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Computational Methods to Predict the Fractional Flow Reserve in Coronary Arteries - a Literature Review

M. Fernandes[1,2], L.C. Sousa[1,2], C.C. António[1,2], S.I.S. Pinto[1,2]

[1]*Faculty of Engineering, University of Porto, Porto, Portugal*
Rua Dr. Roberto Frias, s/n, 4200 – 465 Porto, Portugal
[2]*Institute of Science and Innovation in Mechanical and Industrial Engineering, LAETA-INEGI*
Rua Dr. Roberto Frias, 400, 4200 – 465 Porto, Portugal
mcfernandes@fe.up.pt, lcsousa@fe.up.pt, cantonio@fe.up.pt, spinto@fe.up.pt

Abstract. Coronary artery disease (CAD), characterized by the buildup of plaque in arteries restricting blood flow to the heart, requires an accurate diagnosis with the Fractional Flow Reserve (FFR) assessment. Traditional FFR measurement involves invasive procedures, but non-invasive computational methods have been explored to mitigate risks and costs. This study reviews recent literature on computational approaches to predict FFR in coronary arteries. Researchers have investigated the use of advanced hemodynamic simulations considering patient-specific real conditions in the non-invasive prediction of the FFR. This approach aims to deliver accurate FFR results for on-site diagnosis in hospitals. The integration of these non-invasive tools could improve the effectiveness of FFR assessment and diagnosis.

Keywords: Fractional Flow Reserve, Coronary Artery Disease, Stenosis, Numerical Methods, Non-Invasive Assessment.

1 Introduction

Cardiovascular disease (CVD) remains the most significant cause of mortality in the world. In the European Union, CVD stands as the leading cause of death, accounting for approximately 37% of all yearly fatalities, resulting in nearly 1.8 million deaths annually [1]. Among CVDs, coronary artery disease (CAD) holds the highest prevalence and fatality rates. CAD can lead to heart attacks and severe complications, and this disease is known for having a slow and gradual progression without displaying evident symptoms. Genetic predisposition, lifestyle choices, and dietary habits significantly impact the risk of developing CAD [2]. Factors such as poor diet, sedentary lifestyle, excessive alcohol consumption, smoking, psychosocial behaviors (like depression, anxiety, and stress), obesity, diabetes, high cholesterol levels, and external factors like healthcare accessibility and air pollution contribute to the increase in the number of cases of this disease [2]. Notably, the elderly population, the people aged 65 and above, are particularly susceptible to this disease, with nearly 90% of CVD-related deaths affecting this age group [1]. As the population continues to age and have an increased average life expectancy, it is imperative to develop effective preventive measures and healthcare interventions to reduce the incidence and impact of CVDs. Coronary artery disease often involves the development of stenosis in the coronary arteries. Stenosis, which is the narrowing of arteries caused by plaque buildup in the lumen of the artery [3], can significantly reduce or even completely block blood flow and lead to adverse events such as ischemia and myocardial infarction [4].

The Fractional Flow Reserve (FFR) became the most widely accepted diagnostic parameter and the gold standard for evaluating the significance of blockages in coronary arteries and guiding clinicians in deciding the best treatment option for their patients [1], [5]. The FFR is the ratio of two pressure values, the pressure distal 20mm downstream of the stenosis and the aortic pressure [5], [6]. In the conventional hospital setting, the FFR is measured in an invasive procedure where a pressure wire is inserted into the artery of the patient to measure the blood pressure in the two previously mentioned locations. However, this approach carries risks to patients with debilitating arteries (such as bleeding or injury) and it is expensive and cumbersome for the hospitals [7]. To address these challenges, researchers have investigated computational techniques to non-invasively estimate the FFR. Using computational fluid dynamics (CFD), numerical modelling, and the recent advances in computing power, it has been shown in the literature that it is possible to accurately model blood flow through mathematical modelling [8]–[10] in reconstructed patient-specific models of coronary arteries [11], [12].

The stenosis has a functional impact on blood flow [13], [14]. In fact, in fluid mechanics, the presence of stenosis is an obstacle to flow, causing changes in dynamic properties such as pressure and velocity, and it introduces strong rotational components to the flow, causing recirculation [15]. These changes in flow are also complemented by the geometric features of the artery, such as its tortuosity and shape [16]. Moreover, the rheology of blood is an important aspect to be considered in the study of blood flow. In larger blood vessels blood is commonly modelled as a Newtonian fluid with constant viscosity [17], but this simplification has been shown not to be accurate in smaller blood vessels, like the coronary arteries [18]. It is known that blood displays non-Newtonian characteristics because of its composition. Even though plasma constitutes the predominant component of blood and has been modelled as a Newtonian fluid in the literature [19], the other constituents, like platelets, leucocytes, and red blood cells (RBCs), exhibit complex and viscoelastic behavior [20].

The use of computational and numerical methods to predict the FFR in coronary arteries with stenosis would be a helpful tool to clinicians to aid diagnosis and avoid the need for invasive, time-consuming, and costly hospital procedures. The development of these methods could result in a decrease in the time taken for diagnosis of CAD, as well as the hospital costs, while increasing the number of assessments of CAD in the same time period, improving the outcomes of each patient.

This scientific paper aims to perform a comprehensive review of the computational methods used in the literature to non-invasively predict the FFR in coronary arteries with stenosis. It mainly focuses on the use of CFD and numerical simulations to calculate the flow equations in patient-specific models of real patients with CAD. A wide range of non-invasive procedures have been studied in the literature as a means to assess the severity of stenosis in patient-specific coronary arteries and measure the FFR. However, regardless of the nature of the methods used, the precision of the results is largely dependent on the accuracy of describing the artery geometry, the blood flow properties, and the boundary conditions.

2 Assessment of stenosis and FFR in Medicine

CTs are the most commonly used imaging method in clinical settings today [6], [21], [22]. The images allow the location of stenoses, and the methods used to objectively quantify their severity have changed throughout the years. Since its conception in 1993, the FFR has become the most common approach for assessing the functional severity of stenoses [23].

On the obtained images, the blockage causes visible anomalies in the inner diameter of the artery, so doctors are able to find the location of the stenosis. To quantify the FFR, medical doctors perform a coronary angiography. First, local anesthesia is administered to the patient in the location where the pressure wire is to be inserted. Afterwards, a catheter coupled to a pressure wire is inserted and moved through the arteries until reaching the place of the stenosis, and x-ray images are used to find the path the catheter does between the assess position and the stenosis location. After placing the pressure wire in the region of interest, hyperemia conditions are induced. This state is induced using medications like adenosine or nitroglycerin, which dilate the coronary arteries and increase blood flow [24]. Then, the aortic pressure, p_a, and the pressure distal by 20 mm downstream the stenosis [25], p_d, are measured. Once the measurements are completed, the pressure wire and catheter are removed and the FFR, a non-dimensional parameter, is calculated as:

$$FFR = \frac{p_d}{p_a}. \tag{1}$$

Qualitatively speaking, medical doctors assess the obstruction using a percentage proportional to the reduction of blood flow. The degree of blockage is divided into three categories: mild, moderate, and severe [26]. In general, mild blockages (FFR > 0.8) can be treated through medication, while severe blockages (FFR < 0.75) require immediate revascularization procedures (like angioplasty and stenting), which increase blood flow. However, intermediate blockages (0.8 > FFR > 0.75) in coronary artery disease have long been a challenge for medical doctors to understand which route to take. In fact, the presence of multiple mild stenoses can have a large impact on the downstream blood flow, even though each stenosis may have only a minor effect [27].

3 Patient-specific artery modelling

Advanced medical imaging technologies have enabled the creation of patient-specific coronary artery models for computational uses, which are valuable assets for personalized medicine. High-resolution images of arteries are required to create a virtual model of patient-specific vessels, and these can be captured by computed tomography (CT) scanners. CT images are commonly used to examine the heart and its arteries. In fact, these images are captured after a contrast agent is administered to the patient to increase the contrast between the blood and the surrounding tissues [28], [29], offering detailed anatomical information like the presence and location of blockages in patients with the potential of having CAD. DICOM (Digital Imaging and Communications in Medicine) is the industry standard for digital medical imaging, and it is used by modern CT scanners to acquire computed tomography scans as well as patient clinical information.

The 2D images are captured in consecutive parallel planes [30]. The number of images can vary depending on the capacity of the CT scanners used by the medical professional, but modern CT scanners can generate hundreds of images for each patient case. The images are then processed using segmentation algorithms to identify and remove areas that are not of interest, like the lungs, rib cage, and other blood vessels. Due to the required elevated number of CT images with high resolution, various image segmentation algorithms have been studied in the literature to obtain 3D models of arteries with different approaches to the segmentation process. Some authors have opted for semi-automatic methods [12], [31], [32], while others use machine learning to automatically identify and segment coronary arteries [11], [33], [34]. However, as noted by Ramesh et al. [35], there is no such thing as a universal theory of image segmentation.

The CT scans can be recorded in resting [36] or hyperemia conditions, which means that when the generated 3D model is in the former condition, the physiological conditions of the patient in maximum vasodilation conditions must be modelled numerically. The resistance-based model used to define the pressure (explained in Section 4) can be altered to consider the physiological changes that occur in the artery during hyperemia. The way this is modelled is not consistent in the literature. In fact, according to Wilson et al. [24], the vessel cross-sectional area increases by a factor of 2.04, the flow rate is scaled up by a factor of 2.16, the heartbeat rate (HBR) rises by 24 bpm, and, the mean arterial pressure (MAP) decreases by 6 mmHg. Yet, Taylor et al. [37] only reduced the microcirculation resistance value by a factor of 4.5, and increased blood flow by 3.6 cm^3/s.

However, these empirical parameters are based on generalized assumptions, which do not fully capture the physiology of each patient. Therefore, other researchers have modelled hyperemia by manually increasing the cross-sectional area of the 3D model of the artery, and this patient-specific method of modelling hyperemia has returned promising and accurate results when comparing the invasive and numerical values of FFR [38].

4 Boundary condition modelling

Many authors have extensively explored and utilized various models to represent the boundary conditions of velocity, pressure, and blood viscosity in computational studies, which are described in this Section.

4.1 Inlet velocity boundary conditions

Obtaining the cardiac profiles for several patient cases is time-consuming and cumbersome, so a solution has been to adapt standard coronary velocity profiles by considering patient-specific properties of cardiac cycle duration and amplitude [39]–[41]. The issue with this approach is the fact that the presence of stenosis impacts the circulatory system, and the use of a velocity waveform of a healthy patient is not an accurate representation of the flow.

The oscillatory and periodic nature of blood flow causes the longitudinal velocity profile to be a complex function not accurately described by the Hagen-Poiseuille profile [42]. Since blood is pumped by the heart, blood flow has a pulsatile and periodic behavior, and a Womersley profile is able to replicate the velocity profile inside the artery [42]–[46]. This can be adapted to the patient by incorporating patient-specific properties such as vessel dimensions, and flow characteristics [25], [38].

4.2 Outlet pressure boundary conditions

Just like the velocity, pressure has been modelled by adapting a waveform from a standard coronary artery, using a Fourier series [47]. Yet, the most common approach to pressure modelling is lumped-parameter modelling. Lumped-parameter models (LPMs) simulate the flow resistance, capacitance and inductance caused by the elements of the circulatory system such as the heart, the arterial, capillary and venous vessels [48] and return flow properties like pressure and flow rate within discreet compartments, like the coronary tree. These models, also called Windkessel models, are highly customizable when it comes to the number of elements (the number of elements used in the literature is variable), and they can be complexified (for instance, by considering the impact of smaller elements such as heart valves) and be closed loop to account for the downstream effect of the different elements [10], [38], [48].

4.3 Viscosity model for blood

Although recent studies have examined blood as a Newtonian fluid [32], [43], [49]–[51], typically it is considered a non-Newtonian fluid due to the presence of different components like plasma, red and white blood cells, and platelets in the blood [20], [52], [53]. Many studies have compared different shear-thinning non-Newtonian rheological models [18], [41]. Despite their shared research focus, the findings and conclusions of these studies are incongruous with each other, which may be attributed to differences in the numerical methodologies.

However, it is well known from the literature that blood also possesses essential viscoelastic properties that are not accounted for in shear-thinning blood models [54], [55]. Through experimental rheological studies, several mathematical models have been used numerically to simulate various fluids, including blood, with excellent accuracy [20]. A study of the importance of the viscoelastic properties of blood in numerical simulations was presented by Miranda et al. [56]. The results of Fernandes et al. [57] and Pinto et al. [52] show that the rheological behavior of blood can be accurately represented by a simplified Phan-Thien/Tanner (sPTT) model.

5 Main findings and future research

The main findings of this study are summarized in Table 1. Overall, the most recent literature in this field has extensively focused on the use of non-invasive methods to predict the FFR, the use of image segmentation and patient information to replicate patient-specific coronary artery models and their cardiac properties in models that replicate realistic blood flow. Numerous studies have explored different possible algorithms for segmenting medical images that lead to a good resolution and geometrical accuracy of the obtained models and have analyzed the impact of the used boundary conditions and rheological models on blood flow.

However, it is worth noting that the current literature places relatively less emphasis on the complete representation of blood flow by simultaneously using more complex boundary conditions on the different variables related to blood flow. In fact, the consideration of patient-specific blood flow as pulsatile, the impact of the entire circulatory system in the flow inside of the artery and the viscoelasticity of blood have not been studied concomitantly in the literature, which is a crucial aspect in accurately mimicking blood flow numerically. While studies have tackled each of these aspects separately, very few have applied them at the same time.

Table 1. Summary of several recent scientific papers related to the non-invasive FFR calculation.

Reference	Patient-specific artery modelling	LPM for pressure	Womersley profile for velocity	Viscoelastic rheology
Buoso et al. [58]	✓	✓	✗	✗
Carson et al. [49]	✓	✗	✗	✗
Chahour et al. [36]	✓	✓	✗	✗
Fossan et al. [59]	✓	✗	✗	✗
Gutierrez et al. [60]	✓	✓	✗	✗
Itu et al. [27]	✓	✓	✗	✗
Mirramezani et al. [51]	✓	✓	✗	✗

Renker et al. [61]	✓	✗	✗	✗
Sankaran et al. [62]	✓	✓	✗	✗
Fernandes et al. [38]	✓	✓	✓	✓

6 Conclusions

Recent literature regarding this field has focused extensively on non-invasive methods to predict FFR, promoting the creation of an alternative to the invasive measurement procedure. The mentioned studies have explored different coronary artery 3D model generation, and the impact boundary conditions have on blood flow. However, the complete representation of blood flow using more complex boundary conditions and simultaneous consideration of multiple models at once has been less explored.

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