Structure (Epicardial Stenosis) and Function (Microvascular Dysfunction) That Influence Coronary Fractional Flow Reserve Estimation †

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Abstract: Background. The treatment of coronary stenosis is decided by performing high risk invasive surgery to generate the fractional flow reserve diagnostics index, a ratio of distal to proximal pressures in respect of coronary atherosclerotic plaques. Non-invasive methods are a need of the times that necessitate the use of mathematical models of coronary hemodynamic physiology. This study proposes an extensible mathematical description of the coronary vasculature that provides an estimate of coronary fractional flow reserve. Methods. By adapting an existing computational model of human coronary blood flow, the effects of large vessel stenosis and microvascular disease on fractional flow reserve were quantified. Several simulations generated flow and pressure information, which was used to compute fractional flow reserve under several conditions including focal stenosis, diffuse stenosis, and microvascular disease. Sensitivity analysis was used to uncover the influence of model parameters on fractional flow reserve. The model was simulated as coupled non-linear ordinary differential equations and numerically solved using our implicit higher order method. Results. Large vessel stenosis affected fractional flow reserve. The model predicts that the presence, rather than severity, of microvascular disease affects coronary flow deleteriously. Conclusions. The model provides a computationally inexpensive instrument for future in silico coronary blood flow investigations as well as clinical-imaging decision making. A combination of focal and diffuse stenosis appears to be essential to limit coronary flow. In addition to pressure measurements in the large epicardial vessels, diagnosis of microvascular disease is essential. The independence of the index with respect to heart rate suggests that computationally inexpensive steady state simulations may provide sufficient information to reliably compute the index.

Keywords: coronary vasculature; lumped parameter model; fractional flow reserve; computational cardiology

1. Introduction

This manuscript is an extension of work originally presented in Functional Imaging and Modelling of the Heart, 2021 [1].

Clinical relevance of and potential sources of uncertainty in fractional flow reserve estimation: Coronary vessel severity of stenosis is clinically quantified using a quantity called fractional flow reserve (FFR) [2,3]. Quantities such as FFR allow objective clinical decision making, especially when computed tomography subjectively indicates intermediate coronary stenosis. Several clinical trials have led to a partial clinical acceptance of FFR for objective
diagnostics [4–6]. FFR is clinically measured by determination of the ratio of blood flow through a stenosed vessel to that in the same vessel in the absence of stenosis [7]. In recent times, non-invasive computed tomography angiography combined with computational fluid dynamics (CFD) have become increasingly prevalent in estimating FFR, and aim at reducing the significant risks associated with invasive pressure wire measurements [8]. However, multiple complex physiological processes render uncertain FFR estimation [9]. In particular, the clinical literature suggests that micro-vascular dysfunction and stenosis morphology play a significant role in the estimated FFR. In addition, surgical and pharmacological sensitivity remains limited where adverse events often occur in critically ill patients, such as those with renal failure [10], where diagnostics are sub-optimal. As such, the use of FFR to determine clinical intervention depends on quantification of the vascular structure and function.

A brief overview of FFR modelling: Computed tomography angiography-driven computational estimation of FFR is now an advanced technology [11]. Combining imaging with computational fluid dynamics assessment of FFR is known to increase the specificity of diagnosing lesion-specific ischemia [12]. It is facilitated by ready availability of open source advanced scientific platforms [13–16], including those developed in house (Virtual Cardiac Physiology Laboratory) [17,18]. Typically, computation of FFR combines an imaging-generated 3D coronary geometry coupled to models of coronary hemodynamic physiology. Others have used the approach to study a spectrum of processes involving FFR estimation refinement [19], interplay among multiple stenosis complexes [20], and perioperative treatment assessment [21], among several other applications. Computer modelling can be performed at a simple lumped parameter or detailed 3D spatial scales. As a specialized high performance computing application, 3D modelling cannot be performed onsite by the clinician. Due to the large variety of data collection resulting in the need to explore parameter spaces [22,23], large scale computations remain unwarranted in a clinical environment. Recent studies demonstrate the deployable nature of lumped parameter (0D) modelling in a clinical environment. Our recent study, where the role of peripheral arterial disease in hypertension was addressed, illustrates a 0D model deployable nature [24]. We also used 0D hemodynamic modelling of the whole human model to test the effects of treatments such as hypothermia and exercise on systemic circulation [17]. The debilitating effects of atrial fibrillation on cerebral circulation were illuminated recently by Hunter et al. [25]. However, the availability of computationally efficient coronary blood flow models remains limited [26]. It was therefore relevant to develop an open source and extensible coronary model.

Study aims: In this work, an existing lumped parameter (0D) model of the coronary vasculature [27] was further developed and used to demonstrate important factors that regulate FFR. Specifically, the dependence of FFR on the nature of stenosis (focal or diffuse) and on micro-vascular status was investigated. Further, a partial rank correlation coefficient (PRCC)-based sensitivity analysis [1,28,29] was performed to determine the impact of model parameters on FFR. For this purpose, a 0D modelling approach was found to be suitable as the study’s goal was to understand coronary flow in the presence of pathological conditions. It can be appreciated that model identification (personalization), although highly desirable, was not essential in this theoretical study. As such, the presented model is theoretical in nature, in which a better understanding of pathophysiological processes was prioritized over model personalization.

2. Methods

Model development: A recent model of the coronary circulation [27] was adapted. It consists of 16 epicardial coronary artery segments, including the left anterior descending (LAD), left circumflex artery (LCX), right coronary artery (RCA), and several of their clinically significant daughter segments. The closed loop connectivity of the structured tree network is illustrated in Figure 1 and the names of all arteries are elaborated in Table 1. Each artery segment is characterized by the Windkessel time-independent parameters
that consist of a hydraulic resistance (R_n), the inertia to flow of blood represented by an inductance (L_n), and the elastic capacity of the vessel, C_n [30]. The Windkessel parameters are determined using vessel lengths, vessel wall thickness, diameters, elasticity, blood viscosity, and blood density. In this study blood viscosity was taken to be $4 \times 10^{-3}$ kg/(m-s) and density to be 1.06 $\times$ 10^3 kg/m^3, and Young’s modulus (inverse of elasticity) to be 2 $\times$ 10^10 Pa, in agreement with current knowledge [31–33]. Vessel wall thickness was estimated as h = 0.08 D [30]. Each artery segment entering a capillary bed leading into the venous circulation was further assumed to experience a microvasculature terminal impedance (Z_i) that was estimated using a structured tree model by Olufsen [34] as

$$Z_i = \frac{8\mu \lambda ((2\gamma^3)^{-(N+1)} - 1)}{\pi r_0^3(0.5\gamma^{-3} - 1)}, \quad i = 1, \ldots, 9. \quad (1)$$

where $\gamma = 2^{-\frac{1}{3}}$ and $\epsilon$ represents the daughter vessel radius taper exponent, $\lambda$ is the ratio of microvascular length to its diameter, and $r_0$ is the root vessel radius of the structured tree. N represents the number of generations for each structured tree [27,30,34]. The lumped coronary system was further developed by incorporating a detailed four chamber heart description (Figure 1A) [35]. For simplicity, this model does not account for the phase altering effects of cardiac contractility on microvascular coronary flow.

A. Model Circulation.

![Diagram of model circulations](image)

B. Typical vessel.

![Diagram of typical vessel](image)

C. Legend.

- Vessel resistance (resistance).
- Vessel inertia (inductance).
- Vessel elasticity (capacitance).
- Vessel resistance due to head loss (variable resistance).
- Intramyocardial left and right ventricular pressure generators (LVPG & RVPG).

Figure 1. The modelled lumped parameter coronary vasculature tree network. (A) Closed loop vascular structure including tree network and functional components. See Table 1 for vessel names. Z_i (i = 1 to 9) represent terminal vessel impedances. Vessels as well as impedances shown in red were used in the simulation experiments. (B) Typical blood vessel represented by a resistance (R_n), inductance (L_n), and a capacitance (C_n). P_{n-1}: vessel inlet pressure; Q_n: flow through vessel; P_n: pressure in vessel; Q_o: outlet flow; P_{n+1}: outlet pressure, or pressure in distal vessel. (C) Symbols used in panels (A, B), and elsewhere in this work.
Table 1. Model parameter values. See Figure 1 for vessel connectivity. The rows are colour-coded to suggest the major epicardial coronaries, either LAD, LCX, or RCA.

| Vessel | R (mmHg-s/mL) | C (ml/mmHg × 10⁻³) | L (mmHg-s²/mL) |
|--------|--------------|---------------------|---------------|
| LMCA   | 0.2299       | 2.9                 | 0.00228       |
| LAD    | 0.4662       | 1.6                 | 0.0298        |
| LAD1   | 0.5729       | 1.6                 | 0.0342        |
| LAD2   | 1.7077       | 3.4                 | 0.0916        |
| LAD3   | 3.7484       | 1.3                 | 0.1115        |
| LAD4   | 3.2930       | 0.4                 | 0.0716        |
| LCX    | 0.3929       | 1.2                 | 0.0241        |
| LCX1   | 0.4730       | 0.7                 | 0.0231        |
| LCX2   | 1.0264       | 0.7                 | 0.0380        |
| LCX3   | 3.2342       | 1.1                 | 0.0944        |
| MARG1  | 1.7351       | 1.2                 | 0.0655        |
| MARG2  | 2.9195       | 0.8                 | 0.0787        |
| MARG3  | 3.0683       | 1                   | 0.0896        |
| RCA    | 1.8302       | 6.3                 | 0.1171        |
| PLA    | 2.4412       | 1.1                 | 0.0799        |
| PDA    | 1.2571       | 1.8                 | 0.0596        |

Using the parameters given in Tables 1 and 2, summarized from the parent model [27] and microvascular impedances calculated using Equation (1), pressure at each node of the model (Figure 1) was computed as

\[
\frac{dP_n}{dt} = \frac{Q_n - Q_0}{C_n} \tag{2}
\]

and the flow through each vessel (resistance) was calculated as

\[
\frac{dQ_n}{dt} = \frac{P_{n-1} - P_n - R_nQ_n}{L_n} \tag{3}
\]

Table 2. Parameters used to compute microvascular impedances.

| Z (Figure 1). | Root Vessel Radius, r₀ (mm). | N. | Control Z Values (mmHg-s/mL). |
|---------------|-------------------------------|----|------------------------------|
| Z₁            | PDA                           | 0.108 | 19 | 134.100                      |
| Z₂            | PLA                           | 0.130 | 20 | 083.710                      |
| Z₃            | LAD1                          | 0.146 | 20 | 059.059                      |
| Z₄            | LAD3                          | 0.103 | 19 | 154.592                      |
| Z₅            | LAD4                          | 0.088 | 18 | 227.185                      |
| Z₆            | MARG1                         | 0.116 | 19 | 108.224                      |
| Z₇            | MARG2                         | 0.098 | 19 | 179.482                      |
| Z₈            | MARG3                         | 0.102 | 19 | 159.184                      |
| Z₉            | LCX3                          | 0.102 | 19 | 159.184                      |

Legend: Z: terminal impedance; N: number of generations in microvasculature.

Further, the flow through each of the terminals was calculated as

\[
Q_{z,n} = \frac{P_{n-1} - P_n}{Z_n} \tag{4}
\]
Simulation experiments: In all simulations, fractional flow reserve (FFR) was computed as the average of the ratio of the time-dependent distal pressure, $P_d$, (pressure downstream from stenosis) to the time-dependent proximal (aortic) pressure, $P_a$:

$$FFR_{vessel} = \frac{1}{M} \sum_{n=1}^{M} \frac{P_{vessel,n}}{P_{aorta,n}}$$  \hspace{0.5cm} (5)

where $M$ represents the total number of fractions over a given time $T$, which consisted of $M$ time step recordings. $T$ was taken to be 100 heart beats and the final 20 were analyzed. Simulations were designed to explore the effects of stenosis severity in the largest epicardial vessels (either LAD, LCX, or RCA; see Figure 1) or microvascular disease, or both. A sensitivity analysis was performed as described below.

Stenosis in three large vessels, namely the left anterior descending artery (LAD), the left circumflex artery (LCX), and the right coronary artery (RCA), was investigated. Simulations were performed by imposing focal or diffuse stenosis in a given large vessel.

To simulate focal stenosis, the blood vessel was divided into two and its biophysical parameters (Table 1) were revised using

$$R_s = R_o \alpha^{-2}$$
$$C_s = C_o \alpha^{3/2}$$
$$L_s = L_o \alpha^{-1}$$

where the stenosis severity, $\alpha$, is given by the parameter

$$\alpha = \frac{A_s}{A_o}.$$  \hspace{0.5cm} (7)

which is always between 0 and 1 by definition. To simulate diffuse stenosis extended through a certain length percentage $x_s$ ($0 \leq x_s \leq 1$) of a vessel, the revised parameters were calculated as

$$R = R_o x_s + R_o (1 - x_s)$$
$$L = L_o x_s + L_o (1 - x_s)$$
$$C = C_o x_s + C_o (1 - x_s)$$

and used in Equations (2)–(4). Microvascular disease was simulated by decreasing the terminal vessel radius by a predefined amount in all terminals. In this model, radius regulated microvascular impedance was increased by decreasing the $\epsilon$ in Equation (1)'s $\gamma$ parameter.

Sensitivity analysis: Sensitivity of multiple model parameters, including stenosis lengths, focal stenosis severity, heart rate, terminal vessel impedances, microvascular vessel taper parameter ($\epsilon$), and number of downstream vasculature generations to FFR, was computed. To do so, we used our implementation of partial ranked correlation coefficients (PRCC) [17,36]. The coefficients were used to rank the parameters in descending order of significance, and the most relevant results reported.

Numerical methods: The model is a system of 36 coupled stiff ordinary differential equations. Pressures and flows were computed as state variables according to governing ordinary differential equations, Equations (2)–(4), for each vessel. The system was solved using our robust implicit solver available in our simulation software [18,24]. The method used in the solver is based on implicit backward difference formulae that provides $O(dt^6)$ accuracy. A maximum user time step of 0.005 s gave stable solutions which remained unaffected when the maximum time step was halved and doubled. Each instance generated 500 s of simulated dynamics from which the final 10 s of activity were used to generate results. Simulations were performed on local and national clusters. Each instance of the model is a serial run that took 15 s. To construct results in the presented work, a large number of model instances ($10^6$) for predefined values of physiologically relevant parameters were executed within 4 h using 48 processors. The trivially parallel simulations
were performed using GNU Utilities [37]. The simulation outputs were post-processed using a combination of UNIX and MATLAB scripts.

3. Results

Model FFR during the cardiac cycle: Time-dependent FFR in the three major coronary arteries (LAD, LCX, and RCA) under predefined large vessel stenosis and microvascular disease is illustrated in Figure 2. The control simulation (Figure 2, top row) devoid of stenosis or microvascular disease shows that FFR is high (more than 0.8) during the complete cardiac cycle in all three vessels. Due to flow distribution from the aorta to the smaller coronary network, the time dependent FFR was seen to reduce during systole. The time dependent FFR when either LAD, LCX, or RCA were focally stenosed by 90% ($\alpha = 0.9$) is shown in Figure 2, middle row. When there was a full vessel length stenosis the FFR values reduced to 0.56 for the LAD, 0.52 for the LCX, and 0.5 for the RCA. Whereas the overall FFR was observed to reduce significantly in all three simulations, large vessel stenosis led to minimal FFR during the cardiac cycle’s diastole. Simulated microvascular disease, simulated by augmenting all terminal impedances by 50% ($\epsilon = 2.55$, a reduction of $\epsilon$ increases impedance, $Z$), led to amplifying the difference between the aortic and respective distal pressures and gave a minimal FFR estimate during the systole (Figure 2, bottom row). When microvascular disease was simulated, the maximum time dependent FFR value was calculated to be 1 and minimum to be 0.7 in all three blood vessels.

![Figure 2. Pressure profiles and FFR in the LAD (column A), LCX (column B), and RCA (column C). In all columns, top row shows non-stenosed model behavior, second row shows the result of focal stenosis ($\alpha = 90\%$), and third row shows the result of downstream microvascular disease in the absence of focal stenosis ($\alpha = 100\%; \epsilon = 2.33$). In all panels, black lines and axis represent aortic pressure (proximal pressure) while red lines and axis represent the pressure of vessel of interest (distal pressure). Time dependent FFR is shown as orange dashed lines.](image)

The coronary flow in the control coronary model (Figure 3, top row) and its reduction due to focal stenosis (Figure 3, middle row) and microvascular disease (Figure 3, bottom row) was computed. Relative to the control case (Figure 3, top row), focal stenosis (Figure 3, second row) restricted flow significantly in all three blood vessels. When microvascular disease was implemented, the maximum flow and overall flow in the network decreased. Further, the impact of individual artery resistances, inertances, and compliances were blunted as reflected in the flow profiles (Figure 3, bottom row).
was more susceptible to FFR reduction due to stenosis in comparison to the LAD and LCX. (100% microvascular disease) which represents turbulent flow [22]. At diameter reductions (90%), microvascular exacerbates the effect of the stenosis on FFR values. However, an almost unique value of diameter reduction for each, LAD, LCX, and RCA, was observed when the stenosis was diffuse to a certain extent. Conversely, diffuse stenosis in the absence of focal stenosis (vertical axis in Figure 4) also did not reduce FFR. Progressive focal stenosis alone was found to minimally impact the estimated FFR (Figure 4, bottom row) due to the model formulation (see above). As such, a reduction of FFR was observed when the stenosis was diffuse to a certain extent. Conversely, diffuse stenosis in the absence of focal stenosis (vertical axis in Figure 4) to a greater extent than the severity of diffuse stenosis (horizontal axis). Progressive focal stenosis alone was found to minimally impact the estimated FFR (Figure 4, bottom row) due to the model formulation (see above). As such, a reduction of FFR was observed when the stenosis was diffuse to a certain extent. Conversely, diffuse stenosis in the absence of focal stenosis (vertical axis in Figure 4) also did not reduce FFR. Progressive focal stenosis in the RCA caused the largest reduction in FFR (Figure 4, third row) as compared to focal stenosis in the LAD and LCX in the presented model. In the presented model, the RCA was more susceptible to FFR reduction due to stenosis in comparison to the LAD and LCX. Simultaneous presence of focal and diffuse stenosis caused the most severe reduction of FFR in the RCA, followed by the LAD and LCX.

**Focal and diffuse stenosis interplay:** The dependence of average flow (flow), maximum flow, and FFR on simultaneous presence of reduced vessel diameters (focal stenosis) and diffuse stenosis (reduction of diameters along a predefined length) were quantified (Figure 4). In all vessels, the detrimental effects of stenosis on flow (Figure 4, top row) and maximum flow (Figure 4, middle row) were impacted by the severity of focal stenosis (horizontal axis) to a greater extent than the severity of diffuse stenosis (vertical axis).

**Role of microvascular disease in the modelled FFR:** The average flow (flow), maximum flow, and FFR values of simultaneous focal stenosis and microvascular disease are shown in Figure 5. Microvascular disease was simulated by varying the daughter vessel’s radius taper exponent \( \epsilon \) (Equation (1)) from 2.76 (0% microvascular disease, control) to 2.33 (100% microvascular disease) which represents turbulent flow [22]. At diameter reductions below 70%, the flow in each blood vessel (Figure 5, top row) is significantly restricted by up to half of the control flow with the increase in severity of microvascular disease. At similar diameter reductions in the LAD and LCX however, the peak reduction in maximum flow values (near 0.5 of the control values) occur at 50% microvascular disease and returns to near control values at maximal microvascular disease. At diameter reductions above 80%, microvascular exacerbates the effect of the stenosis on FFR values. However, an almost unique value of diameter reduction for each, LAD, LCX, and RCA, was observed to characterize a clinically significant FFR transition to below 0.8 in the presence of an arbitrarily severe microvascular disease. While the diameter reduction was 0.7 for LAD and LCX, it was seen to be a much lower 0.55 in the case of RCA.

![Figure 3. Flow profiles in the LAD (column A), LCX (column B), and RCA (column C). In all columns, top row shows non-stenosed (control) model flow, second row shows flow under focal stenosis (\( \alpha = 90\% \)) and the third row shows the flow under microvascular disease in the absence of focal stenosis (\( \alpha = 100\%; \epsilon = 2.33 \)).](image-url)
Figure 4. Dependence of flow rate (top row), maximum flow (middle row), and mean FFR (bottom row) on stenosis length (vertical axis, all panels) and vessel diameter (horizontal axis, all panels). Columns (A–C) show LAD, LCX, and RCA results, respectively. The black line in the bottom row demarcates the FFR = 0.8 threshold.

Figure 5. Dependence of flow rate (top row), maximum flow (middle row), and mean FFR (bottom row) on microvascular resistance increase (microvascular disease, vertical axis in all panels) and vessel diameter (horizontal axis, all panels). Columns (A–C) show LAD, LCX, and RCA results, respectively. The black line in the bottom row demarcates the FFR = 0.8 threshold.

Sensitivity analysis to stratify FFR impacting parameters: The results of the sensitivity analysis are shown in Figures 6 and 7. The histograms of FFR values obtained during the PRCC calculation are shown in Figure 6. As can be seen, the model did not produce any instances with FFR less than 0.3 due to the ranges of parameters considered. The model appears to produce FFR values centered around 0.54. Further, in all three coronaries, the FFR values appear to be distributed in a left-skewed Gaussian manner.
Figure 6. Histograms of FFR obtained from PRCC simulations (see Figure 7). Panel (A) shows the data for LAD, panel (B) for LCX, and panel (C) for RCA.

Figure 7. PRCC sensitivity of FFR to model control parameters. In all panels, the sensitivity of FFR to the six most relevant parameters are shown. Panel (A) shows the PRCC for LAD, panel (B) for the LCX, and panel (C) for the RCA. In all panels, HR: heart rate; fs: focal stenosis; ds: diffuse stenosis; r0: root radius of microvascular bed; Z: microvascular impedance; ε: microvasculature taper exponent; and E_{sys,rv}: systolic elastance of the right ventricle.
The sensitivity analysis generated PRCC coefficients are shown in Figure 7. Heart rate (HR) is the most impactful model parameter regulating the FFR. Consistently, focal stenosis (fs) is also a significant regulator of PRCC. Both HR and fs negatively regulate FFR. Diffuse stenosis (ds) and the right ventricular systolic elastance ($E_{sys,rv}$) also negatively regulate FFR. The microvascular parameters (microvascular root radius $r_0$ and tapering factor $\epsilon$) also affect FFR according to our sensitivity analysis.

4. Limitations and Future Directions

Whereas blood is known to be a non-Newtonian liquid [38] whose rheology depends on blood vessel size, especially at special scales, from coronary epicardial vessels to capillaries, the extant literature appears to use standard blood viscosity and density values [31–33]. Inclusion of detailed blood rheology into the model is planned but is not expected to alter presented results.

Further development of the presented model will lead to its clinical applicability. The sensitivity of FFR to heart rate requires further investigation. Although the sensitivity analysis presented heart rate as a primary regulator of FFR, the results of past work indicate its significance is unsettled. Kwasiborski et al. [39] found a significant correlation between FFR and heart rate in the LAD yet no correlation in the RCA in their porcine model. However, an investigation by Kolli et al. [40] found no statistically significant effect on mean FFR due to fluctuations in HR. Due to the increasing prominence of FFR regarding revascularization procedure design, further investigation into the measurement of heart rate as a potential FFR affecting factor is necessary. Patient specific model identification will increase the applicability of the model and reduce its prediction uncertainty. The inclusion of vessel-specific biomechanical properties and inclusion of a reactive vascular tone module [41–43] is expected to allow simulation of clinical parameters such as pulse wave velocities and residence times [44–49]. The inclusion of autoregulatory processes will further assist making the model’s FFR estimates quantitatively reliable [50].

Although lumped parameter models for clinical bedside patient-specific hemodynamic simulation have potential, a significant limitation is the identification of initial parameters to ensure accuracy. The vessel parameters and microvascular impedances in this study were summarized from the literature [27,30]. Estimating the resistances, compliances, and inductances, for each three-element Windkessel model representing each blood vessel requires measurements of blood vessel diameters and lengths. Patient-specific model identification will increase the applicability of the model and reduce its prediction uncertainty. Time domain or frequency domain methods for parameter investigations from pressure and flow profiles have been developed [51,52]. Recent work demonstrated the capability of the unscented Kalman filter to personalize parameters for lumped parameter models using iterative simulations between 0D and 3D [53]. However, this method extinguishes the advantage of time and resource use by resorting to multi-scale simulations. Advancements in image processing algorithms for the visualization and quantification of vessel morphometry can be used to calculate the necessary parameters [13,54,55]. In addition, this study demonstrates that further investigation into the influence of cardiac parameters is permitted. Whereas a detailed heart model [56] was incorporated into the lumped parameter description [27], the simulated aortic root inflow to the coronary vasculature remains generic. Upon availability, patient-specific aortic root blood flow profiles will alleviate the limitation. Furthermore, the parameters of the heart model, such as ventricular and atrial elastances, require personalization. The development of high-resolution echocardiography and magnetic resonance imaging have demonstrated potential in estimating heart chamber volume [57,58]. Patient-specific estimation of blood rheology parameters such as blood viscosity will require clinical measurements [38]. By measurement of blood pressure and heart rate, the blood flow into the coronaries can be personalized. Using routine hematocrit blood tests, the viscosity can be personalized to a certain extent [20]. Also with potential, 4D flow MRI data can provide subject-specific temporal inlet flow information. Using all the temporal signals and spatial imaging data, a large number of
modelling parameters can be estimated [59] using sophisticated methods such as steepest gradient algorithms and particle swarm techniques [60]. Multi-electrode noninvasive electrocardiogram may act as a confirmative test for existing ischemia, i.e., the presence of downstream sub-perfused myocardium [61]. Autoregulatory processes can be personalized using a combination of ultrasound, transcranial doppler and similar noninvasive routine clinical measurements [62].

Although the model is theoretical in nature, the presented results will guide our future work. As such, the findings of the study remain informative for deeper lumped parameter modelling and will inform our spatially extended modelling.

5. Conclusions

Focal and diffuse coronary stenosis were both observed to modulate FFR (Figure 3). However, our simulations indicate that FFR estimation must consider other conditions, such as AF and microvascular disease, both of which are routinely diagnosed among patients using non-invasive techniques. Furthermore, it appears that blood flow to the right ventricle is more severely affected due to extra-coronary and RCA stenosis conditions (Figures 4 and 5).

As seen in Figure 4, focal as well as diffuse stenosis reduces FFR relative to the control case. However, it can also be seen that extra-coronary conditions such as microvascular disease also affect FFR estimates. It is therefore clear that consideration of the effects of co-morbidities is essential in FFR estimation. The result also indicates that our approach is suitable for ranking the severity of co-morbidities. Figure 3, especially, indicates that microvascular disease alone does affect FFR estimation (see definition of FFR). Furthermore, the left and right heart’s coronary are affected differentially. Whereas imaging studies are optimized to provide information regarding left coronaries, the model suggests that the right coronaries should also be considered. Our model suggests that stenosis may not be an exclusive focal or diffuse phenomenon. As Figure 4 shows, consideration of a combination of the two natures of stenosis is essential, especially in our future higher dimensional modelling (see Figure 8). In future studies, the 0D models in this detailed investigation will be useful as boundary conditions to 3D model computational fluid dynamics [63]. In addition to detailed geometry, Figure 5 indicates that a priori knowledge of microvascular health status will permit 3D models to provide better FFR estimates. Within the confines of the presented model, the sensitivity analysis (Figure 7) suggests that heart rate and severity of the large vessel occlusion are prime regulators of FFR. In addition, systolic heart function was found to be relevant.

![Figure 8](image-url)

**Figure 8.** Pressure (arbitrary units) distribution in two representative solid models (geometries) generated using our recent imaging data (unpublished). (A) Geometry 1 with the “*” in panel (A) indicates the stenosis location. (B) Geometry 2 where the location of the stenosis is being investigated.
6. Discussion

We appreciate that model clinical testing routinely acquires immense amounts of data specific to the subject/patient. This includes the special organ that is the heart. The pulsatility provided by the heart is important in measurements such as FFR. However, modelling is an essential complement of CTA-driven FFR. In addition, modelling is essential due to existing heterogeneity among clinical providers.

The ready availability of high performance computing combined with high resolution clinical imaging modalities have augmented the application of computational fluid dynamics for in silico modelling and simulation-based investigation of complex biological processes [64]. However, due to the time and resource-intensive nature of large, multi-scale hemodynamic simulations, the clinical uptake of 3D modelling remains limited as it presently cannot be performed in real time. In contrast, the predictive capability of reduced order surrogates such as 1D and lumped parameter models have shown promise in their reliability relative to 3D models [17,56].

The wide use and reputation of FFR as the gold standard for coronary artery disease diagnosis motivates an investigation into the factors affecting FFR. Bearing in mind the utility and credibility of reduced order models for CFD simulation, a lumped parameter model of the human coronary vasculature [27] was further developed in this study. The model is capable of personalization based on clinical measurements of aortic pressure waves, imaging based vascular geometry (lengths, radii, and morphometry), as well as cardiac wall motion kinematics [65]. As such, the model permits imaging-clinical data assessment as a computationally efficient instrument, prior to detailed 3D computational fluid dynamics simulations. Novel imaging protocols that account for cardiac chamber to chamber diastole will further fortify refinement of the diagnostic instrument. This theoretical study illuminates the relative relevance of focal and diffuse stenosis. It also suggests that knowledge of co-morbidities will improve our clinical diagnostics. Furthermore, it informs our upcoming 3D investigation regarding the clinical data that will permit both validation as well as prediction.

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Data Availability Statement: The authors agree to make the model data openly available upon the publication of the manuscript. The model code is available in our laboratory’s GITHUB, available online (accessed on 25 February 2022): https://github.com/mccsssk2/MDPI2022_JermiahsCoronary.

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