Stress phase angle depicts differences in coronary artery hemodynamics due to changes in flow and geometry after percutaneous coronary intervention

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ATHERSCLEROSIS IS LINKED to low and oscillating wall shear stress (WSS) (4, 20, 22), which is determined by detailed blood flow patterns in arteries. Low and oscillating WSS tends to occur where the flow separates and recirculates. Typically, this occurs downstream of a stenosis, near the inner wall of a tightly curved section or in the vicinity of a bifurcation. Studies focusing on the relationship between hemodynamics and atherosclerosis have shown that the sites of separated and disturbed blood flow correlate well with common sites of atherosclerosis (1, 3, 20). From a fluid mechanics point of view, the main factors influencing flow disturbance in a separation region are vascular geometry (19, 21, 26) and pulsatile flow conditions (13, 18, 34). Myers et al. (23) examined a number of factors influencing hemodynamics in the right coronary artery (RCA) and showed that local geometry was more important than pulsatile flow. In previous studies, comparisons have been made between flows with physiological and idealized waveforms (23, 34), flows with physiological waveforms at rest and exercise conditions (18), and flows with physiological waveforms from different locations in the arterial tree (13). However, the influence of varying flow conditions in different pathological states still remains to be investigated, although significant differences in flow conditions have been reported among healthy, pathological and postoperative states in coronary arteries (25, 33). In this study, the effects of the difference in flow velocity waveform before and after percutaneous coronary intervention involving balloon angioplasty followed by stent placement (PCI) on hemodynamics in a patient-specific RCA were investigated using computational fluid dynamics (CFD).

Time-averaged WSS (TAWSS) and oscillatory shear index (OSI) are commonly used in studies of the relationship between hemodynamics and atherosclerosis. In addition to these indexes, the stress phase angle (SPA), defined as the phase angle between circumferential strain in the arterial wall and instantaneous WSS, has been recently suggested as a potentially important parameter due to its role in regulating the release of vasoactive molecules, nitric oxide (NO), prostacyclin (PGI2), and endothelin-1 (ET-1) (6–9, 28). For example, Dancu et al. (6) reported that the production of NO and PGI2 by bovine aortic endothelial cells is strongly suppressed when SPA = 180° (asynchronous hemodynamic conditions) compared with when SPA = 0° (synchronous hemodynamic conditions). The reduction in NO and PGI2 production was also accompanied by an increase in the production of ET-1, a proatherogenic vasoconstrictor. Computational and theoretical investigations on SPA have also been carried out for end-to-end anastomoses (27), coronary arteries (29), the carotid artery bifurcation (37), and cellular plasma membrane (36). The results of these studies show that SPA is highly negative at sites that are prone to atherosclerosis and suggest that SPA plays an important role in atherogenesis. Hence, SPA was...
included as an additional hemodynamic parameter in this study because it measures the degree of asynchrony between pressure and flow waveforms and is the only parameter that combines the influences of wall mechanics (through circumferential strain) and fluid mechanics (through WSS) factors. In addition to pre- and postangioplasty flow conditions, the effects of arterial geometry (i.e., stenosed and stenosis free) were investigated in this study.

**MATERIALS AND METHODS**

An RCA from a patient with a stenosis was reconstructed based on multislice computerized tomography (CT) images acquired at mid-istole, 75% into the duration of the cardiac cycle, using a Philips Mx8000 IDT 16-detector multislice CT scanner (Philips Electronics, Guildford, UK). The in-plane image resolution was ~0.43 mm/pixel, and the slice interval was 0.5 mm. The RCA was first delineated with CMRtools (CVIS, London, UK). The planes perpendicular to the centerline were computed at 1-mm intervals and used to reslice the data set with cubic B-spline resampling (38). The RCA was then semiautomatically segmented from the resulting stack of cross-sectional images (40). The luminal surface was constructed by an interpolation of the extracted cross-sectional outlines (Fig. 1) using cubic B splines. A model without stenosis was constructed based on the stenosed geometry by eliminating the stenosis and interpolating the luminal surface, assuming a smooth variation in diameter along the centerline. The two RCA models are shown in Fig. 2.

Blood flows in the RCA models were simulated in conjunction with pulsatile inflow conditions based on waveforms acquired with a catheter-delivered ultrasonic-Doppler probe (ComboWire, Volcano) in the RCA of a different patient undergoing PCI. The pressure waveform in the RCA was acquired simultaneously using a pressure transducer located at the tip of the same probe. The output analog signals of pressure and flow were digitized at 1 kHz along with an electrocardiogram using a National Instruments DAQ-Card AI-16E-4.

The velocity waveforms before and after PCI were analyzed. Figures 3 and 4 show the acquired velocity and pressure waveforms that were ensemble averaged for ~60 cardiac cycles. In both figures, three sets of waveforms are shown: waveforms before and after PCI in two patients with severe (> 90%) stenosis and the mean ± SD waveforms of 10 patients whose RCAs were lesion-free upon angiogram examinations (all acquired in the RCA). The velocity waveforms differed after PCI as a result of the change in arterial impedance following PCI, which was not simply caused by the correction of the stenosis but was also likely to be due to effects on the distal coronary circulation (33). The improvement in flow after PCI was witnessed throughout the cycle for

![Fig. 1. The vascular centerline and segmented cross sections of the right coronary artery (RCA).](image)

**Table 1. Computational states**

<table>
<thead>
<tr>
<th>State</th>
<th>Geometry Waveform</th>
<th>Waveform</th>
<th>Before PCI</th>
<th>After PCI</th>
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| 1     | Stenosed          | Stenosis | 18-mm-length drug-eluting stent (Endeavour, Medtronic) for patient 2. The study complied with the Declaration of Helsinki and was approved by the local Research Ethics Committee; all subjects gave written consent. Commercial finite volume CFD suite CFX10 (ANSYS, Canonsburg, PA) was used to obtain numerical solutions. Womersley’s velocity profiles (42) calculated for the measured waveforms were prescribed at the inlet. The inlet was extended for five lumen diameters to let the flow develop sufficiently following local geometry. The outlet was also extended to minimize the influences of the outflow boundary condition on the numerical solutions. In the CFD simulations, the arterial wall was assumed to be rigid because the deformation of the wall is small in the RCA (31). The dynamic motion of the arterial wall owing to cardiac motion was not considered at the present stage because there is evidence that the effects of the motion are secondary to the effects of pulsatile flow conditions (43). Blood was assumed to be Newtonian, and its density and viscosity were set to 1,050 kg/m³ and 4.0 × 10⁻³ Pa·s, respectively. Based on the fluid properties, velocity condition, and arterial geometry, the cycle-averaged Reynolds number and the Womersley parameter were 276 and 2.70, respectively.

An unstructured computational mesh for CFD simulations was generated using ICEM CFD 10 (ANSYS). The mesh resolution, 0.52 mm in axial, 0.32 mm in circumferential directions, and 0.26 mm in cross section (0.041 mm near wall), was optimized by comparing our computational results for pulsatile flow in a curved pipe with published experimental data (30).

Four combinations of geometry and flow conditions were examined (summarized in Table 1): stenosed and nonstenosed geometries, and velocity waveforms before and after PCI. The two flow waveforms are called before-stent waveform and after-stent waveform hereafter. **State 1**, in which the before-stent waveform is applied to the stenosed geometry, represents the diseased (worst) scenario, and **state 4**, where the after-stent waveform is applied to the stenosis-free geometry, represents a normal case. **States 2 and 3** were included to evaluate the individual effects of geometry and flow waveform.

**RESULTS**

**Input waveforms.** First, waveforms acquired before and after PCI were analyzed. Figures 3 and 4 show the acquired velocity and pressure waveforms that were ensemble averaged for ~60 cardiac cycles. In both figures, three sets of waveforms are shown: waveforms before and after PCI in two patients with severe (> 90%) stenosis and the mean ± SD waveforms of 10 patients whose RCAs were lesion-free upon angiogram examinations (all acquired in the RCA). The velocity waveforms differed after PCI as a result of the change in arterial impedance following PCI, which was not simply caused by the correction of the stenosis but was also likely to be due to effects on the distal coronary circulation (33). The improvement in flow after PCI was witnessed throughout the cycle for
patient 1 (Fig. 3, left) but more pronounced in diastole for patient 2 (Fig. 3, middle). Although the difference is less for patient 2, both cases show more even systolic and diastolic flows after PCI than before. The mean ± SD velocity waveforms of normal coronaries (Fig. 3, right) show a wide range of individual variation, but a common feature is that the flows in systole and diastole are at similar levels. This suggests that the different waveform after PCI is likely to be a result of normalization. Conversely, pressure waveforms remained similar after PCI, although the amplitude of the pressure was higher by ≈20 mmHg for both patients. The mean ± SD waveforms of the normal coronaries also show the same shape, indicating that the pressure waveform is not affected by stenosis apart from its magnitude. Only the set of waveforms of patient 1, which differed more markedly after PCI, was used hereafter for detailed analysis. This would be a good starting point to evaluate potential differences in hemodynamics before and after PCI. The waveforms were decomposed into harmonics by a Fourier transform, and the impedance and impedance phase angle (IPA), which is the phase lag between the temporal variation of pressure and flow, were calculated (shown in Fig. 5 for the first 10 harmonics). The impedance at the dominant first harmonic decreased after PCI, indicating that the resistance to flow was reduced after PCI. The impedance at the other harmonics mostly remained unchanged after PCI, but a higher impedance at the fifth and eighth harmonics could be seen after PCI. The IPA changed drastically after PCI. The IPA for the before-stent waveform was always more negative than for the after-stent waveform and reached −175° after PCI as the order of the wave increased. The IPA for the before-stent waveform was flatter and closer to a plug flow than the after-stent profile. This is because the steep temporal variation in the before-stent waveform is characterized by increased high-frequency components, which are known to result in plug-form velocity profiles (12), owing to the higher Womersley parameters associated with them. Conversely, the spatial velocity profile was more parabolic after PCI because of the more gradual temporal change of the velocity.

WSS: TAWSS and OSI. Figure 7 shows a comparison of TAWSS profiles for all four states. TAWSS levels were generally higher for the states when the after-stent waveform was used because of the higher flow, particularly in the midperiod of the cardiac cycle. However, TAWSS patterns were qualitatively similar for the same geometry (states 1 and 2 with stenosis, and states 3 and 4 without stenosis). Low WSS occurred in the poststenotic region for the stenosed states but disappeared for the stenosis-free conditions, although a small region of focal low WSS could still be seen as a small irregularity and on the inside of the curve of the artery. TAWSS was generally lower on the inner, epicardial-facing side, which was on the inner curvature, since the flow was centrifugally skewed to the outer wall due to the centrifugal pressure gradient and the resulting secondary flow, and a higher velocity gradient was caused near the outer, pericardial-facing wall, resulting in a high WSS. The WSS was <1.5 Pa in the poststenotic region. According to Malek et al. (22), in a survey based on a large range of in vitro and in vivo studies, 1.5 Pa is the lower limit of the normal physiological range of WSS and WSS < 0.4 Pa is considered to switch the endothelial phenotype to a proatherogenic state, although it has also been

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**Fig. 3.** Velocity waveforms acquired with a commercial intravascular ultrasound-Doppler probe ComboWire (Volcano) at 1.0-kHz sampling rate at the proximal RCA of patients 1 (left) and 2 (middle) with a severe stenosis, and mean ± SD waveforms of 10 patients without angiographically significant stenosis (right).

**Fig. 4.** Pressure waveforms acquired with a commercial intravascular pressure probe ComboWire (Volcano) at 1.0-kHz sampling rate at the proximal RCA of patients 1 (left) and 2 (middle) with a severe stenosis, and mean ± SD waveforms of 10 patients without angiographically significant stenosis (right).
reported that the physiological WSS levels vary between regions in human arterial networks and between species (5).

Figure 8 shows a comparison of OSI profiles for all four states. The OSI was high in the poststenotic region because of flow separation. Another focal high OSI area was observed in the distal section on the epicardial-facing side. The RCA curves steeply at this site (cf. Fig. 1), causing flow separation. The fact that the maximum OSI in these regions was close to 0.5 indicated that the WSS was extremely oscillatory. Relatively high OSI also occurred at some other locations on the epicardial-facing side, owing in part to the curvature of the artery and occasionally associated with small irregularities (possibly early atheromatous plaque) on the wall. The OSI profiles for the same geometry (states 1 and 2, states 3 and 4) were qualitatively similar, but the magnitude of the OSI was slightly higher for the states with the before-stent waveform. It was also noted that the area of high OSI was larger for the states with the before-stent waveform, particularly in the poststenotic region.

Stress phase angle. SPA is defined as the phase difference between variations of circumferential stretch and WSS variation (28). Circumferential stretch can be approximated by a pressure variation because a temporal variation of circumferential stretch is nearly in phase with that of pressure (2, 15) even for complicated geometries such as the carotid bifurcation (37). SPA can be separated into two parts as follows:

\[ \phi(D - \tau) = \phi(D - Q) - \phi(\tau - Q) \]

where \( D \) is diameter, \( Q \) is flow, \( P \) is pressure, and \( \tau \) is WSS. Here the first term on the right-hand side is IPA, and the second term is the phase angle between flow and WSS, the WSS-flow rate phase angle (WQPA).

Figure 9 shows the comparison of the spatial SPA profile of the first harmonic between all four computational states. In this study, SPA was calculated by the summation of IPA, based on the input waveform, and the WQPA, based on the result of blood flow simulation, and we focused on the first harmonic, which is the dominant component both in the velocity and pressure (cf. Fig. 5). The medians of SPA were 63.9°, 10.8°, 64.8°, and 10.4° for states 1 to 4, respectively, more negative with the before-stent waveform. The range of SPA was wider with stenosed geometry (204° to 10.0° for state 1 and −177° to 105° for state 2) and narrow with nonstenosed geometry (−117° to −46.2° for state 3 and −71.1° to 25.4° for state 4). Similar patterns of SPA were observed for the states with the same waveform (states 1 and 3, states 2 and 4), except

Fig. 5. Normalized amplitude of harmonics for the velocity (top, left) and pressure (top, right) waveforms, and amplitude of impedance (bottom, left) and impedance phase angle (IPA; bottom, right) for each harmonic before and after percutaneous coronary intervention. Patient 1 (cf. Figs. 3 and 4, left) was chosen as the most apparent case. \( V_n \) and \( P_n \), amplitude of nth harmonics for velocity and pressure, respectively; i.e., the amplitude was normalized by that of 0th harmonic which is the average over the cardiac cycle.

Fig. 6. Velocity profiles at various time moments during a cardiac cycle based on before- (left) and after-stent (right) waveform. \( r \) and \( R \), radial coordinate in the cross section and radius of the lumen, respectively.
for the vicinity of the stenosis. The magnitude of SPA was high in a number of focal areas on the epicardial-facing side of the artery and particularly high in the poststenotic region. The minimum SPA was close to $-180^\circ$ for state 1 (before-stent waveform applied to stenotic geometry). The SPA was highly negative at a number of locations with before-stent waveform even without a stenosis (state 3). When one looks at WQPA in addition to SPA, the contribution of the disturbance in the blood flow to SPA can be estimated.

Figure 10 shows the comparison of WQPA between all four states. The range of WQPA was $0^\circ$ to $90^\circ$. Flow separation caused a large WQPA in the poststenotic region for stenosed geometry models. The regions with high WQPA generally coincided with the sites of high OSI, because both of them are highly related to oscillatory flow owing to separation and recirculation. The area of high WQPA ($-60^\circ$) in the poststenotic region persisted further downstream with the before-stent waveform, but the WQPA was larger when the after-stent waveform was employed ($-90^\circ$). Higher WQPA with the after-stent waveform was observed at the downstream section as well. The WQPA was, in general, lower on the pericardial-facing side, approaching zero in a wide area when the before-stent waveform was used. When we compared the difference in the IPA and WQPA caused by the difference in before- and after-stent waveforms, it was clear that the difference in IPA was more evident than that in WQPA, and the SPA was dominantly affected by the difference in IPA.

DISCUSSION

The changes in coronary blood flow following PCI have been investigated in a number of studies. However, these have been reported only in terms of averaged velocity and pressure over a cardiac cycle, although the phasic change in velocity can...
be seen even between normal and maximal hyperemia induced by 10 mg of papaverine in a stenosis-free artery (25). The present results suggest that the phasic change in velocity following PCI is significant; the impedance to the first harmonic is smaller after PCI than before, resulting in a higher flow in the middle of the cardiac cycle. Although the impedance coefficients for the fifth and eighth harmonics were higher after PCI than before, the overall impedance was lower since the first harmonic was dominant. According to Womersley’s (42) theoretical work on pulsatile flow in a pipe, IPA is ideally $-90^\circ$ when inertia dominates the flow, whereas it is $0^\circ$ when the viscous effect is dominant (39). Therefore, the IPA is theoretically close to $0^\circ$ for low-order harmonics and tends to $-90^\circ$ as the number of harmonics, with the effect of inertia, increases. The trend in the IPA for the after-stent waveform (cf. Fig. 5) follows the theory quite well; the IPA starts from $0^\circ$ and tends to $-100^\circ$ as the number of harmonics increases. The IPA range for the before-stent waveform is larger, from $0^\circ$ to $-175^\circ$, although a similar decreasing trend with the number of harmonics is observed. In addition, there are peaks in the IPA at the fourth harmonic for the before-stent waveform and at the seventh harmonic for both waveforms. The difference between the theory and the present result is attributed to the nonuniformity of the patient-specific geometry that is curved with a noncircular cross section. It is difficult at this stage to investigate in more detail what causes the difference in input waveforms pre- and post-PCI because the overall impedance is determined not only by the events within the upstream section of the RCA but also by events influenced by the ventricular pressure, the pressure in the peripheral coronary circulation in conjunction with intramyocardial pressure, and the varying elastance of the myocardium (41). Further investigation on the velocity-pressure relationship in the input waveforms is necessary, such as by wave intensity analysis (10).
Among the computational states, states 1 and 4 represent real cases before and after PCI, both in terms of flow condition and geometry, whereas states 2 and 3 have been added for illustration to separate the effects of waveform and geometry. The lower TAWSS and higher OSI in the poststenotic region for state 1 (cf. Figs. 7 and 8) imply that the hemodynamic condition is more atherogenic in the presence of a stenosis if the link between low and oscillatory WSS and atherosclerosis is accepted (4, 20, 22). Moreover, the SPA profiles for states 1 and 4 shown in Fig. 9 are markedly different; the SPA for state 1 is more highly negative than state 4 on the entire RCA luminal surface, particularly on the epicardial-facing side. This means that the endothelium on the epicardial-facing side of the RCA is exposed to significantly asynchronous mechanical stimulation. Asynchronous SPA (̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅̅..
SPA profiles for states 3 and 4, the before-stent waveform causes more asynchronous SPA even if the arterial geometry is stenosis-free, whereas the SPA shows a more synchronous pattern if the waveform is “healthy” even in the presence of a stenosis (state 2). SPA clearly depicted differences in the hemodynamic condition, which are not captured by TAWSS and OSI. This may indicate the importance of SPA as a metric in patient-specific hemodynamic analysis, particularly when the impact of the different types of waveforms is studied (27, 29, 37).

WSS is a function of the velocity gradient at the wall, i.e., WSS is determined by the velocity profile in the artery. If the artery is straight and no-flow separation occurs, the axial velocity profile can be described by the Womersley solution (42) as shown in Fig. 6. The temporal evolution of the velocity profiles causing the temporal change in the velocity gradient at the wall results in oscillating WSS, the variation of which lags that of the flow. Temporal variations of WSS in a straight tube were calculated based on the velocity profiles and are shown in Fig. 11. Because of the sharp temporal peak, the trape-
zoidal velocity profile at the peak flow for the before-stent waveform (cf. Fig. 6) causes a higher velocity gradient at the wall, which results in higher WSS than the states with the after-stent waveform. The WQPA for both the before-and after-stent waveforms were also calculated and are shown in Fig. 12 for the first 10 harmonics. The WQPA for the first harmonic is 15°. The WQPA increases as the number of harmonics increases and reaches 32°. The trend in WQPA for the flow in a straight pipe is nearly identical for the before- and after-stent waveforms. The WQPA for the realistic geometries (cf. Fig. 10) is close to 15° (in the second color bands) in a wide area on the pericardial-facing side for the states with after-stent waveform, particularly without a stenosis (state 4). This means that the flow conditions in the artery are similar to the flow in a straight tube with the after-stent waveform. However, the WQPA is generally smaller on the pericardial-facing side and larger than 15° on the epicardial-facing side. The WQPA is also large in the poststenotic region.

Figure 13 illustrates and separates the hemodynamic effects of geometry and waveform. The subject-specific RCA shows a skewed flow toward the outer wall of the curvature. The axial velocity profiles at various locations along the artery shown in Fig. 13 depict the skewed flow characteristics adjacent to the pericardial wall. The skewed high-flow velocity near the pericardial-facing wall with a relatively thin velocity boundary layer confers high WSS on the pericardial-facing side and means that the velocity gradient at the wall and the resulting WSS are more likely to vary in phase with the bulk flow. However, the velocity near the epicardial-facing (inner) wall is low and varies independently of the bulk flow, particularly when a stenosis exists as shown in the profiles at L2, L3, and L4. The flow then separates immediately after it passes through the stenosis, and the flow recirculation is formed at the peak flow and in the decelerating phase at locations L2 and L3. The flow recirculation is also formed at L4 in the decelerating phase; steep curvature causes separation in the flow. This recirculating flow results in low and oscillating WSS and a large-phase lag of WSS compared with bulk flow. Flow recirculation is most prominent in the deceleration phase since flow becomes most disturbed when it decelerates, but the flow is free of recirculation in the acceleration phase for all states. The difference in the flow waveform causes a marked change in the flow in the recirculation region. The negative flow region at L2 is larger with the before-stent waveform (state 1) than with the after-stent waveform (state 2). In addition, the recirculation region persists further downstream with the before-stent waveform; negative flow is observed at L3 for state 1, whereas the negative flow region completely diminishes at L3 for state 2. The difference in the flow waveform also alters the flow at L4; flow recirculation is only observed for states 1 and 3, which are with the before-stent waveform. This is because of the sharp peak in the before-stent waveform. A sudden retardation in the flow yields a highly disturbed flow. It is also shown that the velocity profile near the epicardial wall at the throat varies more for the before-stent waveform but is relatively stable with the after-stent waveform. This flow feature also leads to the larger recirculation region in the epicardial-facing side for state 1 than for state 2. The larger and more oscillatory flow recirculation caused by the before-stent waveform is reflected in the OSI and WQPA (eventually in SPA) profiles; the high OSI and WQPA region persists longer distal to the stenosis for state 1 compared with state 2. The before-stent waveform causes a larger area of high WQPA (>45°) than the after-stent waveform does even without a stenosis. However, the maximum WQPA in the post-stenotic region is larger with the after-stent waveform than with the before-stent waveform. The time profile of WSS at a point on the wall in the post-stenotic region (near L2 in Fig. 13) shown in Fig. 14 reveals the reason for the difference. A number of evident peaks in WSS (>2 Pa) coinciding with flow acceleration are observed for both states. But the WSS with the after-stent waveform (state 2) is mostly close to zero apart from the peaks, which means that the flow is nearly stagnant in the recirculation region, whereas the transient WSS for the before-stent waveform follows the trend in the flow waveform due to highly oscillating flow recirculation. The temporal WSS variation with the after-stent waveform is completely out of phase with the flow, and the resulting WQPA is larger than that for the before-stent waveform.
Fig. 13. Normalized axial velocity profiles on the centerline of cross sections L1–L4 (from top to bottom) in accelerating (left), at the peak (middle), and at decelerating (right) phases. $V_{\text{max}}$, maximal velocity magnitude in the cross section. Horizontal axis denotes relative location on the centerline, and positive and negative signs correspond to pericardial- and epicardial-facing side. Positive velocity means the flow to downstream.

Fig. 14. WSS and flow rate variation at a point on the wall in the recirculation region for states 1 (left) and 2 (right).
Differently from the WQPA in a straight pipe, the WQPA for subject-specific geometry is affected by the difference in the waveforms. This is because flow disturbance caused by non-uniform geometries (such as curvature, constriction, and plaques) is sensitive to the temporal change in the flow waveform. A relatively large WQPA (~45°) is caused even by small bumps inside of the curvature, resulting in a largely negative SPA. Therefore, the combined effect of the small variation of the arterial geometry and a pathological flow waveform could cause proatherogenic conditions in the endothelium. This corresponds to experimental observations showing atherosclerotic lesions at the inner curvature of the coronary arteries (1) and is consistent with observations showing endothelial apoptosis induced by low WSS in the poststenotic region of atherosclerotic plaques (35). By decomposing SPA into IPA and WQPA, it was shown that the contribution to the difference in the flow waveform is greater in the IPA, although differences in WQPAs also exist.

This study has a number of limitations that need to be addressed in the future. First, the velocity waveforms and CT images for RCA geometry were not acquired from the same subject. The velocity waveform following PCI is broadly similar to the waveform seen in the disease-free RCA in that it exhibits two peaks (24) and is therefore probably reasonably representative of the post-PCI situation. However, the impact of disease on the flow waveform is likely to be variable, and additional waveforms from individuals with stenosed RCAs should be obtained to ascertain how representative the changes in waveform observed in this study are. Second, possible dynamic changes in vessel geometry were neglected. Dynamic vessel motion is caused by cardiac motion as well as pulsatile blood pressure and arterial wall distensibility. The cardiac-induced vessel motion was not considered, because there is evidence that the effects of the motion are less significant than the pulsatile flow conditions (43). The arterial wall compliance was not considered because in vivo observations have shown that the circumferential strain for the coronary arteries is <2% (31), and another computational study showed that such small wall displacements do not significantly affect blood flow patterns (12). The wall distensibility would be extremely small in the stented segment where the wall is highly stressed by the stent (17) and the impact of pulsating pressure would be small. Hence, the SPA would be irrelevant there. But regions of highly negative SPA were observed in nonstented segments in states 3 and 4, and the overall level of the SPA should not be affected by the distensibility in the stented region. Third, the direction of WSS was not taken into account in this study, but the SPA was calculated based on the variation of the WSS magnitude because previous experimental results (6–9, 16, 28) were derived from positive WSS variation. Finally, the effect of PCI was not assessed directly due to difficulties imaging the vessel with CT after the placement of a radio-opaque stent. It was therefore assumed that PCI achieved a complete normalization of the lumen diameter. An alternative approach in subsequent studies might be to use intravascular ultrasound and angiography for geometric reconstruction.

In conclusion, differences in pulsatile flow waveform are associated with marked differences in SPA, without necessarily having major effects on WSS or OSI. SPA may be a useful novel measure in assessing the importance of the hemodynamic factors in atherogenesis.


