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Coronary Artery Bifurcation Biomechanics and Implications for Interventional Strategies

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The treatment of atherosclerotic plaques near and involving coronary bifurcations is especially challenging for interventional procedures. Optimization of these treatment strategies should begin with an understanding of how disease came to be localized to these regions, followed by careful design of the interventional tools and implanted devices. This manuscript reviews the basic biomechanics of coronary bifurcations, stented arteries, and the complex biomechanical challenges associated with bifurcation stenting. Flow patterns in bifurcations are inherently complex, including vortex formation and creation of zones of low and oscillating wall shear stress that coincide with early intimal thickening. Bifurcation geometry (in particular, the angle between the side branches), is of paramount importance in creating these proatherogenic conditions. This predilection for disease formation leads to a large number of bifurcation lesions presenting for clinical intervention. Therefore, several strategies have developed for treating these challenging lesions, including both dedicated devices and creative adaptation of single vessel lesion technologies. The biomechanical implications of these strategies are likely important in short and long term clinical outcomes. While the biomechanical environment in a stented coronary bifurcation is extremely challenging to model, computational methods have been deployed recently to better understand these implications. Enhancement of clinical success will be best achieved through the collaborative efforts of clinicians, biomechanicians, and device manufacturers.

Key words: branching vessels; hemodynamics; mechanobiology; atherosclerosis

INTRODUCTION AND BACKGROUND

Coronary atherosclerotic disease (CAD) tends to form near branching points where blood flow patterns show strong spatial dependence [1], and stents are the preferred treatment for CAD. Unfortunately the success of stents is limited by excessive regrowth of tissue known as restenosis, the primary component of which is neointimal hyperplasia (NH). Studies have shown that blood flow disturbances caused by the stent can influence restenosis [2,3]. Although the presence of blood flow alterations through stents and at bifurcations suggests that stents should be specifically designed and optimized for these regions of the coronary vasculature, clinical results to date have not shown conclusive favorable evidence for their widespread use. The goal of this article is to review flow dynamics of bifurcations and their putative link to atherogenesis, followed by a discussion of the insight garnered by more recent in silico techniques, most notably computational fluid

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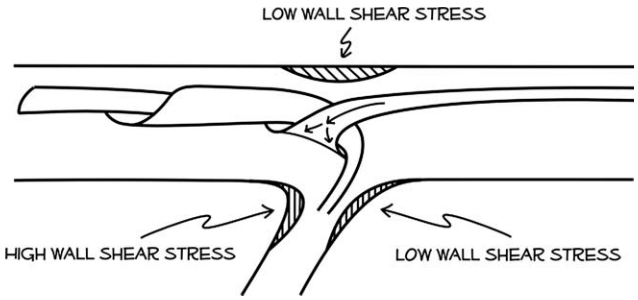

Fig. 1. Illustration of flow patterns in the region of a branching vessel. When the side branch takes away more than 10% of the main vessel flow, secondary flow patterns and spatial variations in wall shear stress result.

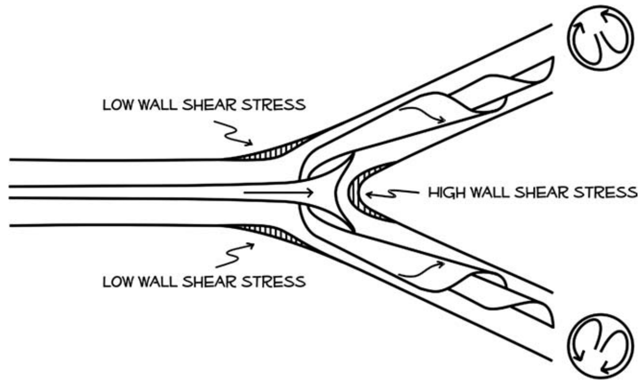

Fig. 2. Illustration of flow patterns in the region of a bifurcation. Fluid swirls into each of the branches, and spatial variations in wall shear stress result.

dynamics (CFD). Ultimately, this information may be useful for collective teams of clinicians, scientists, and engineers to facilitate translation to improved bifurcation stent designs or techniques.

Biomechanics, Disease Development, and Interventions

Hemodynamic alterations colocalize with atherosclerosis. Flow patterns in and around bifurcations have been linked with the development of atherosclerosis. Patterns of early intimal thickening in several arteries coincide with locations of low and oscillating wall shear stresses [WSS; 4–6]. (*The term "wall shear stress" refers to the stress on the artery wall that is due to the friction associated with the viscous fluid flowing past the artery wall. In this context, its simplest definition is the product of the viscosity of the fluid and the radial gradient of axial velocity*). Such flow patterns influence the behavior of endothelial cells, including morphological adaptations, and expression of inflammatory cell attractors. It is a consistent observation that low and oscillating WSS provoke the production of substances that encourage smooth muscle cell proliferation and inflammatory cell recruitment, and inhibit the production of atheroprotective substances such as nitric oxide. There are other effects of these flow patterns that may be equally important in disease initiation, such as convective transport of oxygen, LDL, and blood-borne cytokines.

In all arteries prone to atherosclerosis, patterns of low and oscillating WSS develop in part due to the presence of bifurcations and branches. A branching artery can have a significant effect on flow patterns in the main vessel (MV) if it takes away more than ~10% of the flow. Secondary flow patterns (often manifesting as vortices) can develop in the MV because enough of the fluid is being forced to change direction toward the side branch (SB, Fig. 1). As a result of these deviations away from the primary direction of flow down the axis of the MV, regions of low WSS can develop opposite the SB, as well as along the lateral wall of the branch itself. The percentage of MV flow exiting the branch is by far the dominant factor in determining the likelihood of these flow phenomena, with geometric factors such as branch angle and diameter ratio playing secondary roles.

Flow patterns in bifurcations, where the flow split is ~50/50, can be thought of as a special case of branched vessel flows. Secondary flow patterns do indeed develop as a result of changing the flow direction from purely axial to the directions of the daughter branches (Fig. 2). WSS is low along the lateral walls of the parent and daughter vessels, and high near the flow divider. The presence of pulsatile flow accentuates the effects of branches and bifurcations, particularly during flow deceleration. The slower moving fluid near the lateral walls is more easily reversed, and can completely reverse direction even if there is no reversal in volume flow rate.

The combination of branches, curvature, and pulsatility produce the proatherogenic flow patterns mentioned above. In the abdominal aorta, the bifurcation is preceded by curvature in the saggital plane and important branches. Combined with a distinct reverse flow phase in early diastole, the result is a concentration of low and oscillating WSS on the lateral-posterior walls in the bifurcation which coincides with patterns of early intimal thickening. Flow in the internal carotid artery is affected not only by the bifurcation, but also by the carotid sinus. Low and oscillating WSS were noted at the lateral wall of the sinus, which again correlates with early intimal thickening.

In the coronary arteries, flow is highly pulsatile, with reversing flow in systole, and high forward flow in diastole. These arteries also feature curvature in multiple planes. The likelihood of low and oscillating

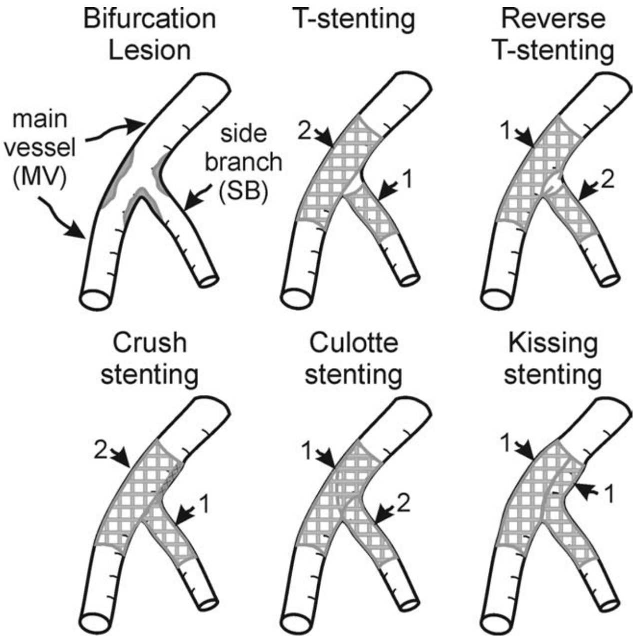

Fig. 3. Techniques for coronary bifurcation stenting with multiple stents. Numbers show implantation order. The most common plaque distribution is also shown (top left).

WSS is high, depending on the individual geometry. There is in fact considerable variability in left main/LAD/LCx geometries among patients. A study of 17 casts of this bifurcation showed a mean bifurcation angle (between LAD and LCx) of 84.3°, with a standard deviation of 14.2°, and most notably, a range from 47.1° to 107.1° [7]. A larger value of this angle would increase the disparity in wall shear stress between the medial and lateral walls. In other words, a larger bifurcation angle, with no change in the amount of branch flow, increases the likelihood of low and oscillating WSS at the lateral walls. Indeed, larger values of this angle have been associated with higher degrees of early intimal thickening.

Biomechanical environment in stented arteries. The treatment of restenosis in coronary stents has cost the US healthcare system an estimated 2.5 billion dollars since 1999. Restenosis rates depend on various contributing factors, including stent design, lesion type, diabetes mellitus, and placement of multiple stents [1,8].

The apparent role of stent design in determining risk for restenosis has led to a number of studies concerning the effects of strut configuration on blood flow patterns and artery wall stresses [9,10]. Early studies showed that axial stent strut spacing has a strong effect on near-wall flow stagnation. Later studies in full 3D showed that strut alignment also plays an important role in determining local WSS and stagnation patterns [11–13], which in turn affect the degree of platelet adhesion.

In addition to hemodynamic alterations, the placement of a stent also has considerable effects on the solid mechanical stresses in the artery wall. Besides high balloon inflation pressures during deployment, the chronic outward force of the stent induce extremely high, nonphysiologic stresses on the artery wall. Computational studies have indicated that alterations in both commercially available and generic stent designs lead to large variations in the stress distributions [10,14].

Use of stents in coronary bifurcations. Of the ~650,000 percutaneous coronary interventions (PCIs) coupled with stenting performed annually, 15–20% are performed to treat diseased coronary bifurcations [15,16]. Stenting of bifurcating lesions carries considerably higher risks. In particular, SB occlusion due to redistribution of the plaque across the carina of the ostium ("plaque shift") is a major concern, as it can lead to infarcts distal to the SB blockage as well as restrict future access to the SB. The success rate of bifurcating lesion intervention is also much lower than that of nonbifurcating lesion therapy. Although stenting of both the MV and SB has been adopted for treating bifurcating lesions, clinical data indicates that bare metal stent (BMS) treatment of the MV alone has a lower incidence of restenosis than performing the technically challenging implantation of a stent in both the MV and SB [17].

Recently drug-eluting stents (DES) have been used to combat NH and the development of restenosis in bifurcating lesions. While DES have reduced restenosis rates in the MV of bifurcating lesions, long-term restenosis in the SB remains a problem. As with BMS, clinical data suggest that implanting a single DES (MV only) has lower incidences of restenosis than implanting multiple stents [MV and SB; 18,19]. The antiproliferative agents on some DES may not facilitate healing of the intima thereby limiting coverage of struts by endothelial cells and increasing the likelihood of late thrombosis (>9 months post-op; [20]). The incidence of late thrombus in recent DES trials has been 1–4% for bifurcating lesions [18,21]. While studies have indicated DES offer higher procedural success rates, there are limited data that directly compare the treatment of coronary bifurcating lesions (MV and SB or MV alone) with either BMS or DES.

Currently there are several dedicated bifurcation stents for approved and investigational use. Unfortunately, long-term data are not yet available or have not shown conclusive favorable evidence for many of these dedicated bifurcation platforms [18,22–25] and their contribution to altered blood flow and artery wall stresses has yet to be determined. Alternatively, some clinicians use multiple stents in the treatment of bifurcating lesions despite more pronounced restenosis and vascular damage with a multistent approach [17,18,26]. Treatment of bifurcations with traditional nonbifurcating stents or DES [16], however, seems to favor MV stenting with "elective" SB stenting if there is shifting of plaque or the carina. Benefits to this approach include quicker procedure times, reduced cost, shorter hospitalization and reduced restenosis. Unfortunately poor coverage in the ostium (Fig. 3) may cause elevated restenosis with this approach and a number of alternatives have subsequently emerged. The choice of technique in Figure 3 varies with each center, clinician preference, and lesion morphology. Many of these techniques have the potential for vascular damage. Cases of stent fracture and dissection have been reported [27,28]. Perhaps not surprisingly, restenosis rates continue to be elevated in the SB after multistent implantation making treatment of bifurcation lesions one of the most challenging problems in modern interventional cardiology [16,18].

Computational Biomechanics Studies of Stented Coronary Bifurcations

Computational analysis of blood flow patterns in stented bifurcations. The ability to model the biomechanics of stented arteries has been enhanced in recent years with the emergence of powerful computer hardware and sophisticated modeling software. Investigation of blood flow patterns has benefited from recent advances in CFD software, while the solid mechanical stresses in the artery wall can be modeled with finite element analysis (FEA). Requirements for the study of flow in bifurcations include creating a vessel geometry (typically reconstructed in a subject-specific or idealized manner based on medical imaging data), specifying rheological properties such as blood density and viscosity, prescribing the hemodynamic state at the entrance and exit of vessels (known as boundary conditions) and a powerful computer [29]. It is worth noting that the estimation of WSS is best done with medical image-based CFD, rather than direct measurement of fluid velocities. The spatial resolution of techniques such as Doppler ultrasound and phase-contrast MRI is insufficient for WSS estimation in all but the largest arteries.

While the process of restenosis differs from that which led to the initiation of an atherosclerotic lesion, certain patterns of flow disruption can similarly increase the likelihood for NH and subsequent restenosis or thrombus formation and dislodgement. However, a causal link to adverse clinical outcomes has not yet been established and a concerted effort within the biomedical engineering research community is underway for this purpose. For example, several of the multistenting techniques shown in Figure 3 appear to establish extremely deleterious flow patterns, and reports have suggested an increased thrombus potential due to the presence of stent struts not apposed to the artery wall. Although a bifurcation angle $\geq 50°$ is a predictor of major adverse events [30], mostly from difficulties with catheter access, to date only a limited number of CFD studies have been conducted for bifurcation stents. CFD has been used to characterize flow disturbances from virtual MV stenting, assess the severity of flow alterations caused by a change in carina position or bifurcation morphology after MV stenting and subsequent SB balloon angioplasty in a theoretical model based on intravascular ultrasound (IVUS), and quantify how flow distributions near the bifurcation impact drug transport after DES implantation.

As alluded to above, obtaining an accurate representation of vascular geometry is crucial for identifying regions of flow separation or reversal using CFD. Several studies have been conducted to characterize coronary bifurcation morphology with application to stent design and assessing lesion severity by angiography or FFR. Finet et al. quantified 173 left main, LAD and coronary bifurcations from 47 patients to arrive at a ratio of 0.678 between diameters of the proximal MV and the sum of daughter vessels [31]. Interestingly, a subsequent idealized CFD analysis using Finet's ratio, a bifurcation angle of 46°, and flow distributions that result in equal nominal values of WSS for each branch, demonstrated that there were no areas of the intima subjected to mean WSS of <4 dyn cm^{-2} [a proposed putative adverse threshold for the coronary arteries; 32]. Similar findings were seen in a previous flow visualization study, suggesting that outcomes after bifurcation stenting should strive to reestablish the native geometric and flow environment [33].

An example of the utility of CFD for gaining insight into stent performance is provided in Figure 4. Two stent designs (A and B) were virtually implanted into a CFD model created from computed tomography data of a normal coronary artery bifurcation to show how stent design may influence distributions of WSS and intrastrut deformation. The objective of this example is not to show superiority of one design over another, but rather underscore how scaffolding and strut spacing can influence distributions of WSS as well as intrastrut deformation elucidated by CFD which, in this case, includes some of the solid-mechanics functionality discussed in more detail in the following section. Stent A, with greater intrastrut spacing permits more deformation of the vascular wall between struts, but also produces slightly lower distributions of WSS since its struts are less aligned with the primary direction of fluid flow than stent B.

Another recent study quantified altered hemodynamics after MV stenting and SB angioplasty to restore carina position using CFD models based on IVUS data [34]. MV stenting introduced eccentric areas of low time-averaged WSS along the lateral wall consistent

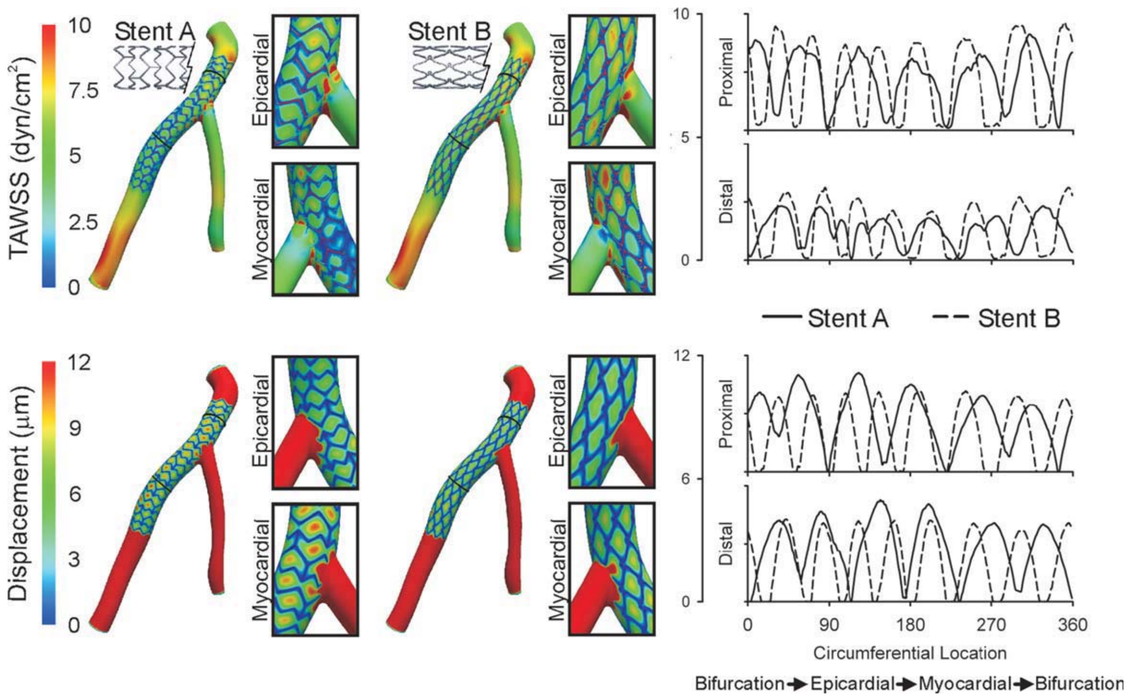

Fig. 4. Example of how computational methods can be used to gain insight into stent performance. Two stent designs (A and B) were virtually implanted into CFD models created from computed tomography data of a normal coronary artery bifurcation through the use of computer-aided design software in order to show how scaffolding and strut spacing may influence distributions of WSS (top row) and intrastrut deformation (bottom row). Both quantities are revealed in more detail for insets from the epicardial and myocardial luminal surfaces of each stent, and results along the vessel wall were further queried at two circumferential locations (values directly over struts were omitted for clarity). Plots from these circumferential locations (right) indicate that stent A with greater intrastrut spacing permits more deformation of the vascular wall between struts (solid lines), but also produces slightly lower distributions of WSS since its struts are less aligned with the primary direction of fluid flow than stent B (dashed lines). TAWSS: time-averaged wall shear stress. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with where pronounced leukocyte adhesion, neointimal hyperplasia and fibrin deposition had been observed in a previous chronic porcine study [33]. SB angioplasty restored carina position in the computational study, but also introduced concentric areas of adverse and oscillating WSS in the distal MV due to repositioning of the carina. The total area of luminal surface exposed to these adverse indices remained similar before and after SB angioplasty, suggesting that improved angiographic results may offer no benefit from a fluid dynamics perspective. Adverse distributions of WSS were primarily due to stent-induced flow alterations rather than overall changes in vessel geometry, further supporting the importance of stent design.

These insights are particularly interesting when coupled with drug transport modeling following DES implantation. Kolachalama et al. placed a slotted-tube DES at three MV positions within an idealized coronary bifurcation: proximal to the SB ostium, across the bifurcation entrance and distal to the carina [35]. The flow patterns described earlier for vessels with non-50/50 flow splits, and reiterated after idealized MV bifurcation stenting above caused asymmetric drug deposition with 8–15% greater concentration along the lateral wall opposite the flow divider when the stent was positioned across the SB ostium.

Computational analysis of artery wall stresses near stented bifurcations. While there are numerous studies that examine the stress induced following stent deployment in nonbifurcating arteries, computational studies examining the solid mechanical impact of stenting in coronary bifurcations are extremely limited. In addition to the complexities associated with modeling this contact mechanics problem (e.g., nonlinear, anisotropic material properties; heterogeneous artery wall; large deformation; residual strain), inclusion of a complex geometry and possibly multiple stent deployments further complicates this problem. Mortier et al. examined the stresses induced on the MV of a nondiseased bifurcating coronary artery, as determined from rotational angiography, following deployment of three commercially available DES [Cypher Select, Cordis/Johnson and Johnson, Miami, FL; Endeavor, Medtronic, Minneapolis, MN; Taxus Liberté, Boston

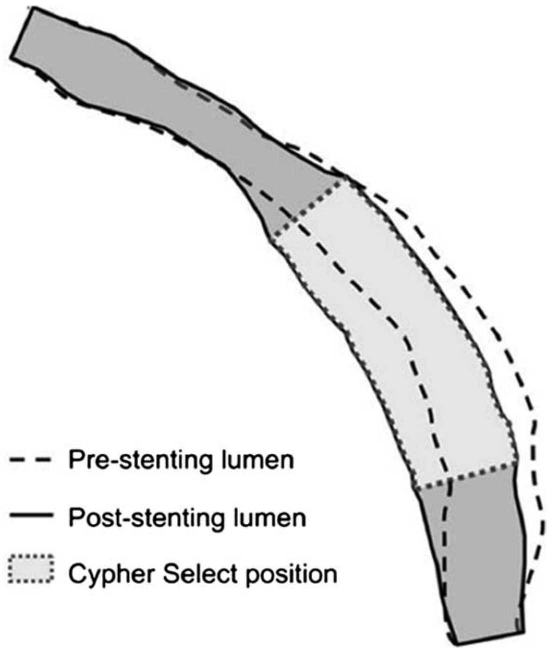

Fig. 5. Illustration of the effect of stenting curved coronary arteries and the level of arterial straightening that occurs. Note that arterial straightening can have deleterious effects on both the fluid and solid biomechanical environments. Reprinted with permission from Mortier et al. [36] in *Annals of Biomedical Engineering*. Copyright 2010, Springer.

Scientific; 36]. While significant arterial straightening occurred among all designs (Fig. 5), circumferential (hoop) stress distributions varied among the three designs, which further demonstrates the importance of stent design and its mechanical impact following implantation. In another study, Mortier et al. investigated SB access following deployment of either a Cypher or Multi-Link (Guidant/Boston Scientific) stent in the MV [37]. Following stent deployment, SB dilation resulted in significant stent distortion. In particular, distortion of the Multi-Link compromised the MV lumen as stent struts distal to the SB protruded into the lumen. Using a similar FEA approach, Gastaldi et al. calculated stent as well as vessel wall stresses in the MV, SB and ostium of an idealized coronary bifurcation model that included three moderate concentric plaques (60–65% area reduction) in a Medina (1,1,1) classification [38]. The MV was stented with subsequent SB angioplasty via intrastrut regions in the proximal, central or distal portion of the SB ostium. For the central access case, comparisons were then also made between an additional kissing procedure and redilatation of the MV alone. Central access to the SB resulted in the greatest percentage of unrestricted ostial SB area with the least vessel stress. Conversely, proximal and distal SB access caused elevated circumferential stresses in the MV proximal to the bifurcation and SB ostium, respectively, while also leaving struts across the ostium. Simultaneous kissing balloon inflation and subsequent secondary MV angioplasty did not differ in their arrangement of struts near the SB ostium, and computational results concerning vessel and stent shape qualitatively agreed well with previous experimental findings. However, equivalent plastic strain values in the connecting linkages of stents were 14% higher in the kissing balloon case (34% vs. 20%) and caused pronounced stress in the proximal MV wall. The authors therefore recommended redilatation of the MV as a preferred final step after SB angioplasty is performed through struts in the center of the SB if possible.

Given that computational studies have provided insight into possible reasons why restenosis rates vary amongst stent designs in nonbifurcating lesions, it is likely that similar studies could provide information to increase the success rate of treating coronary bifurcating lesions. Of particular interest is the debate of whether to stent only the MV or both the MV and SB. Examination of these various treatment options will yield quantitative information on the mechanical stresses that are subjected to the bifurcating arteries and provide explanations for the variations in restenosis rates between the two options. Furthermore, dedicated bifurcating stents could be modeled to determine designs that will reduce the stresses while still providing sufficient radial support to restore blood flow to distal tissues. Ultimately, with the advancement of computational techniques to tackle this difficult problem, stent designs and treatment options can be optimized to identify the most beneficial therapies to treat diseased coronary bifurcations.

CONCLUSIONS

Interventional treatment of coronary bifurcation lesions remains one of the most challenging problems in modern interventional cardiology. Discrepancies persist related to the benefit of dedicated bifurcation stents as compared to multiple stent approaches, identifying regions of susceptibility prior to or after implantation, and deciding whether or not to treat SB lesions and to what extent. As illustrated by the examples above, computational methods can be used to provide insight for each of these questions in hopes that the results can be used by clinicians, scientists and engineers to ultimately improve clinical outcomes.

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