficients $\psi_2, \psi_3 \in (0, 1)$ to reduce the amplitude of the non-linear relationships between the vessel lumen and the transluminal pressure ($p_i - P_{im}$). By scaling down these reference areas ($\psi_k < 1$), we effectively diminished the compartment permeabilities K_i and the inter-compartment conductances β_{ij} governing the Darcy problem.

This approach allowed us to simulate a coherent lumen reduction, up to $\approx 40\%$ compared to

original sectional areas, in accordance with clinical data. Consequently, the model penalizes the flow and impairs the blood supply, effectively increasing the microvascular resistance.

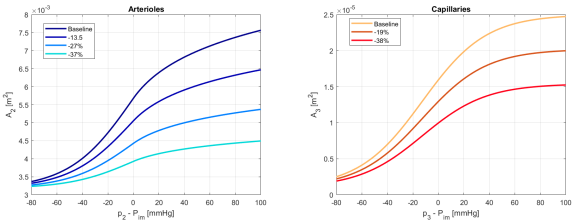

Figure 2: Constitutive curves representing the average cross-sectional areas for arterioles (left) and capillaries (right) as functions of the transluminal pressure. The curves illustrate the progressive lumen reduction modeled via the scaling coefficients ψ_2 and ψ_3.

4. Numerical Results

4.1. Electromechanics

The computational pipeline begins with the electromechanical simulation of the left heart, which serves as the physical driver for the subsequent perfusion analyses.

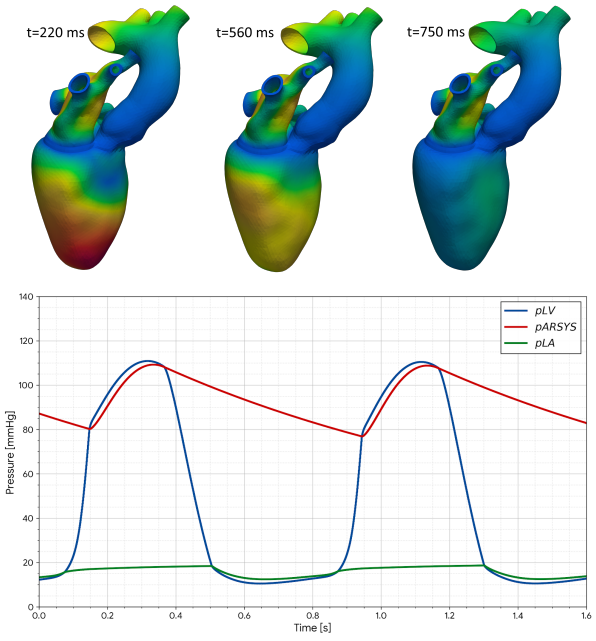

Figure 3: Electromechanical simulation results: displacement field evolution (top), p_{LV}, p_{LA}, $p_{\mathrm{AR}}^{\mathrm{SYS}}$ curves in last two heartbeats (bottom).

The model successfully reproduced a physiological cardiac cycle, yielding a Stroke Volume of 70.6 mL and an Ejection Fraction of 52.8%. This simulation provided the temporal evolution of the intraventricular (p_{LV}) and systemic arterial (p_{AR}^{SYS}) pressures (Figure 3, bottom), which dictate the intramyocardial pressure and the boundary condition at the aortic outlet for the fluid problem, respectively. Moreover, from this simulation we extract the displacement field (Figure 3, top) that determines the ALE velocity and drives the macroscopic hemodynamics.

4.2. Model Validation on Idealized Geometry

For what concerns hemodynamics and perfusion, the computational framework was initially validated on an idealized bifurcation geometry, illustrated in Figure 4, to assess the model sensitivity at a low computational cost, and subsequently applied to a realistic 3D human biventricular myocardium. The Darcy domain was subdivided into two perfusion regions, one for each branch, and the tests were performed varying the parameters of only one region.

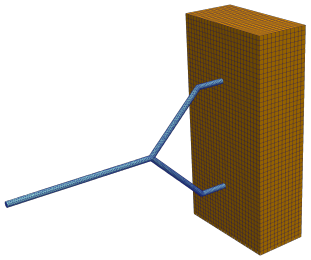

Figure 4: Idealized geometry comprising fluid domain in blue and Darcy domain in brown.

The tests on this idealized geometry confirmed the model ability to capture the phasic nature of coronary blood flow, governed by the cyclic rise in intramyocardial pressure. This mechanical compression correctly induced the phenomenon of diastolic dominance, increasing distal resistance during systole and allowing rapid flow acceleration during diastole. Quantitatively, the baseline physiological simulation yielded an average subendocardial Myocardial Blood Flow (MBF) of 239.2 mL/min/100mL and a subepicardial MBF of 261.0 mL/min/100mL, computed in two probe locations and averaged over the last heartbeat simulated, producing a realistic endocardium-to-epicardium perfusion ratio of 0.92, consistent with hyperemic physiological

ranges. This simplified geometry allowed us to perform different tests to evaluate the impact of the variation of CMD target parameters, whose effects are illustrated in Figure 5.

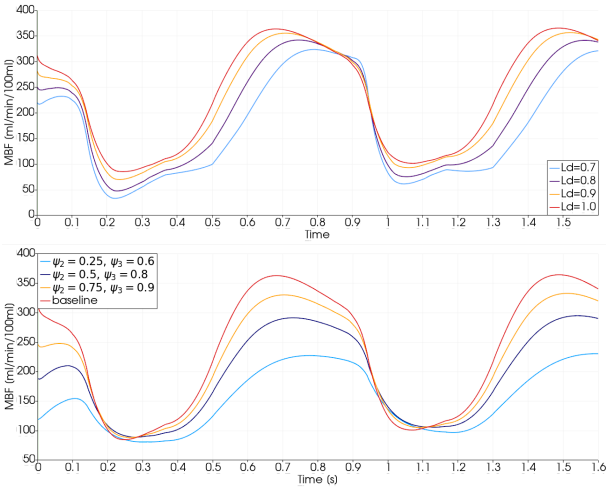

Figure 5: Endocardial MBF with different length density values (left) and different modulations of constitutive curves (right).

Upon introducing a severe CMD scenario ($\psi_2 = 0.25$, $\psi_3 = 0.6$, $\delta_{CMD} = 0.3$), the endocardial MBF drastically dropped to 106.7 mL/min/100mL. This plunged the perfusion ratio to 0.54, suggesting that the characterization developed accounts for the transmural severity gradient of the pathology. Furthermore, the model captured the emergence of systolic retrograde flow in the branch perfusing the pathological region, a recognized hemodynamic marker of severe microvascular dysfunction.

4.3. Baseline Hemodynamics in Realistic Geometry

When translated to the realistic left heart geometry, the fully coupled Navier-Stokes-Darcy simulation successfully reproduced standard macroscopic and microscopic physiological targets. To achieve this, the solid displacement field obtained from the electromechanical simulation was linearly projected onto the fluid domain to explicitly compute the Arbitrary Lagrangian-Eulerian mesh velocity. Moreover, the RIIS parameters were carefully calibrated to synchronize the aortic and mitral valve dynamics, strictly matching their opening and closing timings with the pressure curve intersections (p_{LV} vs. p_{AR}^{SYS}, and p_{LA} vs. p_{LV}) extracted from the electromechanics.

This setup accurately captured the macroscopic ventricular filling and ejection phases (Figure 6), recording a peak aortic outflow of 575.97 mL/s and a peak mitral inflow of 323.5 mL/s. Under these baseline conditions, the inverted coronary pressure gradient registered at the systolic onset did not translate into a reversed flow, due to the brevity of this phase and the inertial forces that characterize a healthy hyperemic condition.

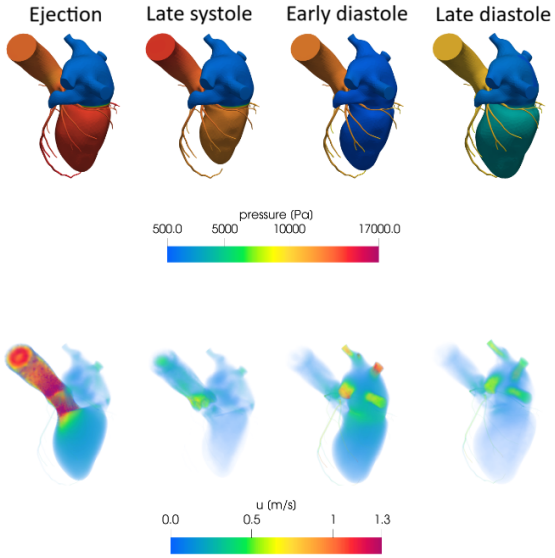

Figure 6: Temporal evolution of macroscopic hemodynamics (pressure and velocity magnitude) across the cardiac cycle in the realistic left heart geometry.

To analyze the microscale hemodynamics results we took two target regions, corresponding to perfusion regions 6 and 7. The regional hyperemic MBF exhibited accurate transmural gradients and systole-diastole oscillations, as shown in Figure 7. For instance, in target region 7, the baseline endocardial MBF reached 268.1 mL/min/100mL, which, compared to the epicardial value of 274.74 mL/min/100mL, resulted in a perfusion ratio of 0.98, perfectly falling into the physiological range. By applying a clinical healthy CFR factor of 3.74, we estimated a resting endocardial baseline flow of 71.69 mL/min/100mL, which is consistent with the clinical physiological range of 65.10 ± 13.65 mL/min/100mL. This value will be the basis to evaluate the falling of the CFR marker under increasingly severe pathological conditions.

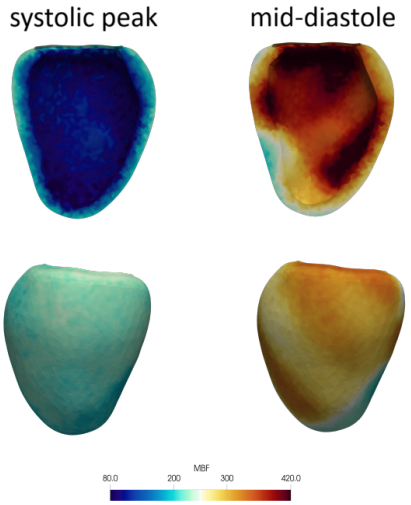

Figure 7: MBF in left ventricle at systolic peak (left) and mid-diastole (right). Endocardium view (top), epicardium view (bottom).

4.4. Pathological Scenarios and Clinical Biomarkers

The targeted introduction of structural microcirculatory alterations yielded a severe drop in perfusion capabilities, identifying the subendocardium as the most vulnerable layer to microvascular ischemia.

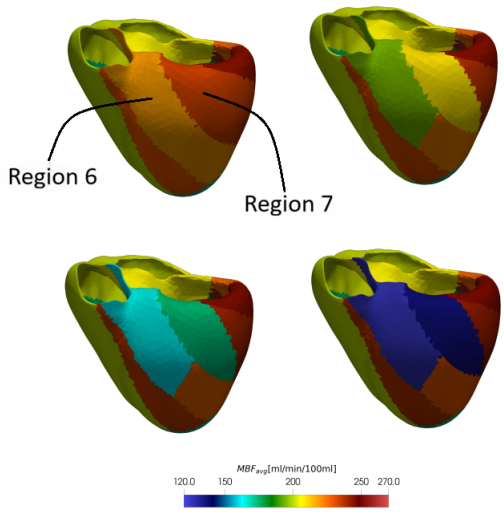

Figure 8: Reduction of Myocardial Blood Flow induced by the progressive scaling of CMD structural parameters.

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. Evaluating the average MBF in each probe location in the second heartbeat, we can observe that there is a gradual drop in every analyzed biomarker as the severity of the simulated CMD increases from Test 1 to Test 3.
Notably, the reduction in MBF is not uniform across the myocardial wall. The subendocardial layer (MBF_{endo}) exhibits a significantly steeper decline compared to the subepicardial layer (MBF_{epi}). For instance, in region 7, MBF_{endo} drastically dropped from 268.13 to 124.54 mL/min/100mL, while MBF_{epi} dropped from 274.74 to 189.86 mL/min/100mL. This disproportionate impairment is clearly captured by the perfusion ratio, which drops progressively from physiological baseline values (0.98) to ischemic values in Test 3 (0.65).
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, we observed the gradual decrease of this marker from the physiological value of 3.74, which is the mean value found in clinical literature, to pathological values registered in Test 3 of 1.81 and 1.73 in regions 6 and 7, respectively, denoting a compromised baseline-to-hyperemia adaptability. The

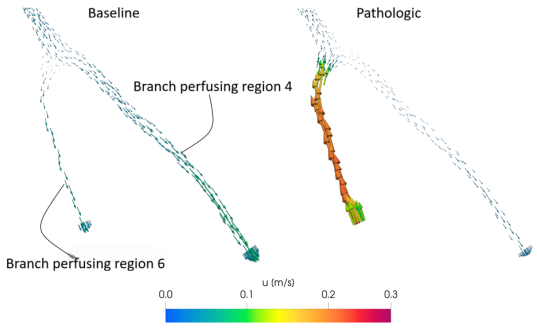

Figure 9: Comparison between systolic coronary flow in baseline and pathological simulations, with zoom over the branches perfusing region 7 (pathologic) and region 4 (unaltered)

last evidence of increased distal resistance observed is the appearance of systolic flow reversal in branches perfusing pathological regions, as illustrated in Figure 9.
To conclude, we performed a sensitivity analysis to evaluate the effects of parameters ψ_2 and ψ_3 on both endocardial and region-averaged MBF.

Specifically, we performed different independent simulations varying exclusively the parameter ψ_2 (while keeping all other parameters at their baseline values) and fitted the extracted MBF data with an exponential regression curve. The same procedure was then repeated to isolate the effect of ψ_3. For the sake of brevity, Figure 10 illustrates the exponential regression results exclusively for the localized subendocardial MBF.

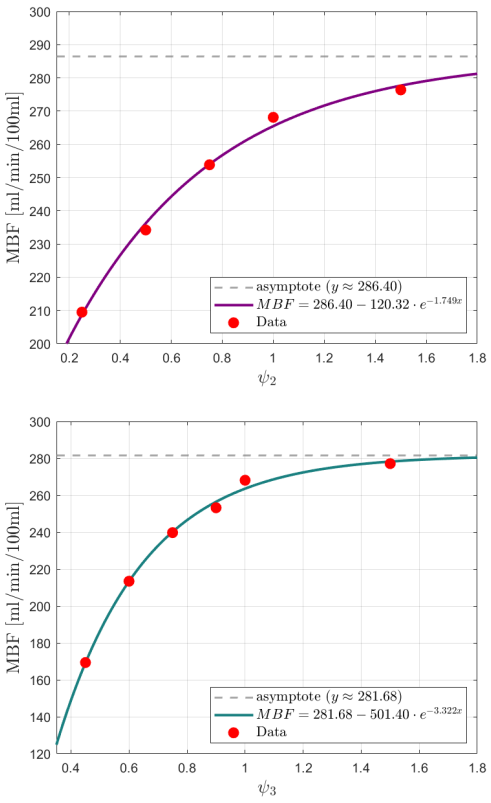

Figure 10: Sensitivity analysis on parameter ψ_2 (top) and ψ_3 (bottom).

5. Conclusions and Future Developments

This work demonstrates that structural remodeling at the microscale directly compromises global perfusion efficiency, predominantly affecting the innermost myocardial layers. The proposed multiscale framework successfully translates microscopic anatomical alterations, embedded in the developed mathematical characterization of CMD, into macroscopic hemodynamic markers. Indeed, the simulations reproduced a realistic and gradual decline from physiological conditions to ischemic states, measured by the progressive decrease of all clinical biomarkers considered, such as MBF, CFR and perfusion ratio, which dropped below established pathological thresholds.

Despite these promising results, some limitations must be acknowledged. The limited number of outlets in the anatomical coronary reconstruction required an artificial volume scaling of the largest perfusion regions. Furthermore, the use of a uniform intramyocardial pressure, derived exclusively from the left ventricle, restricts the validity of the current analysis to the left heart.

Future developments should address these geometrical constraints and implement a chamber-specific intramyocardial pressure formulation. A further valuable development would be establishing a two-way coupling to account for the feedback effect of ischemia on electromechanics.

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