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Sensitivity of Coronary Flow Reserve to Cardiovascular Parameters: A Computational Model-Based Study

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***Abstract*—Coronary flow reserve (CFR), as an index for assessing the functional severity of coronary artery stenosis, has gained wide clinical applications. However, it still remains unclear how and to what extent CFR is affected by various cardiovascular parameters that may differ among patients and vary in their responses to pharmacologic stimulation during CFR measurement. In this study, we performed a series of numerical experiments using a computational model of the coronary circulation to quantitatively investigate the impacts of the variations in various cardiovascular parameters on CFR. Obtained results revealed that CFR was highly sensitive to the vasodilation function of coronary microvasculature under the hyperemic conditions, and moderately affected by ventricular contractility, heart rate (*HR*) as well as the total systemic vascular resistance. Furthermore, the sensitivities of CFR to microvascular dilatation function and heart rate were found to be dependent on the severity of coronary stenosis. These findings may contribute as theoretical references for guiding the clinical application of CFR.**

Keywords—Coronary Flow Reserve, Computational model, Cardiovascular factors, Sensitivity analysis

I. INTRODUCTION

Coronary flow reserve (CFR), which is defined as the ratio between the hyperemic and resting blood flow rates in coronary artery, is an index used for evaluating the functional severity of focal or diffuse coronary atherosclerotic lesions. Despite the well-documented clinical utility, the outcome of CFR measurement has been found to be affected by multiple physiological or pathological factors unrelated to coronary atherosclerosis [1]. Variations in these factors may reflect the inter-patient differences in baseline cardiovascular status or responses to pharmacologic stimulation during CFR measurement. Vasodilators used to induce coronary hyperemia can be administrated in different ways (e.g., intravenous or direct intracoronary injection). Ideally, different vasodilators are expected to induce maximal dilation of coronary microvasculature, while having no or minor effects on systemic hemodynamics [2]. However, the hemodynamic consequences of vasodilation stimulation have been observed to vary depending on the type of vasodilator or method of drug administration. For instance, Papaverine was found to cause complete coronary vasodilation but lead to severe arterial hypotension with intravenous administration compared to intracoronary infusion [3]. Adenosine, on the other hand, could induced sufficient dilation of coronary microvasculature in about 90% of the patient cohorts without significantly altering *HR* and perfusion pressure, but with the occurrence of considerable side effects in the remaining 10% patients [2]. In addition to uncertainties in hemodynamic responses to pharmacologic stimulation, recent studies demonstrated that hyperemic microvascular resistance had significant influence on the result of CFR measurement [4]. Furthermore, the presence of left ventricular dysfunction was found to complicate both coronary and systemic hemodynamics and thereby induce variations in measured CFR [5]. Despite the useful insights from these clinical studies, a quantitative analysis of CFR that involves all major physiological or pathological factors was absent, due mainly to technical limitations of in-vivo measurements. As a consequence, it remains incompletely understood what factors most strongly affect the outcome of CFR measurement and how and to what extent these factors exert their influences.

In this study, we carried out a series of numerical experiments using a computational model of the coronary circulation to quantitatively address the influences of various cardiovascular parameters on CFR measurement, aiming to provide some theoretical insights for assisting the interpretation of clinical observations or the application of CFR.

II. METHODOLOGY

The coronary circulation was modeled by representing large coronary arteries and intramyocardial vessels with the one-dimensional (1-D) and lumped-parameter (0-D) modeling methods, respectively (see Fig.1). The coronary model was further coupled to a 0-1-D model of the remaining cardiovascular portions to build a closed-loop cardiovascular model capable of simulating both coronary hemodynamics and its interaction with systemic hemodynamics [6]. Such a model furnished a practical tool for quantifying the responses of CFR

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to variations in not only coronary but also systemic cardiovascular parameters that represent inter-patient differences in pathological or physiological conditions.

The 1-D governing equations for blood flow in a coronary artery were derived by means of spatially integrating the three-dimensional continuity equation and Navier-Stokes equations over the cross section of the coronary artery [6]:

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = 0, \tag{1}$$

$$\frac{\partial Q}{\partial t} + \frac{\partial}{\partial z}\left(\gamma \frac{Q^2}{A}\right) + \frac{A}{\rho}\frac{\partial P}{\partial z} + F_r \frac{Q}{A} = 0, \tag{2}$$

Herein, t and z represent the time and the axial coordinate of the coronary artery, respectively; A is the artery's cross-sectional area, Q the volumetric blood flow rate, and P the intravascular blood pressure; γ is the momentum-flux correction coefficient determined by the cross-sectional flow velocity profile; and F_r represents the blood viscous force per unit length. To complete the system of (1) and (2), a constitutive equation representing the viscoelastic behavior of vessel wall upon varying transmural pressure was introduced [7]:

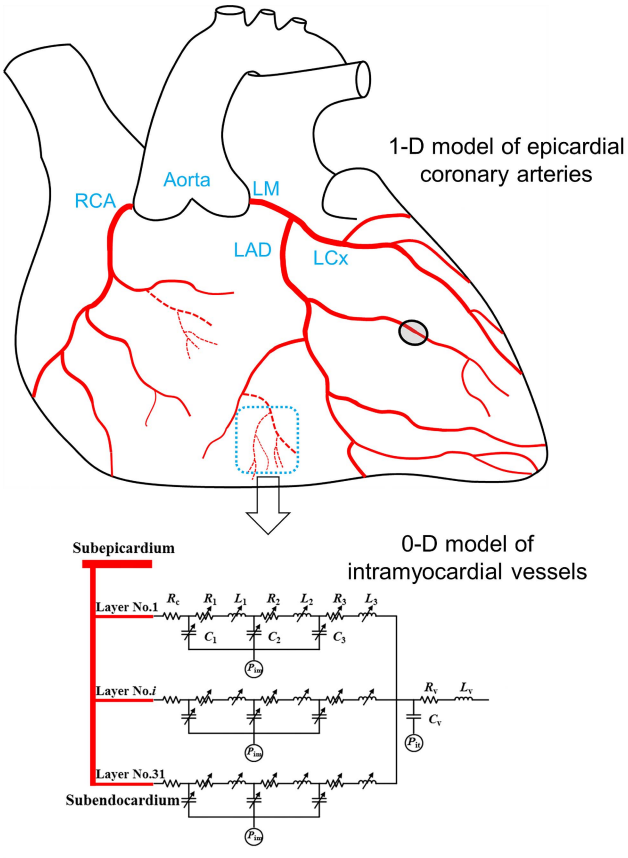

Fig. 1. Schematic description of geometrical multi-scale modeling of the coronary circulation. See the text for the full names of the abbreviations (i.e., LAD, LCx, RCA).

$$P + \tau_\sigma \frac{\partial P}{\partial t} = \phi(A) + \tau_\varepsilon \frac{\partial \phi(A)}{\partial t}, \quad \text{with} \tag{3}$$

$$\phi(A) = \frac{Eh}{r_0\left(1-\sigma^2\right)}\left(\sqrt{\frac{A}{A_0}} - 1\right) + p_0$$

Herein, τ_σ is the relaxation time of constant stress; τ_ε is the relaxation time of constant strain; E and h denote respectively the Young's modulus and thickness of the artery wall; P_0 is the reference pressure at which the lumen area and radius of coronary artery are denoted by A_0 and r_0 , respectively; and σ is the Poisson's ratio.

In addition to the equations that govern blood flow in a single coronary artery, equations that represent mass and momentum conservation at the bifurcation were introduced to link blood flows in adjacent coronary arteries [8].

The distal ends of the 1-D coronary artery model were coupled to 0-D models of intramyocardial vessels that supply blood to the myocardium (see the dashed box in Fig.1). Herein, each intramyocardial vascular subsystem was assumed to consist of vessels distributed in 31 myocardial layers [6]. The vessels in each layer were again separated into the arterial, capillary and venous compartments to account for the physiological distribution of compliance and resistance along the vascular system. Intramyocardial pressure was estimated based on the cardiac cavity blood pressure and shortening-induced intramyocyte pressure [9], and distributed in a linear manner among the myocardial layers according to their penetration depths. Moreover, the resistance and compliance in each vascular compartment were set to be functions of local vascular volume to represent the time-varying vascular load over a cardiac cycle.

In a coronary artery with stenosis, the occurrence of flow turbulence in the post-stenosis region may induce considerable energy loss that cannot be fully described by the 1-D hemodynamic equations. To solve this problem, we separated out the stenotic segment from the 1-D artery model, and instead represented it with a lumped-parameter stenosis model [10], in which the pressure drop (ΔP) across the stenosis was related to the local blood flow rate (Q) according to:

$$\Delta P = \frac{K_v \mu}{A_0 D_0} Q + \frac{K_t \rho}{2A_0^2}\left(\frac{A_0}{A_s} - 1\right)^2 Q|Q| + \frac{K_u \rho L_s}{A_0}\frac{dQ}{dt}, \tag{4}$$

Herein, A_0 is the lumen area of the normal artery segment; A_s and L_s represent the lumen area and length of the stenotic segment, respectively; μ denotes the viscosity of blood. K_v, K_t and K_u are empirical coefficients determined by fluid dynamics experiments.

The values of model parameters were estimated through calibrating model predictions to population-averaged clinical data [6]. The resting baseline values of the total resistances of the intramyocardial vascular systems distal to the three coronary branch arteries (i.e., left anterior descending coronary artery, LAD; left circumflex coronary artery, LCx; and right coronary artery, RCA) were set to 78.53, 126.53 and 122.91 mmHg·s/ml, respectively. They were further reduced to 20.54,

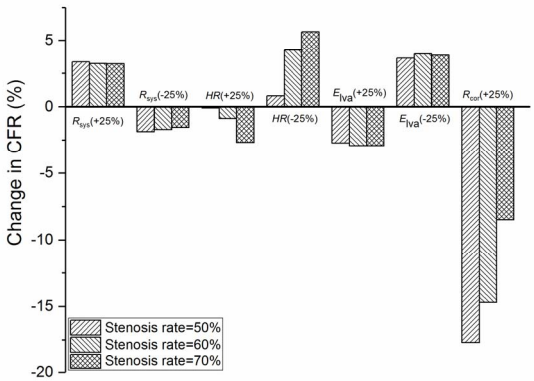

Fig.2. Effects of variations in cardiovascular parameters (±25%) on CFR.

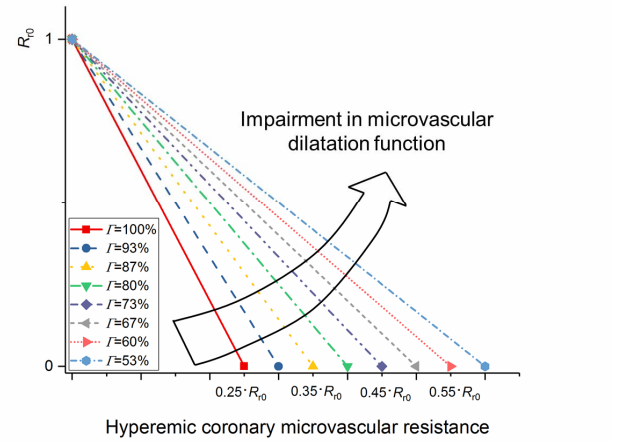

Fig.3. Index (Γ) of microvascular dilatation function calcuated based on hyperemic coronary microvascular resistance. R_{r0} is the normal resting resistance, while $0.25 \cdot R_{r0}$ represents the ideal hyperemic resistance corresponding to a Γ of 100%.

38.34 and 33.92 mmHg·s/ml, respectively, when simulating the vasodilator-induced hyperemic conditions [11].

CFR was calculated based on the simulated resting and hyperemic blood flow rates in a branch artery of the LAD (denoted by the filled gray circle in Fig.1). A stenosis was introduced into the artery, with its stenosis rate being set respectively to 50%, 60% and 70% to represent different stenotic conditions. The sensitivity of CFR was investigated with respect to several cardiovascular parameters considered to affect coronary blood flow in the resting conditions or at maximal vasodilation. The parameters included the total systemic vascular resistance (R_{sys}, which is a major determinant of the perfusion pressure of the coronary circulation), the hyperemic microvascular resistance (R_{cor}, which reflects the maximal dilatation capacity of coronary microvasculature), heart rate (HR), and the maximum value of the left ventricular active elastance (E_{lva}, which represents the ventricular contractility). In the numerical simulations, R_{sys}, HR and E_{lva} were each increased and reduced relative to its default value by 25%, respectively; whereas, R_{cor} was only increased by 25% for the hyperemic conditions to represent the impairment in microvascular dilatation function. To facilitate a quantitative comparison among the changes in CFR induced by the variations in different parameters, the percentage changes in CFR relative to the reference values (simulated before varying the parameters) were calculated.

III. Results

Fig.2 shows the percentage changes in CFR in response to variations in different parameters. CFR was affected significantly by the variation in R_{cor}, and moderately by the variations in E_{lva}, HR and R_{sys}. When the sensitivity of CFR to parameter variation was examined in the context of various stenosis severities, different patterns were observed. For instance, the impact of HR variation on CFR was remarkably enhanced at high severity of stenosis compared with the low stenosis severity case, in contrast, the sensitivity of CFR to R_{cor} decreased gradually following the increase in stenosis severity.

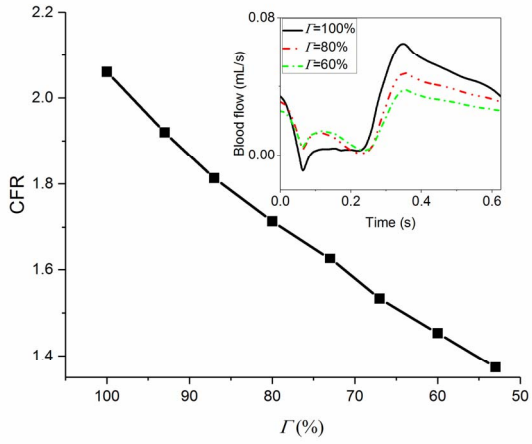

Fig.4. Effect of impairment in coronary microvascular dilatation function (i.e., decrease in Γ) on CFR. The embeded figure shows the changes in flow waveform in the post-stenosis coronary artery segment with Γ.

Relatively, the influences of E_{lva} and R_{sys} on CFR were independent of stenosis severity.

Additional numerical simulations were performed to investigate in more detail the effects of R_{cor} on CFR since the dilatation function of coronary microcirculation has been extensively demonstrated to be an important predictive factor for clinical outcomes [4]. Herein, we introduced a new index (Γ) to quantify the status of microvascular dilatation function, which was calculated based on the baseline vascular resistance in the normal resting conditions (R_{r0}), the actual hyperemic vascular resistance (x), and the expected ideal hyperemic vascular resistance (R_{h0}, estimated to be $0.25R_{r0}$ according to the clinical data [2]): $\Gamma = (R_{r0} - x)/(R_{r0} - R_{h0}) \times 100\%$. As shown in Fig.3, when x was varied from $0.25R_{r0}$ to $0.6R_{r0}$, Γ decreased from 100% to 53.3%, representing the progressive impairment in vasodilation function of coronary microcirculation. In this

set of numerical simulations, the diameter stenosis rate of the coronary artery was fixed at 70% , a critical value for clinical decision-making. Obtained results showed that the impairment of coronary microvascular dilatation function was accompanied by a progressive decrease in CFR and changes in coronary artery flow waveform characterized by the reducing mean flow rate and diastolic flow proportion (see Fig.4).

IV. Discussion

Our study revealed that CFR was subject to the influence from various cardiovascular parameters unrelated to coronary artery stenosis. In particular, the sensitivity of CFR to some parameters was found to vary with the severity of stenosis. These findings are basically in accordance with the clinical observations published previously [4], implying the complex responses of CFR to variations in coronary and systemic cardiovascular conditions.

Among the cardiovascular factors investigated in the study, the dilatation function of coronary microcirculation was found to have the strongest influence on CFR. Insufficient dilatation of coronary microcirculation under the hyperemic conditions may be caused by microvascular dysfunction often present in patients with left ventricle hypertrophy, diabetes mellitus or severe arterial hypertension [1]. In addition, hyperemic response may differ depending on the type of vasodilator or method of vasodilator administration [2], leading to different degrees of microvascular dilation. Moreover, the microvascular dilatation capacity per se has been found to exhibit considerable variability among patients without evident microvascular dysfunction [2]. All these factors would introduce uncertainties in CFR measurement. From our numerical results, such uncertainties are expected to be especially significant when the severity of a stenosis is mild to moderate.

In summary, our study demonstrates that various cardiovascular properties unrelated to the severity of coronary artery stenosis could affect the outcome of CFR measurement. Therefore, knowledge of the patient-specific conditions of the global cardiovascular system, especially the vasodilation function of coronary microvasculature, is essential for clinicians to better understand the implications of CFR.

Acknowledgement

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