Impact of main branch stenting on endothelial shear stress: role of side branch diameter, angle and lesion

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In-stent restenosis and stent thrombosis remain clinically significant problems for bifurcation lesions. The objective of this study is to determine the haemodynamic effect of the side branch (SB) on main branch (MB) stenting. We hypothesize that the presence of a SB has a negative effect on MB wall shear stress (WSS), wall shear stress gradient (WSSG) and oscillatory shear index (OSI); and that the bifurcation diameter ratio (SB diameter/MB diameter) and angle are important contributors. We further hypothesized that stent undersizing exaggerates the negative effects on WSS, WSSG and OSI. To test these hypotheses, we developed computational models of stents and non-Newtonian blood. The models were then interfaced, meshed and solved in a validated finite-element package. Stents at bifurcation models were created with 30\degree\ and 70\degree\ bifurcation angles and bifurcations with diameter ratios of SB/MB = 1/2 and 3/4. It was found that stents placed in the MB at a bifurcation lowered WSS dramatically, while elevating WSSG and OSI. Undersizing the stent exaggerated the decrease in WSS, increase in WSSG and OSI, and disturbed the flow between the struts and the vessel wall. Stenting the MB at bifurcations with larger SB/MB ratios or smaller SB angles (30\degree) resulted in lower WSS, higher WSSG and OSI. Stenosis at the SB lowered WSS and elevated WSSG and OSI. These findings highlight the effects of major biomechanical factors in MB stenting on endothelial WSS, WSSG, OSI and suggests potential mechanisms for the potentially higher adverse clinical events associated with bifurcation stenting.

Keywords: bifurcation stents; endothelial shear stress; stent sizing; provisional stenting; incomplete apposition

1. INTRODUCTION

It is well-known that vascular bifurcations are prone to atherosclerosis. The branching geometry causes flow separation and low endothelial wall shear stress (WSS) [1,2]. In-stent restenosis (ISR) and stent thrombosis remain clinically significant problems in the treatment of bifurcation lesions. Stenting at bifurcations is associated with worse clinical outcome than stenting of single vessels [3]. To understand the haemodynamic basis for these clinical observations, we hypothesized that the presence of a side branch (SB) has a negative effect on MB endothelial haemodynamics and that the bifurcation diameter ratio (SB diameter/MB diameter) and angle are important contributors. We further hypothesized that undersizing exaggerates the negative effect on endothelial shear stress. As stent implantation alters local shear stress distribution, stenting near bifurcations is likely to create further blood flow perturbations [4,5].

Since stenting of MB only (a single stent approach) is currently the most common treatment of percutaneous coronary interventions (PCIs) at bifurcations (approx. 70\%), we focused the study on this type of intervention (single MB stent approach) [3]. Although MB stenting is the current default treatment approach for bifurcation anatomy (diameter ratio, angle, etc.) [6–8]. Hence, the objective of this study is to understand these variables through a physics-based approach.

Computational fluid dynamics (CFD) has emerged as a powerful tool to evaluate the endothelial shear stress in arteries and bifurcation vessels [5,9,10]. Despite the clinical significance, there have been far fewer CFD studies of bifurcation stenting than single vessel stents [11,12]. A recent study found that stenting of MB lowered WSS on vessel wall, especially downstream of the bifurcation [13]. Here, we investigated the effects of major biomechanical factors that influence bifurcation stenting; e.g. stent/vessel size mismatch, bifurcation angles, diameter

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ratios and stenosis, which have not been previously considered. These are major factors that influence endothelial WSS, WSS gradient (WSSG), oscillatory shear stress (OSI) and hence endothelial function and potentially clinical outcome.

2. MATERIAL AND METHODS

Computational models of stents and artery were created in Pro/Engineer, which is a computer-assisted design package. The models were then interfaced, meshed and solved in well-validated finite-element and CFD packages ANSYS and FLUTRAN. Correct-sized as well as 5 and 10 per cent under-sized stent models (diameters sized relative to vessel diameter of 3 mm) were created for the simulations. Stents at bifurcation models were created with 30° and 70° bifurcation angles as well as bifurcations with diameter ratios of SB/MB = 1/2 and 3/4. The bifurcation angle was defined as the distal angle between MB and SB (e.g. figure 1a shows a 70° bifurcation). Figure 2a shows the stent geometry and the position of stent relative to the vessel. The meshes of the stent and fluid consisted of highly structured and refined elements in order to ensure the accuracy of simulation results. About 1.8 million mesh elements were used in the simulations (figures 1–6). A mesh-convergence test showed that doubling the number of elements resulted only in less than 2 per cent difference in WSS. The WSS distributions also did not change significantly. Hence, the mesh density was deemed sufficient for the simulations.

For blood, a non-Newtonian Carreau model was used to account for the shear thinning behaviour of blood (see appendix A). The model has been known to accurately describe the behaviour of red blood cell suspensions and the viscosity matched closely with experimental measurements of Chien et al. [14,15]. The density of the blood was taken as 1060 kg m$^{-3}$. The blood was modelled as incompressible with flow based on human left coronary artery pulsatile velocity measurements applied at the inlet of the vessel. The mean and maximum flow velocities were 9 and 17 cm s$^{-1}$, respectively, at 60 cycles per minute frequency [16]. For the outlet of the vessels, a traction-free boundary condition was imposed, as in publications of Stroud et al. [17] and Lorhois et al. [18] on carotid bifurcations with stenosis since the SB stenosis modelled in the current study is relatively mild at 40 per cent area stenosis [9]. More severe stenosis (e.g. 80% or 90%) may affect the outlet traction more significantly.

The flow was assumed to be non-turbulent since the Reynolds number in the coronary artery is an order of magnitude lower than that required for turbulence (Reynolds number > 4000) and Womersley number was approximately 2.1. At the wall interface, we assume no slip between blood and the endothelium and no permeability of the vessel wall. The no-slip and the no-penetration boundary conditions were applied at the stent strut surfaces. The time-averaged WSS was computed at the endothelial surface of the stented vessel wall (stent end-to-end), and averaged both spatially over the entire length of stent and temporally over a cardiac cycle for comparisons between the various cases. Since the struts are thin relative to the SB diameter, the stent did not cover the opening to the SB and did not alter the flow into the SB significantly.

The laws of physics (conservation of mass and momentum) that describe the blood motion along with the mathematical definitions of WSS, WSSG and OSI are given in appendix A.

3. RESULTS

The Reynolds numbers for the computational models of the various cases ranged from 70 to 120. This range is an order of magnitude smaller than the Reynolds number for transition to turbulence (2300–4000) and hence justifies the current models. A stent at a bifurcation lowers WSS in the stented vessel wall, as shown in figure 1a. The presence of SB lowers WSS in both correct and undersized cases (figure 1b). The stent struts lower WSS and disrupt smooth distribution of WSS,

![Figure 1. Effect of SB and sizing. (a) Stent at bifurcation shown in the case of a 70° bifurcation with 10% undersized stent (1 Pascal = 10 dyne cm$^{-2}$). The effect of SB and sizing on (b) WSS, (c) WSSG and (d) OSI in the bifurcation region.](http://rsif.royalsocietypublishing.org/Downloaded from http://rsif.royalsocietypublishing.org/ on April 18, 2017)
thereby elevating WSSG (figure 1c). This effect is more pronounced in the case of undersized stents. Low WSS is located at the stented lateral surfaces to the junction, as well as opposite to flow-divider in the MB. High WSSG is located at the flow-divider, because the WSS changes spatially rapidly there. High OSI is located at the stented lateral surfaces to the junction, as OSI has an approximate inverse relationship with WSS. In comparison with an un-bifurcated vessel, bifurcations with both correct sizing and undersized stents resulted in higher OSI (figure 1d). Figure 2b shows the overall flow field with undersized stent at MB. Disturbed and stagnant flow is shown between the undersized stent and the vessel wall. The blue colour indicates low velocity. (c) A zoom-in view of the carina region is shown. The tiny flow vectors between the struts and the vessel wall indicate stagnant flow.

Undersized stents result in lower WSS than in correctly sized stents (figure 3a). A 5 per cent undersized stent results in the lowest WSS, highest WSSG and OSI owing to the small gap between the struts and the vessel wall (figure 3a–c). Stent placement in the MB at a bifurcation using a 5 per cent undersized stent of a smaller SB angle (30°) results in lower WSS, higher WSSG and OSI, although the effect is not as prominent as stent sizing (figure 4). Figure 5 shows the effects of diameter ratios of SB/MB = 1/2 and 3/4. With larger SBs, the WSS in the stented region was decreased more than in the case of smaller SBs. This was the case for both correct sizing and undersizing, probably owing to more flow diversion into the larger SB. Larger SB/MB ratios (3/4) resulted in higher WSSGs and OSIs (figure 5b,c). Figure 6 shows that plaque at the SB lowers WSS, while elevating the WSSG and OSI, especially at the base of the plaque.

4. DISCUSSION
PCI of coronary bifurcation lesions is still one of the most challenging endeavours in interventional cardiology. The best technique to treat a particular bifurcation anatomy remains elusive because of the heterogeneity of bifurcation anatomy [6]. Computational modelling has
the potential to be an invaluable tool to simulate a broad variety of bifurcation anatomy and study the impact of various stenting techniques on the local haemodynamic profile. This study focused on single stenting of MBs and confirmed the hypothesis that the presence of a SB has a negative impact on endothelial WSS, WSSG and OSI. Bifurcations with larger SB to MB diameter ratios and small bifurcation angles have unfavourable flow profiles. Undersized stents amplified the negative flow profiles and may be thrombogenic owing to stagnant flow and gaps between the struts and the vessel wall.

A stent at a bifurcation lowers WSS for various stent sizing cases (figures 1 and 3). The stent struts prominently lower WSS and create unsmooth distribution of WSS, thereby elevating the WSSG, which has been found to expand the intracellular gap junctions and disrupt intracellular junctions, making the vessel wall more vulnerable to the infiltration of inflammatory cells and low-density lipoprotein [19]. These effects are more pronounced in the case of undersized stents. When compared with non-bifurcation cases, bifurcations with both correct-sized and undersized stents resulted in higher OSIs, a measure of the extent of oscillatory behaviour of flow which has been found to promote pathological processes in arteries (figure 1c). The oscillatory shear and associated reversed flow were found to reduce nitric oxide which may lead to endothelial dysfunction and platelet adhesion [20,21]. These findings are in agreement with clinical observations that bifurcation stenting is associated with higher adverse clinical events [3,12,22].

Figure 4. Effect of bifurcation angle and sizing on (a) WSS, (b) WSSG and (c) OSI in the bifurcation region.

The undersized stent struts result in stagnant flow near the vessel wall (figure 2b). The stagnant flow and gaps between the struts and the vessel wall are inductive to accumulations of red blood cells, platelets, lipids, all of which are thrombogenic (figure 2c) [23,24]. There is a tendency for white blood cells (WBCs) and platelets to become trapped in areas of flow stasis or recirculation [25]. Local thrombosis may occur when the flow is reduced. The reason that the 5 per cent undersized stent severely affected the WSS is due to the tiny gaps between the stent struts and the vessel wall which induce stasis. In 10 per cent undersizing, as the struts were further away from the vessel wall, the effect became less prominent, although still significant. Figure 2a,b show that local flow stasis exists between the undersized stent and the vessel wall, as well as between the struts. Flow obstruction and disturbance owing to the undersized struts protruding into the lumen may be inducive to thrombosis. In the case of drug-eluting stent (DES), it is known that delayed re-endothelization predisposes to stent thrombosis [26,27]. With stent undersizing or incomplete apposition causing stagnant flow or stasis, the denuded vessel wall is even more susceptible to WBC adhesion and platelet accumulation which may amplify the problem of thrombosis.

In clinical studies, it was found that incomplete apposition is associated with stent thrombosis [23,28,29]. Stenting at bifurcations with 5 per cent undersized stents of smaller SB angles (30°) resulted in lower WSS, higher WSSG and OSI (figure 4). Most of the stented
area has low WSS which may be intimal hyperplasia (IH)-prone. This is probably owing to easier flow diversion into SBs in the case of smaller SB angle. Interestingly, a recent clinical study found that one of the independent predictors of major cardiovascular events was a bifurcation angle <40°. Smaller angles in coronary bifurcations predicted higher restenosis rates [8]. The effects of diameter ratios are shown in figure 5. For smaller SBs, less flow was diverted, thus the WSS in the stented region was higher than in the case of larger SBs. Larger SB/MB ratios (3/4) resulted in lower WSS, higher WSSGs and OSIs (figure 5). Hence, the simulations are in qualitative agreement with the clinical findings [6].

Stenting of MB may lead to plaque shift into the SB. Figure 6 shows that plaque at the SB lowers WSS while elevating WSSG and OSI, especially at the base of the plaque which may further enlarge the plaque. This may amplify the impact of plaque shift, leading to severe stenosis in the SB.

The results of the current simulations suggest that for bifurcations with large SBs diameter, small angle and SB stenosis, MB stenting may not be optimal because of lowered WSS, elevated WSSG and OSI in the MB. In the case of larger SBs, SB occlusion may lead to myocardial infarction [30]. In fact, it has been observed clinically that ST-elevation MI resulted after MB stenting [6,30]. A recent study by Gil et al. [8] has shown an occlusion rate of 17 per cent after MB stenting, and smaller angle was identified as an independent predictor for higher restenosis rates.

4.1. Limitations

For undersized case, the stent may not be located symmetrically in the vessel. Owing to lack of data on the extent of asymmetry, the stent was modelled as located symmetrically. Given the small degree of undersizing, this assumption is unlikely to significantly affect the conclusions. The current models simulated bare metal stents with smooth surfaces. For polymer-coated stents, it is possible that rough surfaces may occur with uneven erosion which may induce turbulence. The arteries may be tortuous but become straight once the stent is implanted, since the clinically observed restenosis mainly occurs within the stented region, a straight segment was simulated here. The current generation DES is more flexible where some curvature may amplify the impact of plaque shift, leading to severe stenosis. Additionally, as stent struts strongly alter the WSS locally, the effect of curvature is expected to be much less than the effects of struts. For the outlet of the vessels, a traction-free boundary condition was imposed because the SB stenosis modelled in the current study is relatively mild at 40 per cent area stenosis [9,17,18]. More severe stenosis (e.g. 80% or 90%) may affect the outlet traction more significantly. Stent tapering was not considered in the current model, which may result in the narrower end having higher WSS, as the flow accelerates. Prolapse of tissue between struts was not modelled, which may influence intrastrut WSS. This effect, however, is not expected to be nearly as strong as the effect of stent struts.

4.2. Summary

This study reveals the effects of major biomechanical parameters on endothelial WSS, WSSG, OSI and suggests that larger SB/MB diameter ratios and smaller bifurcation angles have the worst haemodynamics in MB stenting. The importance of correct stent sizing at bifurcations is highlighted as undersizing exaggerates the negative haemodynamic effects on the endothelium. The current models build the foundation for future comparisons of MB stenting and dual stenting, as well as the effects of various dual-stenting techniques (i.e. T stenting, V stenting, Crush, Culotte, etc.) on endothelial haemodynamics in future studies. These findings may provide guidance for the optimal interventional strategy for specific types of bifurcations and to stent manufacturers.

This research was supported in part by the National Institute of Health—National Heart, Lung and Blood Institute (grants HL087235 and HL084529).

APPENDIX A

The governing equations for blood flow are the Navier–Stokes and continuity equations [4,5]: i.e. conservation of momentum and mass:

$$\frac{\partial V}{\partial t} + V \cdot \nabla V + \frac{\nabla p}{\rho} - 2 \frac{\eta}{\rho} \nabla \cdot D = 0 \quad (A1)$$

and

$$\nabla \cdot V = 0, \quad (A2)$$

where $V$ is fluid velocity, $p$ the fluid pressure, $\rho$ the fluid mass density, $\eta$ the fluid dynamic viscosity, $\nabla$ the gradient operator, $D$ the fluid rate of deformation tensor.

The WSS is given by the product of viscosity and shear rate. The shear rate is defined as follows [19]:

$$\gamma = 2 \left[ \left( \frac{\partial u}{\partial x} \right)^2 + \left( \frac{\partial v}{\partial y} \right)^2 + \left( \frac{\partial w}{\partial z} \right)^2 \right] + \left( \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right)^2$$

$$+ \left( \frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right)^2 + \left( \frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right)^2 \right]^{1/2}, \quad (A3)$$

where $u$, $v$ and $w$ are the x, y and z components of velocity vector, respectively.

The WSSG, which has been found to expand the intracellular gap junctions and disrupt the intracellular junctions, is defined as [19]:

$$WSSG = \left[ \left( \frac{\partial \tau_{w,z}}{\partial z} \right)^2 + \left( \frac{\partial \tau_{w,\theta}}{\partial \theta} \right)^2 \right]^{1/2}, \quad (A4)$$

where $\tau_{w,z}$ and $\tau_{w,\theta}$ are WSS in the axial and circumferential directions, respectively. The oscillatory shear index (OSI) is a measure of the extent of oscillatory behaviour of flow which has been found to promote intimal hyperplasia and endothelial dysfunction. The OSI is defined as [10]:

$$OSI = \frac{1}{2} \left( 1 - \frac{1}{T} \int_0^T \left| \tau_{\text{d}t} \right| dt \right)^{1/2}, \quad (A5)$$
Both WSSG and OSI were computed once the respective stress components were calculated from the CFD analysis.

For the non-Newtonian blood property, the Carreau model was used to account for the shear thinning behaviour of blood:

$$\mu = \mu_\infty + (\mu_0 - \mu_\infty)[1 + (\lambda \dot{\gamma})^{2(n-1)/2}]$$

where $\mu$ is the effective blood viscosity, $\mu_\infty = 0.0035$ and $\mu_0 = 0.25$ kg m$^{-1}$ s$^{-1}$ are the blood viscosities at infinite and zero shear rates, respectively, $\dot{\gamma}$ is the shear rate, $\lambda = 25$ s is a time constant associated with the viscosity changes with shear rate, and $n = 0.25$ is a power law index [14,15].

REFERENCES


**Figure 6.** Effect of SB stenosis: (a) undersized stent at the MB and stenosis at the SB (1 Pascal = 10 dyne cm$^{-2}$). Effect of SB stenosis on (b) WSS, (c) WSSG and (d) OSI.


