Vessel Diameter: A Key Factor Influencing Fractional Flow Reserve

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Abstract

In this study, we explored the effect of vessel diameter of coronary artery where the stenosis is located on FFR at the same vascular level. This study is divided into two parts: clinical statistics and numerical simulation. In the clinical statistics section, we compared the blood vessel diameter where the stenosis is located of the ischemic group and the non-ischemic group. In the numerical simulation section, we further explored the effect of diameter on myocardial ischemia by using an ideal model. With the increase in stenosis rate and stenotic vessel flow, the FFR rate of the larger stenotic vessels was higher than that of smaller stenotic vessels. The larger blood vessels are more prone to ischemia when coronary artery stenosis occurs.

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death and morbidity globally ^[1]. Coronary artery disease (CAD) ^[2] is the most common CVD and is closely linked with atherosclerosis ^[3]. Atherosclerosis causes stenosis of the lumen of the coronary arteries. However, there is no absolute correlation between the degree of coronary arterial stenosis and functional myocardial ischemia myocardial ischemia does not necessarily positively correlate with coronary stenosis ^[4]. Myocardial ischemia is influenced by many other factors, such as the nature of the plaque, the location of the stenosis, the length of the stenosis and the minimum diameter of the stenosis, among others ^[5].

At present, the gold standard assessment of the hemodynamic significance of coronary stenosis is fractional flow reserve (FFR) ^[6–8], which is the ratio of maximal coronary blood flow through a stenotic artery to the maximum achievable blood flow in the same vessel in the hypothetical absence of the blockage. Considering that FFR is of paramount importance, it is crucial to acknowledge all potential bias during the assessment. In recent years, with the development of computational fluid dynamics, personalized hemodynamics simulation based on medical imaging and noninvasive numerical computation of FFR has become a reality, thus providing a new noninvasive method for the functional determination of coronary artery stenosis ^[9–19]. FFR_{CT} is a noninvasive indicator for the diagnosis of functional ischemia.

Taking into account the paramount position of FFR, it is important to explore the relationship between myocardial ischemia and FFR. In clinical statistics, we found that under the condition of the same stenosis rate, patient 1 presented myocardial ischemia and patient 2 presented no myocardial ischemia. The specific situation is shown in Fig. 1. We found that the blood flow in patient 1 was higher than that in patient 2 at the same stenosis rate. The distribution of flow depends on the diameter of the vessel, according to Allometric scaling laws ^[20]. Therefore, we suspect that vessel diameter of coronary artery where the stenosis may have a certain effect on myocardial ischemia in the same level of coronary artery.

The mathematical relationship between vessel size and flowrate was first proposed by Murray^[21]in 1926, as $Q \propto d^k$, where Q is the flow rate through a blood vessel, d is its diameter, and k is a constant derived

empirically for which Murray proposed a value of 3. So, the diameter of the blood vessel decreases as the blood flow decreases. The instantaneous value of the distal to the aortic pressure ratio (P_d / P_a) approximates 1 at the moment of systole when the flow is close to zero. In steady-state fluid dynamics, zero flow implies no pressure gradient [22]. When the stenotic vessel diameter varies, the FFR will change.

In this study, we did clinical statistics and calculated the mean diameter of the stenotic vessels in the ischemic and non-ischemic groups of patients with moderate stenosis.

On the other hand, we conducted two experiment of numerical simulations to explore the relationship between diameter and myocardial ischemia

2. Methods

2.1 Clinical statistics: Enrolled patients

This study is a retrospective multi-center trial study. We counted 150 stenosis vessels of 136 patients who underwent FFR catheter surgery in Peking University People's Hospital, Beijing An Zhen Hospital of the Capital University of Medical Sciences and The Second Affiliated Hospital of Zhejiang University from 2017 to 2020. All patients underwent CTA scanning. Every central institution has undergone an ethical review, all patients signed informed consent forms. We confirmed that all experiments were performed in accordance with relevant guidelines and regulations. The exclusion criteria of the clinical trial in this study included poor CTA image quality, coronary artery occlusion, and patients undergoing thoracotomy with Tavi, as shown in Fig. 2 for the inclusion process.

We need to conduct THREE-DIMENSIONAL reconstruction of patients' CTA images, obtain personalized coronary artery vascular structure of patients, and measure the coronary artery vessel diameter of each patient. The resolution of CTA image was 512×512 pixels, the adjacent slice layer was 1mm and the pixel quality of each slice was $0.5\text{mm} \times 0.5\text{mm}$. Mimics 20.0, an interactive medical image control system, was used for image reconstruction in this study, and the diameter of vessel stenosis was measured in the software, as shown in Fig. 3. All patients' clinical data were processed by the Statistical software IBM SPSS Statistics. We compared differences between the ischemic group and the non-ischemic group by one-way ANOVA using the F-test for diameter.

2.2 Numerical simulation experiment: Idealized construction of the three-vessel model of coronary artery

According to the standard structure of the patient's coronary artery model, we established 8 idealized coronary artery models (1, 2, 3, 4, 5, 6, 7 and 8) containing three vessels (right coronary artery, left anterior descending branch (LAD) and left circumflex artery (LCX)). For the 3D model of the coronary artery, it was assumed that the vessel wall was rigid^[23]. Models of coronary artery stenosis were divided into two groups based on the diameter.

The stenosis of models 1, 2, 3 and 4 were located in the LAD (diameter 4 mm), and the stenosis rate was 40%, 50%, 60% and 70%, respectively. The stenosis of models 5, 6, 7 and 8 were located in LCX (diameter 3 mm), and the stenosis rate was 40%, 50%, 60% and 70%, respectively. The rate of narrowing was calculated from the diameter of the narrowing. as shown in Fig. 4.

The above models were divided into tetrahedral meshes by ANSYS ICEM CFD software. As shown in Fig. 5. the meshes of all models were analyzed with mesh sensitivity. Through ANSYS CFX finite element simulation, we assumed that the vascular wall was rigid and impermeable without slippage, the blood material property was adiabatic and comprised of incompressible viscous Newtonian fluid, and its flow was unsteady laminar flow. The density of blood flow was set at 1050 kg/m³, and the viscosity of blood was set at 0.0035 Pa · s.

2.2 Geometric multi-scale coupling calculation method

In this study, coronary artery geometric multi-scale methodology^[24] was used to calculate FFR_{CT}. The 0D/3D coupled geometric multi-scale model is composed of two parts, one is the three-dimensional model composed of three vessels of the aortic root and coronary artery, and the other is the local standard coronary artery lumped parameter model, which provides boundary conditions for the three-dimensional model.

As shown in Fig. 6. The entrance of the 3D model of coronary artery is connected with a lumped parameter model simulating a human heart module, and the exit is connected with a lumped parameter model simulating an aorta module and coronary microcirculation model, respectively^[25]. The lumped parameter module provides boundary conditions for the hemodynamic solution of the 3D model of coronary artery.

In the centralized model of multi-scale cardiac modules, the power source cardiac contraction is represented by time-varying capacitance, which can simulate the periodicity of the ventricle. Suga and Sagawa et al.^[26] established the relationship between ventricular pressure and volume through animal experiments. The pressure-volume relationship is represented by the time-varying function $E(t)$ ^[27],

$$E(t) = (E_{max} - E_{min}) * E_n(t_n) + E_{min} \quad (1)$$

$$E_n(t_n) = 1.55 \left[\frac{\left(\left(\frac{t_n}{0.7} \right)^{1.9} \right)}{1 + (t_n/0.7)^{1.9}} \right] \left[\frac{1}{1 + (t_n/1.17)^{21.9}} \right] \quad (2)$$

E_{max} and E_{min} respectively represent end-diastolic and end-systolic ventricular pressures. $E_n(t_n)$ ^[28] is the elastic modulus varying with time and refers to the time of a cardiac cycle. Besides, in the lumped parameter model, we adopted the optimization algorithm (simulated annealing method) to optimize the model's pressure and flow waveform, capacitive inductance and other parameters^[29].

2.3 Calculation of FFR_{CT}

Estimation of FFR based on coronary CTA image comprises five necessary steps: [33]. (1) an accurate personalized epicardium coronary artery anatomical model was constructed based on CTA images; (2) determination of the total coronary artery vessel flow and each branch flow under normal (assuming no vascular stenosis) resting state; (3) determination of the resistance of coronary microcirculation in resting-state; (4) quantification of the change of microcirculation resistance under maximum hyperemia; and (5) the governing equation (N-S equation) of the fluid in the coronary arteries was numerically calculated to obtain the flow rate and pressure in the coronary arteries in resting and congested states, and then FFR was calculated.

2.4 Design of the experiments

According to Kim et al, the total coronary artery flow accounts for 4% of the cardiac output [25]. So, the flow in each branch of the coronary artery can be changed in different models by changing the value of cardiac output. Experiment 1 explored the changes of FFR_{CT} with vessel diameters of 4 mm and 3 mm under different stenosis rates at a specific cardiac output. We used the physiological parameters of standard patients as the initial conditions for multi-scale calculation: heart rate 75 per min, systolic diastolic pressure:120/80 and cardiac output: 5L/min. We calculated FFR_{CT} value and FFR_{CT} rate of change of eight models. Experiment 2 explored the changes of FFR_{CT} with vessel diameters of 4 mm and 3 mm under the same stenosis rate but different cardiac outputs. We took 50% stenosis in the moderate degree as an example, and calculated FFR_{CT} value and rate of change under the condition of model 2 and 6 with a cardiac output of 4 L/min, 5 L/min, 6 L/min and 7 L/min, respectively.

3. Results

3.1 Clinical statistical results

In this study, a total of 131 patients with 144 stenotic coronary artery vessels who underwent FFR catheterization were enrolled, as is shown in Table 1. Patients were divided into ischemic and non-ischemic groups with an FFR=0.8 as the cut-off point. In the ischemic group, there were 47 stenotic vessels with FFR less than 0.8. In the non-ischemic group, there were 97 narrowed vessels greater than 0.8. Statistical analysis showed that the mean (standard deviation) vascular diameter of the ischemic group was 3.67±0.94 mm and that of the non-ischemic group was 3.31±0.90 mm (P<0.05 for difference), as is shown in Fig. 7.

Tab. 1 Basic information on enrolled patients

Stenosis	Ischemic (n=42)	Non-ischemic (n=83)
Gender	31 (male):11 (female)	55 (male):28 (female)
Age (years)	60.00±8.30	60.21±10.80
Heart rate (beat/min)	70.19±10.33	68.93±9.64
SDP/DBP (mmHg)	135.16±14.75 / 80.35±8.79	129.91±17.03 / 75.70±12.00
CO (L/min)	4.84±1.04	4.87±1.40

3.2 Numerical simulation results

It can be seen from Fig.8 that with the increase in stenosis rate, the value of FFR_{CT} decreases gradually. In contrast, the FFR_{CT} value for vessel diameter 4 mm is always lower than that of vessel diameter 3 mm.

Values for resting flow and hyperemia flow are shown in Table 2. Results from Table 2 and Fig. 9 show that with the increase in stenosis, the hyperemia flow of 3mm and 4mm vessels gradually decreases, and the FFR_{CT} also gradually decreases. When the stenosis changes to 70%, the flow rate of the 4mm diameter vessel changes substantially than that of the 3mm diameter vessel.

Tab.2 FFR_{CT} values at different stenosis rates

Experiment 1						
	Diameter 4mm			Diameter 3mm		
	Resting flow (kg/s)	Hyperemia flow (kg/s)	FFR _{CT}	Resting flow (kg/s)	Hyperemia flow (kg/s)	FFR _{CT}
stenosis40%	1.37	5.58	0.86	0.57	2.52	0.90
stenosis50%	1.37	5.20	0.80	0.57	2.36	0.84
stenosis60%	1.37	4.29	0.66	0.57	2.01	0.71
stenosis70%	1.37	2.376	0.35	0.57	1.41	0.50

According to the changes in coronary flow in Table 2, the line graph of the rate of change of FFR with the change of flow is portrayed in Fig. 10. The average change rate of vessel diameter 4 mm is 17%. The average change rate of vessel diameter 3 mm is 13%. The FFR_{CT} changes of blood vessels with a diameter of 4 mm are more pronounced.

It can be seen from Fig. 11. that with the increase in cardiac output, the value of FFR_{CT} decreases gradually. As the flow changes, the FFR_{CT} of stenotic vessel diameter 4 mm is always lower than that of the 3 mm diameter.

With the increase in cardiac output (Fig.12), the flow in stenotic blood vessels increases and the FFR_{CT} value gradually decreases. When the cardiac output is 7 L/min, the hyperemia flow of a stenotic vessel with a diameter of 4 mm changes more. The flow change range of a stenosis of 4 mm diameter is more extensive than that of 3 mm, and the FFR_{CT} is lower.

Tab.3 The FFR_{CT} of model 2,6

Experiment 2						
	Model 2 Stenosis 50%			Model 6 Stenosis 50%		
	Resting flow (kg/s)	Hyperemia flow (kg/s)	FFR_{CT}	Resting flow (kg/s)	Hyperemia flow (kg/s)	FFR_{CT}
4L/min	2.27	4.414	0.841	0.92	1.961	0.879
5L/min	1.98	5.171	0.801	0.81	2.345	0.842
6L/min	1.70	5.755	0.763	0.69	2.659	0.806
7L/min	1.42	6.683	0.721	0.57	3.157	0.765

According to the changes of coronary flow in Table 3, we also presented the line graph of rate of change of FFR with the change of cardiac output (Fig.11). The rate of change of stenotic vessels with a diameter of 4mm is always higher than that of vessels with a diameter of 3mm. As shown in Fig. 13. The average change rate of diameter 4 mm is 4%. The average change rate of diameter 3 mm is 3%.

4. Discussion

In further analysis, patients with stenosis were divided into ischemic and non-ischemic groups, and there were significant differences in vessel diameters between ischemic and non-ischemic groups. All patients with moderate stenosis were selected. The mean diameter of the vessels to stenosis in the ischemic group was larger than the mean diameter of the vessels to stenosis in the non-ischemic group. Coronary arteries with larger diameter had more branches downstream than those with thin diameter, and the area of the myocardial perfusion area was more extensive.

Stenotic vessels with larger diameters are more prone to ischemia than those with smaller diameters, which can be explained from the perspective of human coronary artery physiology. According to the Allometric scaling laws, the relationship between diameter and the corresponding perfusion area downstream of the coronary artery is $D=0.8 \cdot M^{0.8}$, (D is diameter, M is myocardial perfusion area). It can be seen from the formula that the larger the vessels, the greater the perfusion area downstream, and the smaller the perfusion area supplied by the finer vessels. As shown in Fig. 14. When stenosis occurs, the blood flow of the narrowed blood vessels is impaired and the perfusion area supplying the downstream is insufficient. Patients are then more likely to have myocardial ischemia.

In this study, we conducted a numerical simulation experiment which was based on the idealized complete three-vessel coronary artery model of the real structural members of the coronary artery, which includes the right coronary artery, the left main artery, the left anterior descending branch and the left cyclotron branch, which is different from the previous idealized straight model [5]. The idealized three-branch coronary artery model can better reflect the complete hemodynamic environment of the coronary artery. The idealized moderate coronary artery stenosis (40%-70%) hypothesis was proposed because the majority of patients whose clinical information was examined by FFR had moderate stenosis (40%-70% stenosis). The moderate narrowness of the model is a reasonable assumption, which simplifies the calculation in other models.

To ensure the authenticity of FFR_{CT} calculations, we chose the geometric multi-scale calculation method [24], which is internationally recognized [31–32]. Also, to improve the computational efficiency of the model, we optimized the parameters of the lumped parameter model OD [29] to ensure that the pressure waveform and flow waveform are consistent with clinical practice.

Two groups of experiments were conducted in this study. In experiment 1, we varied the stenosis rate on vessels with different diameters, which simulated the stenosis of the anterior descending and circumflex branches with different diameters. With the change of time, the stenosis rate gradually increased. We found that the FFR value of vessels with large diameter changed quickly and was more prone to ischemic changes. In experiment 2, we simulated different patient types by varying the flow across vessels of different diameters. With regards to the same stenosis rate, the larger the diameter of the stenotic vessel, the more extensive the variation range of the stenosis vessel flow, the higher the average rate of FFR change, and the more the ischemic changes. From the two groups of experiments, it can be seen that the change in stenosis rate has a more pronounced influence on the FFR value of coarse vessels. It can be concluded that the stenosis rate increases over time and the vessels with thicker stenosis diameter are more likely to have myocardial ischemia.

The effect of the diameter of the vessel to stenosis on FFR can explain the phenomenon of no absolute correlation between the degree of coronary arterial stenosis and functional myocardial ischemia. When the patient has stenosis and no ischemia, it may be that the patient's stenosis is relatively small and can meet the perfusion area of the downstream coronary artery after stenosis, so the blood vessel is not ischemic. By analyzing the diameter of the narrowed blood vessels, we can provide healthcare professionals with suggestions on the management of multi-branch stenosis and make reasonable surgical treatment plans.

5. Conclusion

We found that in stenotic vessels, for both changes in stenosis rate and flow, the FFR change rate of the thicker vessels was greater than that of the thinner vessels, and the vessels were more prone to ischemia.

A thicker vessel is required to supply a greater area of myocardial perfusion. The larger the diameter of the coronary artery in which the stenosis is located, the greater the risk of ischemia and vice versa.

6. Study Limitations

In this study, we conducted two sets of numerical simulation experiments. When both large and small vessels were stenosed simultaneously, the experiment 1 simulation showed that large vessels were more prone to ischemia than small vessels in the same coronary artery model. The experiment 2 simulation showed that large vessels were more prone to ischemia than small vessels in the different coronary artery models. However, the clinical data results could only validate findings from experiment 2 and not 1; in different patient models of the coronary artery, the larger vessels were more prone to ischemia.

7. Declarations

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Additional Information

This study was approved by the medical ethics committee of Peking University People's Hospital, Beijing An Zhen Hospital of the Capital University of Medical Sciences and The Second Affiliated Hospital of Zhejiang University. The authors declare that they have no conflict of interest.

Author contributions

All authors were fully involved in the study. Jincheng Liu designed the research approach, carried out the clinical statistics and simulation experiments, analyzed results and write the article. Suqin Huang and Bao Li carried out some simulation experiments. Hao Sun and Xiaolu Xi collected clinical data. Liyuan Zhang, Tianming Du and Haisheng Yang revised the manuscript. Jian Liu provided the physiological data. Youjun Liu are the subject guidance.

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Figures

Figure 1

Coronary angiogram of the patient. The clinical FFR value was 0.72 in patient 1, The clinical FFR value was 0.95 in patient 2.

Figure 2

Study enrolled patients

Figure 3

Measurement of coronary artery diameter where the stenosis is located.

Figure 4

(a) Diameter 4 mm, 40%, 50%, 60% and 70%. (b) Diameter 3 mm, 40%, 50%, 60% and 70%.

Figure 5

Tetrahedral mesh of the geometric models.

Figure 6

The 0D/3D coupled model of coronary system.

Figure 7

Mean vessel diameter in ischemic and non-ischemic groups.

Figure 8

(a) Diameter 4 mm, 40%, 50%, 60%, 70%, FFR counter. (b) Diameter 3 mm, 40%, 50%, 60%, 70%, FFR counter.

Figure 9

Relationship between hyperemia and FFR.

Figure 10

FFR CT change rate line chart.

Figure 11

(a)Diameter 4mm, FFR CT countor. (b)Diameter 3mm, FFR CT countor.

Figure 12

Relationship between hyperemia and FFR.

Figure 13

FFR CT change rate line chart.

Figure 14

Schematic diagram of myocardial perfusion area.