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Estimating current and long-term risks of coronary artery in silico by fractional flow reserve, wall shear stress and low-density lipoprotein filtration rate

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Abstract

**Background:** Hemodynamic changes and consequent low-density lipoprotein (LDL) filtration play an important role in the atherosclerotic plaque development of coronary arteries. In this pilot controlled case study, we aimed to investigate the correlation between parameters derived from computational fluid dynamics (CFD) simulation and risks (both current and long-term) of coronary atherosclerosis.

**Methods:** We reconstructed geometric models from the baseline computed tomography (CT) angiography of two subjects, one patient and one healthy control, and performed CFD simulations. We estimated the current risk of ischemia by fractional flow reserve (FFR). We estimated the potential risk of plaque development by wall shear stress (WSS) and LDL filtration rate with follow-up clinical imaging validation. We investigated the effects of simulation methods (transient/static) and rheological models (Newtonian/Carreau-Yasuda) by comparing the corresponding results (FFR, WSS and LDL filtration rate) in the patient’s left anterior descending coronary artery (LAD).

**Results:** In baseline CFD simulation, FFR indicated mild current ischemic risk of the patient, in accordance with existing angina pectoris. Baseline WSS and LDL filtration rate results were related with in-vivo plaque development. The plaque-growth locations in follow-up CT angiogram coincided with areas of low WSS and high LDL filtration rate in the baseline simulation. The LDL filtration rate delineated more specific risky areas than WSS. Between transient and static results, the difference of FFR was less than 5% in the whole model. As to WSS and LDL filtration rate the transient/static difference was within 20% in most areas, but rose up to 50% for WSS and even higher for LDL filtration rate, in areas with low WSS and high LDL filtration rate. As to rheological effects, Newtonian/Carreau-Yasuda difference was negligible for FFR throughout the model, within 30% for WSS and LDL filtration rate in major areas, and 50% or higher in certain segments where low WSS and high LDL filtration rate existed.

**Conclusion:** CFD results appeared to be related with in-vivo development of coronary atherosclerosis. Simulated FFR and its threshold value 0.8 demonstrated the ischemic risk. Both WSS and LDL filtration rate could indicate areas of plaque growth.
Introduction

Coronary artery disease (CAD) constituted significant morbidity, mortality, medical and socio-economic costs.[1] As to coronary artery stenosis, conventional assessment by luminal stenosis alone was insufficient to guide therapy.[2] Fractional flow reserve (FFR) that can reveal adverse hemodynamic changes and mechanical properties of plaques has become an important parameter determining the indication for angioplasty and stenting.[3] FFR can be calculated as a pressure ratio: pressure distal to the stenosis divided by the pressure proximal to the stenosis.

In recent years, various computational fluid dynamics (CFD) models have been applied in the CAD studies.[4] As a hemodynamic parameter derived from CFD, wall shear stress (WSS) might be correlated with atherosclerosis[5], in which, low and oscillatory WSS might predispose to plaque formation and development. Geometry of arteries, such as vessel tortuosity and severity and morphology of stenosis could govern WSS distribution.[6]

Based on the 3-pore filtration model, the low-density lipoprotein (LDL) filtration rate, which was directly related with plaque formation process, could be calculated from CFD simulation results.[7] There was a couple of applications in single coronary arteries.[8, 9] However, recent studies that employed Newtonian fluid model in estimating WSS and LDL filtration might not mirror in-vivo pathophysiology.[10]

The aim of this study was to initially examine if CFD simulation could reflect the current and long-term risks of atherosclerotic stenosis in coronary arteries. We derived FFR to estimate the current ischemic risk. To estimate the long-term risk of plaque development, we calculated WSS and LDL filtration rate. To evaluate the relationship between these parameters and in-vivo plaque development, we compared the risky areas suggested by baseline WSS and LDL filtration rate results with follow-up clinical imaging. Finally, we investigated the effects of simulation types (transient/static) and rheological models (Newtonian/Carreau-Yasuda) on FFR, WSS and LDL filtration rate, by comparing the corresponding simulation results.

Methods

1. Geometry reconstruction and processing

Our data were from General Hospital of Guangzhou Military Command of PLA. To observe the development of atherosclerotic plaques for comparison, we chose the data from a male patient who had baseline and follow-up Computed Tomography (CT) examination in 2011 and
2015, and a healthy male control CT-examined in 2012 and 2016. Individuals were well-informed with agreements signed.

To estimate the correlation between simulated hemodynamic parameters and in-vivo plaque development, we reconstructed models of both individuals from their baseline imaging on software MIMICS 14.0, and subsequently smoothed the initial geometries, with erroneous details amended. Finally we trimmed the distal outlets and aorta. Fig.1 revealed a focal stenosis (arrow) over the patient’s left anterior descending coronary artery (LAD) (80% in diameter and over 90% in area, at throat). Some minor distal stenoses followed this focal one. We retained distal tributaries in the 3D geometry as far as possible to preserve the integrity of the whole patho-physiology.

Figure 1. Initial and processed geometries. The patient had a stenosis in LAD, the CT image in the lower right panel shows this focal stenosis caused by atherosclerosis plaques.
2. CFD simulation

Meshing: We fulfilled the meshing with software CFX-ICEM. The maximum element length was 3, 3, 1 and 0.2mm at inlet, aorta outlet, vessel wall, and coronary outlets. Considering different magnitudes of aorta, coronary arteries and distal branches, we applied curvature-dependent meshing method. The mesh density was validated by density-dependence study. Finally, there were 7665574 and 1894238 elements in the healthy and patient models.

Boundary conditions: At aorta inlet, we imposed 120mmHg and 80mmHg as inlet blood pressure for systolic and diastolic simulations. The systolic and diastolic flow rates at aorta outlet were 400 and 10 ml/s, according to clinical measurements.\[11\] It was impractical to measure blood pressure or flow rate at distal outlets. To avoid the errors caused by unrealistic outlet conditions (blood pressure or flow rate), we applied flow resistances. We derived and applied flow resistances based on two assumptions: Firstly, stenosis in the proximal segment did not largely change distal flow resistance.\[19\] In the patient model, we therefore calculated the corresponding normal flow resistances. Secondly, flow distribution followed Murray’s Law: 
\[r_0^3 = r_1^3 + r_2^3\], where \(r_0\) was the radius of the an artery, \(r_1\) and \(r_2\) were the radius of its downstream branches.\[12\] Flow rate of a branch was proportional to the cube of its radius. We measured the outlet cross-section area of each distal branch and distributed the flow resistances according to flow rates. On vessel walls we applied solid wall and non-slip conditions.

Rheological model: Blood is essentially a non-Newtonian fluid due to its shear-thinning effect. To make the simulated hemorheology comparable with physiological condition, we adopted Carreau-Yasuda blood model. In this model, the viscosity \(\eta\) was a non-linear function of shear stress \(\gamma\): [13]

\[\eta(\gamma) = \eta_\infty + (\eta_0 - \eta_\infty)(1 + (\lambda \gamma)^a)^{(n-1)/a}, \] where \(\eta_0 = 0.16 Pa s\), \(\eta_\infty = 0.0035 Pa s\), \(\lambda = 8.2 s\), \(a = 0.64\) and \(n = 0.2128\).

We fulfilled the simulations with ANSYS 15.0 on Dell T7610 workstation, with convergence standard 5e-5. The solving time of each case was about 20 minutes within 150 iterations. In normal large/middle arteries, blood pressure drops little. In consideration of tandem stenoses, we derived FFR as the ratio of local pressure to aorta inlet pressure.\[24\] We drew WSS distribution in contours thus its threshold values could be shown.
3. LDL filtration model

Liquid leak velocity and LDL filtration:

Our LDL filtration calculation was based on a simplified 3-pore model.[7] In Fig.2, the artery wall model consisted of three layers: endothelium, intima with media, and adventitia. Endothelial cells formed normal and leaky junctions through which LDL molecules filtrated from the lumen into the intima. Leaky junctions were formed when the endothelial cells were deformed, rearranged or detached. The quantity of leaky junctions in a certain area depended on local WSS value. Normal junctions blocked the passage of solutes with a radius larger than 2 nm (LDL has a radius of 11 nm).[7] Thus, leaky junctions were the main paths for LDL filtration and accounted for 90% of LDL filtration into artery wall.[14] Therefore, only LDL filtration in leaky junctions was considered here. In leaky junctions, the LDL filtration rate depended on the solvent leak velocity, the transmural concentration difference of LDL, and other parameters. Consequently, the liquid (solvent) leak flow non-linearly promoted the LDL filtration. In Fig.2, we compared the relationship between liquid leak flow and LDL filtration in leaky junctions to two circuits non-linearly coupled by a light-emitting diode and a photodiode.

After passing through the endothelium from the lumen, LDL molecules filtrated through intima and media towards the adventitia. In intima, the oxidation of LDL molecules and subsequent biochemical changes initialized the formation process of atherosclerosis plaques.[15]

![Figure 2. The LDL filtration and its circuit analogy. The solvent leak flows through normal and leaky junctions are marked as fn and fl. P and P0 are the pressures in the lumen and adventitia. Rn,Rl and Rw are the flow resistances in the normal junction, leaky junction and other layers of artery wall, respectively. The LDL filtration rate in leaky junctions depends non-linearly on its transmural concentration difference and solvent leak velocity in leaky junctions.](image)
Calculation of solvent leak velocity:

The total leak velocity of solvent depended on the flow resistances of normal and leaky junctions ($R_n$ and $R_l$), and of others layer of vessel wall ($R_{wall}$).

$$v_{\text{leak}} = \frac{\Delta P}{R_n R_l / \left( R_n + R_l \right) + R_{wall}}$$

where $R_{wall} = \frac{\mu_p \cdot l_{\text{wall}}}{k_p}$, $R_n$ was a constant and $R_l$ depended on the distribution of WSS:

$$R_l = \frac{3R_{\text{cell}} \cdot \mu_p \cdot l_j}{4w^3 \cdot \phi}.$$

We derived the relationship between WSS and $R_l$ from following equations:

$$SI = 0.38e^{-0.79WSS} + 0.225e^{-0.043WSS}$$

$$#MC = 0.003797e^{14.75SI}$$

$$#LC = 0.307 + 0.805 \cdot (#MC)$$

$$\phi = \frac{#LC \cdot \pi R_{\text{cell}}^2}{UA}$$

Table 1 listed the related parameters.

<table>
<thead>
<tr>
<th>Parameters and Variables</th>
<th>Meanings</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta P$</td>
<td>Pressure difference across artery wall</td>
<td>15 [mm Hg]</td>
</tr>
<tr>
<td>$R_n$</td>
<td>Resistance of artery wall except endothelium</td>
<td>8.62*10^8 [s mmHg m^-1]</td>
</tr>
<tr>
<td>$\mu_p$</td>
<td>Viscosity of blood plasma</td>
<td>0.001[Pa s]</td>
</tr>
<tr>
<td>$l_{\text{wall}}$</td>
<td>Thickness of artery wall[16]</td>
<td>0.58[mm]</td>
</tr>
<tr>
<td>$k_p$</td>
<td>The Darcy permeability of artery wall</td>
<td>1.2*10^-18 [m^2]</td>
</tr>
<tr>
<td>$R_{\text{cell}}$</td>
<td>Endothelial cell radius</td>
<td>15[µm]</td>
</tr>
<tr>
<td>$l_{ij}$</td>
<td>Length of a leaky junction</td>
<td>2[µm]</td>
</tr>
<tr>
<td>$w$</td>
<td>Half-width of a leaky junction</td>
<td>20[nm]</td>
</tr>
</tbody>
</table>
The ratio of the areas of leaky and normal cells

Endothelial cell shape index

Number of mitotic cells per unit area

Number of leaky cells per unit area

Unit area

0.64 [mm^2]

Table 1. The parameters in the calculation of LDL leak velocity.

**Calculation of LDL filtration rate in leaky junctions:**

We calculated the LDL filtration rate in leaky junctions from solvent leak velocity. Parameters in this non-linear relationship included radius of LDL molecule.

Firstly, we calculated the free diffusion coefficient which was a polynomial function of the ratio of LDL molecule radius and width of leaky junction. Subsequently we procured the solvent drag coefficient, hydraulic conductivity and diffusive permeability of the leaky junction. Based on these, finally we derived the filtration rate of LDL. The details were omitted and could be referred in theoretical studies.[7]

Finally, to investigate if WSS and LDL filtration rate could predict the risky areas of plaque growth. The results were compared with follow-up 3-D imaging.

**4. Transient Effects**

To investigate the transient effects on the results, we performed a transient simulation on the patient’s model. We adopted Fourier series to delineate the waveform of inlet blood pressure, as a periodic function of time

\[ p(t) = p_0 + \sum_{i=1}^{10} \left( a_i \sin \frac{2\pi t}{T} + b_i \cos \frac{2\pi t}{T} \right) \]

where \( t \) was time, \( a_i \) and \( b_i \) were the amplitudes of \( i \)th harmonic components, \( T=0.8s \) was the length of cardiac cycle, and \( p_0 = 94 \text{mmHg} \) was the time-averaged blood pressure. The maximum and minimum pressure values were 120 and 80 mmHg, corresponding to values in static simulations. The time step was 0.01s. Other conditions were identical with static simulation. Simulations were performed in three cardiac cycles (2.4s). Analysis was based on the data from the second cardiac cycle (0.8-1.6s) to avoid possible initial effects. The results (FFR, WSS and LDL filtration rate) from temporal steps when inlet pressure was 80 and 120 mmHg were compared with static simulations.
Especially, we calculated the FFR value of the focal stenosis in LAD, as the ratio of pressure averaged on cross-sections distal and proximal to the stenosis.

5. Rheological effects

To investigate the rheological effects on the results, we performed two simulations on the patient model by Newtonian (in which the viscosity was a constant 0.0035Pa*s) and Carreau-Yasuda fluid models respectively, with identical mesh and maximum (120mmHg) inlet pressure. The results (FFR, WSS and LDL filtration rate) on LAD segment were compared.

Results

1. Current ischemic risk: FFR

![Figure 3. Systolic/diastolic FFR distribution in both individuals.](image)

Fig. 3 indicated three characters of the FFR distribution. Firstly, in all branches FFR value gradually reduced towards distal segments. Secondly, lowest FFR values existed in the distal segment of the patient’s stenosed LAD. Thirdly, the minimum FFR value in patient’s LAD
approached the threshold of 0.8.[17] LAD was a predominant artery for cardiac blood supply. Therefore, minor ischemic symptoms might occur, and clinical intervention would be inevitable when FFR value was below 0.8 due to plaque growth.

According to the medical documentary, the patient had angina pectoris for over 10 years before his baseline examination in 2011. Thus FFR with its threshold value of 0.8 was effective in estimating the current ischemic risk in our models.

2. Long-term risks: WSS

Fig.4 showed the WSS distribution in each individual, with inlets of coronary arteries magnified. On LAD and LCX, low WSS areas of the patient seemed to be larger than the healthy. On RCA of both subjects, low WSS value spread on the vessel walls.

Around the stenosis in the patient’s LAD, WSS reached extreme values with vehement spatial fluctuation. Fig.5 showed the velocity isofaces and WSS expansion view in patient’s LAD. The skewed streamlines depicted the jet flow distal to the stenosis. Velocity isofaces delineated a low-velocity area opposite to the jet flow side. On the low-velocity side, WSS was low. The white lines encircled the areas with WSS lower than 0.1Pa. These tortuous boundaries indicated complex distribution of low-WSS area.

Figure 4. Systolic/diastolic WSS distribution in the healthy and patient, with identical scale. LAD: left anterior descending artery. LCX: left circumflex branch. RCA: right coronary artery. Inlets of coronary arteries are magnified.
Figure 5. Velocity and WSS distribution around stenosis in LAD of the patient at maximum flow. Upper: Streamline and isosurfaces of velocity. Lower: The position of stenosis, WSS distribution and its expanded view (cylindrical projection). The white line shows WSS threshold value of 0.1Pa.

3. Long-term risks: LDL filtration rate

Fig.6 showed the distribution of LDL filtration rate. We magnified and compared the LAD of both individuals in Fig.7. Parallel to low WSS, high LDL filtration rate appeared in segments both proximal and distal to the stenosis. However, LDL filtration rate distribution had distinct characteristics from WSS distribution. As to risky areas of plaque growth, areas with high LDL filtration rate were more concentrated than low-WSS areas. In the WSS expansion view of Fig.5, the low WSS area was large even with a low threshold (WSS<0.1Pa), but high LDL filtration areas in Fig.7 were concentrated around several spots. In Fig.4, low WSS extended along RCA of the
healthy, but corresponding LDL filtration rate in Fig.6 was moderate.

Figure 6. Systolic/Diastolic LDL filtration rate distribution in the healthy and the patient.
Figure 7. WSS and LDL filtration rate in the LAD of the healthy and the patient.

4. Comparison with clinical examination

We juxtaposed the baseline and follow-up 3-D CT-scanning imaging in Fig.8. The segments with signal lost indicated severe stenoses. In follow-up imaging of the healthy we did not observe obvious plaque growth in RCA, with LAD narrowed a little. Follow-up imaging of the patient showed aggravated stenoses in LAD, with RCA and LCX narrowed.

Our simulation results accorded with in-vivo changes. Both WSS and LDL filtration results were related with stenosis development. In LAD of the patient, the segments with signal lost approximately coincided with low WSS and high LDL filtration areas in CFD results. However, the low WSS area extended out of the segments with plaque development, while areas with high LDL filtration rate were basically within real plaque-growth areas. For example, low-WSS area extended to the inlet of LAD, while neither high LDL filtration area nor CT signal loss area
extended that far.

![3-D imaging of baseline and follow-up examinations](image)

Figure 8. The 3-D imaging of the baseline examinations on which our simulation models were based and the follow-up examinations for validation, reconstructed by volume rendering technique (VRT) on Siemens Syngo 8.0 Multi Modality workstation (MMWP). Original CT images were from Siemens Somatom Definition 64-slice dual-source CT scanner.

6. Transient effects

Fig.9 showed the differences between transient and static results in the patient’s LAD. As to FFR, both results were comparable. For WSS and LDL filtration rate, major differences located in LAD inlet and segment distal to the stenosis.

Fig.10 delineated the relative differences. For FFR, difference was trivial (within 5%) throughout the vessel walls. However, as to WSS and LDL filtration rate, differences were observable in LAD inlet and the distal segment to the stenosis, within which difference rose to 50% in certain areas.
Figure 9. The comparison of FF, WSS and LDL filtration rate values between transient and static simulations of the patient’s LAD.
Figure 10. Relative differences of FF, WSS and LDL filtration rate between transient and static.
simulations of the patient’s LAD.

Figure 11 Transient FFR of the stenosis in patient’s LAD. Left: Positions for measurement of stenosis FFR. Right: FFR fluctuation in a cardiac cycle.

We derived the FFR of stenosis as the ratio of pressure averaged on the planes distal and proximal to the stenosis (Fig. 11, left). The results indicated that, firstly, the fluctuation in a cardiac cycle was negligible (within 1%). Secondly, the static and transient results were comparable. In static simulation, the stenosis FFR value was 0.986 and 0.988 at its maximum and minimum flow. Therefore, static FFR results were reliable to substitute transient values in estimating the ischemic risk of stenosis in our model.

7. Rheological effects

Fig. 12 showed the results on LAD at its maximum blood flow. Between Newtonian and Carreau-Yasuda models, the relative difference of FFR was within 5% throughout the model. For WSS and LDL filtration rate, the difference was within 30% in major areas, and rose up to 50% or ever higher in certain areas proximal and distal to the stenosis. Noticeably, for LDL filtration rate, both negative and positive differences existed in segment distal to the stenosis.
Figure 12. The rheological effect on FFR, WSS and LDL filtration rate distribution in the patient’s LAD at its maximum blood flow: relative difference between Newtonian and Carreau-Yasuda fluid models.

Discussion

Our results suggested that FFR can be useful to estimate current ischemic risk coronary artery disease. WSS and LDL filtration rate might be related to plaque growth in an intermediate-term. Parallel with coronary studies using 3-pore filtration model,[8, 9] we found the distributive similarity between high LDL filtration and low WSS. In comparing the simulation results with the follow-up imaging, LDL filtration rate appeared to identify specific risky areas in our model.

Concordant with findings by Olgac et al [9], we found a common distribution pattern of LDL filtration rate. In Fig.13, the LAD and LCX results were from our patient, while the referred LDL concentration in RCA was derived from, and positively related with, corresponding LDL filtration rate.[9] In all arteries, areas with high LDL filtration rate existed in segments both proximal and
distal to the stenosis. The proximal segments had even higher values. The relationship between LDL filtration, pressure and WSS could partially explain this phenomenon.

LDL filtration rate was related positively with transmural pressure and negatively with WSS. The blood pressure in proximal segment was not affected by downstream stenosis. For laminar flow in a tube, the pressure drop was \( \Delta P = \frac{8\mu Q}{\pi R^4} \), where \( \mu \), \( l \), and \( R \) were viscosity, length and radius of the tube, and \( Q \) was the flow rate. With stenosis, diminished flow caused less pressure drop. Thus the pressure of proximal segment could be even higher than its non-stenosis counterpart. As a result the transmural pressure was normal or even higher, promoting transmural LDL filtration. As to WSS, the decreased flow reduced the velocity in proximal segment, WSS value was consequently lower. More leaky junctions opened with low WSS, accelerating LDL filtration. Both pressure and WSS characteristics were in favor of LDL filtration. Therefore, severe stenosis could inflict plaque growth on both its distal (as often observed),[18] and proximal segments.

![Figure 13. The LDL filtration rate distribution of the patient’s LCX and LAD with maximum blood flows, and LDL concentration results of RCA from existing study. [9]](image)

In our models, branches were preserved as far as possible. Studies showed that the effect of branches should not be neglected.[17] On the flow distribution, two details might affect the accuracy. Firstly, in the patient model, we used Murray’s law to procure normal distal flow
resistances, and adopted the derived values in the simulations. Although deemed as limited,[19] differences between normal and pathological distal flow resistances needs further study. Secondly, the exponent value in Murray’s Law was 3. Some studies used exponent 2.6[20], while parallel studies derived various exponent values.[21, 22] Therefore we used classical value 3 as in existing study.[17]

Risky areas indicated by WSS and LDL filtration rate were related with in-vivo coronary plaque growth. WSS scale (0.5-5Pa) for contour view was wider than existing studies,[18, 23] although broader scale was found.[24] Low and oscillatory WSS was commonly deemed as related with plaque formation. Related parameters derived from WSS such as its gradient showed better predictive efficiency than WSS itself.[25] However, WSS and its variations were mechanical, not physiological parameters. The mechanism of relationship between WSS and plaque growth was still controversial.[26] The mechanism of plaque formation was not only a mechanical but also a biochemical one.[15]

In LDL filtration rate calculation, besides WSS, other factors were included. These factors might have opposite effects to WSS. For example, in the segment distal to the stenosis both blood pressure and WSS were lower. Low WSS gave rise to leaky junctions, therefore promoted LDL filtration. But lower blood pressure decreased transmural pressure gradient and consequent transmural LDL filtration. Therefore, in view of WSS and pressure, stenosis incurred contradictory effects on LDL filtration in its distal segment. Thus, LDL filtration rate was a more intricate parameter than WSS. However, in calculation, parameters such as the LDL concentration in blood, and artery wall permeability, were procured from literature instead of in-vivo measurements. Even if the in-vivo LDL concentration data were available, they could not include the daily fluctuation of LDL concentration which happened on the time-scale of hours. As a result, derived LDL filtration rate did not accorded with in-vivo value. Although the model did not give accurate quantitative prediction, the distribution differences of LDL filtration could help us to estimate the risky areas of plaque growth.

In this study we adopted Carreau-Yasuda fluid model. Actually, Newtonian model was widely used, even in advanced fluid-structure-interaction (FSI) models of coronary arteries.[20] However, neglecting non-Newtonian effect could incur a 10% error of WSS.[10] Parallel study on carotid artery found that the rheological effect on the distribution of LDL filtration rate was not
negligible.[27] In Fig.12, relative WSS difference between Newtonian and Carreau-Yasuda models was trivial in high WSS areas but observable in low WSS areas. Thus, Newtonian model could be acceptable when the velocity (consequently WSS) was high enough.[28] However, in our model the Newtonian/Carreau-Yasuda difference was 50% or even more in low WSS areas. It was low-WSS area that was focused on due to its plaque growth risk. Therefore, to avoid rheological inaccuracy Carreau-Yasuda model was appropriate.

Focusing on WSS and LDL filtration rate, we compared the effects of simulation types and rheological models in Fig.10 and Fig.12. Firstly, in both figures the difference was within 50% in most areas. Secondly, areas with high transient/static difference approximately coincided (but not in superposition) with areas of obvious rheological difference, but smaller in area. Thirdly, transient/static difference was less than Newtonian/Carreau-Yasuda difference in most areas. Therefore, adopting non-Newtonian fluid model could improve the simulation quality better than performing transient simulation.

The limitations of our study included: Firstly, simulations were basically static. Transient simulation was performed only for error estimating instead of setting a baseline. As to FFR, it mainly depended on stenosis magnitude. Its fluctuation within a cardiac cycle was limited.[29] Our results showed that it was reliable to substitute transient FFR with static value. However, WSS and LDL filtration rate could be affected locally, as shown in Fig.10. The transient flow, consequent turbulence, and time-lag effect, were not considered in static state simulations. However, we still adopted static simulation because of following reasons. Firstly, we were lack of in-vivo cyclic blood pressure or flow rate data. With parameters from literature, derived results would deviate from in-vivo values. Secondly, the location and shape of coronary arteries changed vehemently in a cardiac cycle. At least both systolic and diastolic imaging data were necessary to built physiologically reliable models. Our imaging data were not enough for it. Thirdly, the exact lumen radius of coronary arteries depended transiently on myocardial contractility. For example, during systolic period the contracted LAD decreased it radius and blood flow. A complicated heart model was indispensable to take this phenomenon into consideration. Therefore, we applied static simulation for this pilot study. The results were more qualitative than quantitative. Reliable transient simulations could be fulfilled in further studies with available in-vivo data.

Secondly, we applied solid wall assumption. Although the effect of artery wall elasticity on
WSS was deemed trivial,[30] a study showed that neglecting wall elasticity could cause a WSS error of 15%, larger than the that caused by rheological effect of 10%.[10] An atherosclerotic artery wall consists of various components, with different material properties. To divide these components apart, high-quality imaging is necessary. The material properties could change with plaque development. Due to the limited image quality and lack of material properties, we did not perform further analyses. With reliable imaging and parameters, FSI simulation could improve the results by adding elastic artery wall.

Thirdly, in this pilot study we included only two cases for comparison. They were typical cases with follow-up examinations and clinical documentations. Theoretically, as to plaque growth, the predictive effectiveness of parameters such as WSS and LDL filtration rate should be verified by simulating the formation process of plaque in a healthy coronary artery, with another constantly healthy control. However, people seldom do cardiac CT-imaging without probable coronary problems, thus this ideal verification is hardly available. A practical substitution might be to perform a large-scale comparison between normal and pathological cases.

**Conclusions:**

In this pilot study, the parameters derived from CFD simulation showed accordance with follow-up clinical imaging, in estimating current and long-term risks of atherosclerosis in coronary arteries.

1. FFR with its threshold value of 0.8 was effective to estimate current ischemic risk in CFD simulation.

2. Both WSS and LDL filtration rate indicated the relationship with plaque growth. Compared with WSS, risky areas showed by LDL filtration rate were more specific.

3. With existing stenosis, possible plaque growth could happen in both its proximal and distal segments.

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**References:**


