Local Flow Patterns After Implantation of Bioresorbable Vascular Scaffold in Coronary Bifurcations
— Novel Findings by Computational Fluid Dynamics —

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Background: Development of methods for accurate reconstruction of bioresorbable scaffolds (BRS) and assessing local hemodynamics is crucial for investigation of vascular healing after BRS implantation.

Methods and Results: Patients with BRS that crossed over in a coronary bifurcation were included for analysis. Reconstructions of the coronary lumen and BRS were performed by fusion of optical coherence tomography and coronary angiography, generating a tree model (TM) and a hybrid model with BRS (TM-BRS). A virtual BRS model with thinner struts was created and all 3 models were analyzed using computational fluid dynamics to derive: (1) time-average shear stress (TASS), (2) TASS gradient (TASSG), which represents SS heterogeneity, and (3) fractional flow reserve (FFR). Reconstruction of the BRS was successful in all 10 patients. TASS and TASSG were both higher by TM-BRS than by TM in main vessels (difference 0.27±4.30 Pa and 10.18±27.28 Pa/mm, P<0.001), with a remarkable difference at side branch ostia (difference 13.51±17.40 Pa and 81.65±105.19 Pa/mm, P<0.001). With thinner struts, TASS was lower on the strut surface but higher at the inter-strut zones, whereas TASSG was lower in both regions (P<0.001 for all). Computational FFR was lower by TM-BRS than by TM for both main vessels and side branches (P<0.001).

Conclusions: Neglecting BRS reconstruction leads to significantly lower SS and SS heterogeneity, which is most pronounced at side branch ostia. Thinner struts can marginally reduce SS heterogeneity.

Key Words: Bifurcation; Computational fluid dynamics; Fractional flow reserve; Shear stress; Stents

The introduction of bioresorbable scaffolds (BRS) with the concept of avoiding long-term complications of metallic platforms, as well as restoring physiological vasomotion,1 sparked great enthusiasm among interventional cardiologists. However, recent clinical data on the safety of 1st-generation BRS raised concerns,2 as stent thrombosis rates were high in both the early and late phases and the possible causes are not completely understood. It has been hypothesized that alterations in endothelial shear stress (SS) play an important role.3 SS modulates the neointimal vascular response by stimulating endothelial flow sensors.4–6 As such, patterns of SS distribution might regulate neointimal healing around the implanted stent and potentially be associated with incomplete strut endothelialization, which has been implicated in late and very late stent thrombosis.7,8 Nevertheless, the actual SS patterns after BRS implantation in coronary bifurcations are unknown, so developing methodologies that enable accurate assessment of SS patterns in vivo is of great interest for studying the neointimal healing process after BRS implantation.

Intravascular optical frequency domain imaging (OFDI) allows in vivo imaging of BRS at high spatial resolution. A computational fluid dynamics (CFD) based approach for SS assessment using 3-dimensional (3D) OFDI has been proposed. Side branches (SBs) are often neglected in CFD analyses, which may lead to substantial errors in the SS assessment9,10 and limits its further investigations. We aimed to develop a new approach to in vivo reconstruction of BRS in a naturally tortuous shape and to investigate SS...
distribution and computational fractional flow reserve (FFR) after BRS implantation in coronary bifurcations.

Methods

Study Population
Post-hoc analysis was performed for all patients enrolled in a single center (Aarhus University Hospital, Skejby, Denmark) in the BIFSORB pilot study (NCT02973529), a proof-of-concept, prospective, single-arm study with the primary aim of evaluating the feasibility, self-correcting properties and early healing of the DESolve BRS (Elixir, USA) implanted in bifurcation lesions using the provisional SB stenting technique. Inclusion criteria included age ≥18 years old, stable angina pectoris, stabilized non-ST elevation myocardial infarction (nonSTEMI) or silent ischemia with a de novo bifurcation lesion of Medina class X.X.0, and SB diameter ≥2.5 mm. Major exclusion criteria included STEMI within 48 h, expected survival <1 year, serum creatinine >120 µmol/L, severe tortuosity or calcification of the target lesion or inability to cover the main vessel (MV) lesion with 1 stent. The study was conducted according to the Declaration of Helsinki and was approved by the Central Denmark Region Ethics Committee for Biomedical Research and the Danish Data Protection Agency. All patients provided written informed consent.

Reconstruction of the Coronary Tree and BRS
After implantation of the BRS in the target bifurcations, 2 angiographic image projections >25° were acquired by a flat-panel X-ray system (AlluraXper, Philips, The Netherlands). Final OFDI scans covering the entire stented segment were performed, using the Lunawave OFDI system (Terumo Corp., Japan) at a pullback speed of 15 mm/s and

Figure 1. Fusion of OFDI and X-ray angiography for CFD analysis after BRS implantation. (A) Angiography of a LAD after BRS implantation. (B) OFDI images with delineated LAD lumen. (C) Fusion of 3D angiography and OFDI luminogram with overlapping side branch ostia (zoomed) after restoring the naturally tortuous shape of the OFDI. (D) TM resulting from merging the bent OFDI lumen and the angiographic side branches. Red lines correspond to the 4 slices shown in (B). (E) The reconstructed BRS surface in a naturally tortuous shape. (F) TM-BRS resulting from combining the TM and BRS. (G) Clip image of the hybrid model. (H) Flow velocity after CFD analysis. 3D, 3-dimensional; BRS, bioresorbable scaffold; CFD, computational fluid dynamics; LAD, left anterior descending [coronary artery]; OFDI, optical coherence tomography; TM, lumen tree model; TM-BRS, TM hybrid with BRS.
Accordingly, 2 different geometric models, a fused lumen tree surface and a hybrid model with BRS were generated: (1) the lumen tree model (TM) resulted from merging the lumen of the MV derived from OFDI with the lumina of the SB derived from 3D angiography (Figure 1D); and (2) the hybrid model with BRS (TM-BRS) combined the TM and BRS surface (Figure 1F).

Both models were exported as stereo-lithography files for subsequent CFD analysis.

**Analysis of SS**

The 2 geometrical models (TM and TM-BRS) were discretized into small tetrahedral cells using a commercial software package (ANSYS ICEM 17.0, ANSYS Inc., Canonsburg, PA, USA). Approximately 0.5–6 million tetrahedral cells were generated per model. Navier Stokes equations were implemented in each cell and nonlinear partial differential equations were solved simultaneously using ANSYS FLUENT 17.0 (ANSYS Inc.). A blood density of 1,060 kg/m$^3$ and viscosity of 0.0035 kg/ms were applied. A no-slip condition was applied for the lumen wall. The mean volumetric flow rate was calculated based on the volume of the coronary tree lumen and the dye flowing time estimated by the frame count method. The patient-specific pulsatile flow was created by modulating a fixed pulsatile flow profile so that the average magnitude over a cardiac cycle matched the calculated mean flow.\textsuperscript{14}

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**Figure 2.** Quantification of shear stress (SS) with and without inclusion of the BRS in the CFD analysis. (A, A') SS distribution and spread-out map based on the TM-BRS model. (B, B') SS distribution and spread-out map based on the TM model. Numbers indicate the 2 bifurcations. (C') SS difference between the 2 models (SS\textsubscript{TM-BRS}–SS\textsubscript{TM}). Abbreviations as in Figure 1.
Subsequently, the modulated pulsatile flow was applied as the inlet boundary condition of the CFD analysis. At the outflow boundaries, a fully developed flow condition was applied.

For CFD analysis, meshing and flow simulation were performed separately for the TM and TM-BRS models, while applying the same inlet and outlet boundary conditions. An example of 3D reconstruction and CFD analysis of TM-BRS is shown in Figure 1. After the calculations, 2 computational SS values (i.e., SSTM and SS TM-BRS), respectively corresponding to the TM and TM-BRS geometrical models, were derived at each cell of each time step. Time-average SS (TASS), time-average SS gradient (TASSG), and oscillatory shear index (OSI) were derived for each cell.

The lumen of the MV was divided into portions of 0.15-mm length and 0.15-mm arc-width that assembled the strut thickness. The mean TASS, TASSG and OSI within each portion were calculated for both models and matched for the point-per-point comparison (Figure 2). The inter-strut zone was defined as the lumen surface between struts and the SS in the inter-strut zones was compared between the TM and TM-BRS. To study the effect of portion size on SS values, portions of 1-mm length and 1-mm arc-width were also analyzed in the TM-BRS model for comparison.

To investigate the heterogeneity of SS distribution with respect to the bifurcation location, the MV of the TM-BRS was divided into subsegments by the bifurcation. Thus, 3 subsegments, proximal MV (PMV), bifurcation core, and distal MV (DMV), were created and grouped per bifurcation. When a stent crossed over more than 1 SB, the segment between each 2 consecutive bifurcations was equally divided into 2 parts: DMV and PMV. Mean TASSG was then calculated per subsegment (Figure S1).

**Computational FFR**

The mean volumetric flow calculated from angiographic images acquired without pharmacologically induced hyperemia was converted into simulated hyperemic flow based on a previously published method. Afterwards, the hyperemic flow rate was applied at the inlet boundary and the virtual FFR was calculated separately using the TM and TM-BRS models, based on a CFD approach as previously described.

**Effect of Strut Thickness on Local Hemodynamics**

From the reconstructed BRS model, a virtual model with thinner struts was created by reducing the strut thickness at the inner side from 150 µm to 100 µm. The strut width, shape, structure and strut apposition of this virtual BRS model were kept the same as in the BRS model. Subsequently, the virtual BRS was fused with the TM to generate a new hybrid model (TM-VBRS). SS and computational FFR were analyzed by CFD, applying the same boundary conditions as in the analysis for the TM-BRS.

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Table 1. Baseline Clinical and Lesion Characteristics

| Characteristic | Value |
|---------------|-------|
| Age (years)   | 64±13 |
| BMI (kg/m²)   | 26±3  |
| LVEF (%)      | 57±7  |
| Sex (male)    | 8 (80) |
| Familial IHD  | 6 (60) |
| Dyslipidemia  | 9 (90) |
| Hypertension  | 4 (40) |
| Smoking (active) | 5 (50) |
| Diabetes      | 3 (30) |
| Previous revascularization (n=4) | |
| Previous PCI  | 3 (30) |
| Previous CABG | 1 (10) |
| Target lesion |       |
| LAD/D1        | 5 (50) |
| LAD/D2        | 2 (20) |
| LM            | 2 (20) |
| LCx/OM1       | 1 (10) |

Numbers are given as mean±SD or n (%). BMI, body mass index; CABG, coronary artery bypass graft; D1, 1st diagonal branch; D2, 2nd diagonal branch; IHD, ischemic heart disease; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; OM1, 1st obtuse marginal branch; PCI, percutaneous coronary intervention.

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**Figure 3.** Reconstruction of the vessel and bioresorbable scaffold for all cases.
Shear Stress in Coronary Bifurcation With BRS

Results

There were 10 patients with a BRS implanted in major coronary bifurcations included in the BIFSORB pilot study;11 1 patient had a drug-eluting stent (DES) implanted above the BRS, but only the BRS was reconstructed and used in the subsequent CFD analysis. Table 1 summarizes the patients’ baseline clinical and lesion characteristics. The mean length of the implanted BRS was 22.7±6.2 mm with a mean diameter of 3.1±0.2 mm. An average of 2.9 (range, 2–4) SBs >1 mm were included in the 3D reconstruction. The average number of SBs jailed by the BRS was 2.0 (Figure 3). An optimized implantation protocol with lesion preparation (non-compliant or scoring balloon), sizing to the proximal MV, proximal optimization technique and post-dilating with a non-compliant balloon was prespeci-

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was lower in the TM-BRS than in the TM for both the MVs (0.952±0.017 vs. 0.967±0.014, P<0.001) and their SBs (0.913±0.065 vs. 0.940±0.053, P<0.001) at the stented segments.

**Effect of Strut Thickness**
The comparisons of SS between the TM-VBRS and TM-BRS were summarized in Table 3. The TM-VBRS had slightly lower TASS and TASSG values, and higher OSI than the TM-BRS in the stented MV segments (P<0.001 for all). The differences between the TM-VBRS and TM-BRS were also more pronounced at the SB ostia. In the inter-strut zones, the TM-VBRS had higher TASS and...
lower TASSG and OSI values (P<0.001 for all).

There were minor, yet statistically significant differences in computational FFR by TM-VBRS and by TM-BRS for both the MVs (0.958±0.014 vs. 0.952±0.017, P<0.001) and their SBs (0.921±0.062 vs. 0.913±0.065, P<0.001) at the stented segments.

Effect of Portion size on SS Values

For the stented segments, a total of 118,906 and 3,486 portions were generated by the analyses with smaller portion size (0.15 mm length and 0.15 mm arc-width) and with larger portion size (1 mm length and 1 mm arc-width), respectively. Both the mean and the maximal TASS decreased with increasing portion size: 2.59±4.67 Pa vs. 1.92±2.81 Pa (P<0.001), and 152.78 Pa vs. 52.01 Pa. Minimal TASS was 0 Pa for both analyses.

Discussion

The main findings of this study were as follows. (1) It is feasible to reconstruct a BRS in a naturally tortuous course after implantation in coronary bifurcations and analyze local hemodynamics in vivo. (2) Inclusion of the reconstructed BRS in the CFD analysis resulted in higher TASS values at the stented segments including the strut surface, but lower TASS values at the inter-strut zones. (3) A greater degree of shear oscillation and spatial heterogeneity was observed when including the reconstructed BRS in the CFD analysis, especially at the SB ostia, where BRS with thinner struts appeared to have lower TASS and less spatial heterogeneity than those with thicker struts. (4) Neglecting BRS reconstruction in the CFD analysis resulted in an overestimation of computational FFR at the stented segments, especially in jailed SBs. (5) The computed SS values were affected by the size of portions in which SS was assessed, with smaller TASS when using a larger portion size in the statistical analysis.

The mechanism behind the differences in hemodynamic and functional assessments between the TM and TM-BRS can be explained by the local flow environment. Unembedded stent struts impede fluid flow, resulting in disturbed flow patterns and heterogeneous SS around the struts. Furthermore, the flow velocity was higher because of reduced luminal cross-sectional area, as partly occupied by the stent struts in the TM-BRS, which further increased the disturbed flow and SS heterogeneity. The longitudinal disjunction of the stent struts also contributed to changes in flow velocity and shear rates, causing temporal and spatial fluctuations in SS, manifested as higher OSI and TASSG values for stented segments in the TM-BRS than in the TM.

Hemodynamic differences between the TM-BRS and TM became more pronounced at the ostia of SBs, with substantially higher SS (TASS=13.88±17.33 vs. 0.37±1.64 Pa, P<0.001) and remarkably heterogeneous patterns in the TM-BRS (TASSG=81.80±105.31 vs. 0.16±2.29 Pa/mm, P<0.001, OSI=0.008±0.019 vs. 0.001±0.001, P<0.001). These findings may be explained by the fact that there were jailing struts in front of SB ostia in the TM-BRS. Compared with the stent struts apposed to the artery wall, struts jailing the SB ostia were exposed to higher flow velocity and thus more altered flow streamlines. These resulted in a greater disturbance of flow and shear oscillation around the struts, causing significantly higher TASS, TASSG and OSI values at the ostia. This may also explain our other finding that TASSG was higher in the bifurcation core area compared with that in the proximal and distal segments. Our results are consistent with previous observations of jailing strut leading to more flow disturbance and higher SS rates in DES. We further speculate that dilating the ostia of major jailed SBs could potentially improve flow patterns with clinically relevant implications. Of note, including the BRS model in the CFD analysis increased TASS in the entire stented segment. However, our data also showed that TASS at the inter-strut zones actually decreased, which suggests that the increase in SS occurred predominately at the strut surface because of protrusion of the strut into the lumen. The environment of low and oscillated SS in the inter-strut zones may promote neointimal healing and explain the common observation that the endothelialization process starts at the inter-strut zones, followed by the stent surface.

Inconsistent Findings and Resolution of SS Analysis

Low and oscillatory SS is widely assumed to play a key role in the initiation and development of atherosclerosis. However, current evidence regarding the low/oscillatory shear theory has been challenged and found to be less robust than commonly assumed. Technical issues in SS analysis might explain the inconsistency and we showed earlier that modeling of SBs can substantially affect the results of computed SS values. In the present study we applied highly detailed SS analysis (with the same resolution as the strut thickness) and observed that including the BRS in the computation significantly increased the SS values at the entire stented segment, though the SS actually decreased at the inter-strut zones. In other words, the averaged SS value would be substantially different when calculated for the inter-strut zones compared with a larger portion including both the strut surface and the inter-strut zones.

Besides, we also found that the computed SS values were significantly affected by the spatial resolution in the SS analysis. When the portion size increased, both the mean and maximal TASS values decreased substantially. This finding might partly explain the various findings of the optimal cutoff value of low/high SS for predicting future events, and highlights the importance of standardizing SS analysis. We suggest that an appropriate portion size for the point-per-point analysis of SS would be no larger than the size of the physical structure, such as vessel size for studies of the plaque progression in de novo arteries, or the size of stent struts for studies of neointimal healing after stent implantation. Unlike earlier studies that used spatial resolution of 1–3 mm length with an arc-width of 10–30° in SS analysis, we applied a portion size of 0.15 mm in both length and width, comparable with the size of the stent struts, for detailed analysis of SS. This might strengthen the findings of the present study.

Influence of Reconstruction of BRS on Computational FFR

Increasing evidence suggests that FFR measured after percutaneous coronary intervention (PCI) can be used to assess PCI optimization and might predict clinical outcomes. Angiography-based computational FFR without the use of a pressure wire might increase the utility of FFR assessment after PCI. However, the stent struts cannot be reconstructed from X-ray angiography and the effect of neglecting stent reconstruction in FFR computation is unknown. The present results suggest that computational FFR without including BRS reconstruction has a small
computational error (0.015±0.009, P<0.001) at the MVs, but the error was more pronounced (0.026±0.017, P<0.001) at the SBs. These observations might be explained by the fact that presence of stent struts at the SB ostia could alter the local flow patterns to a larger extent, leading to more energy loss and hence, more pressure drop and reduced FFR in the SBs. These observations also suggest that angiography-based computational FFR might have limitations when assessing the functional significance of SBs after PCI. OFDI-based computational FFR might resolve this limitation by incorporating the effect of SB jailing by struts.

Is a BRS With Thinner Struts Better?
The present study found lower TASS values on the strut surface but higher TASS values at the inter-strut zones when hypothetically implanting BRS with thinner struts. In addition, TASSG was lower with the thinner strut model in all regions. These findings can be explained by the fact that flow patterns were altered by the implanted BRS. The present study found lower TASS values on the strut surface but higher TASS values at the inter-strut zones. As such, SS spatial heterogeneity as reflected by TASSG was also reduced because of the reduced flow disturbance. At the SB ostia, a more pronounced difference in SS was observed in the thinner strut model compared with the thicker strut model, which suggests that strut thickness might have greater effect on local hemodynamics at the bifurcation region compared with non-bifurcation regions. Early studies suggested that less flow disturbance, especially at the inter-strut zones, could help reduce thrombus formation. As low endothelial SS was found to be associated with neointimal formation and stent coverage, our present findings suggest that thinner BRS struts could create a marginally more favorable environment for stent healing, especially for jailing struts at the SB ostia. This supports the need to further investigate the concept of BRS design with thinner struts in longitudinal studies.

Of note, the effect of strut thickness on computational FFR was negligible for the MV, but the difference was pronounced in jailing SBs. This observation is rather intuitive, because jailing struts in front of the SB ostia partially obstructs the blood flow into the SB, compared with the struts apposed to the lateral wall. As a result, computational FFR increased more for SBs when reducing the strut thickness. The true effect on clinical outcome needs further investigation.

Clinical Implications
Bench studies with SS computation as well as clinical studies have shown the risk of early thrombus formation on struts from implantation of BRS. Therefore, it is very important to know the baseline physiological properties of BRS. Understanding the physiological interactions among blood flow, BRS, and vessel wall might help develop models to predict very early thrombus formation from baseline physiological assessment, as well as changing the treatment strategy. The present study found that various factors, including BRS reconstruction, strut thickness, and post-processing portion size, could influence the baseline physiological assessment, especially at the SB ostia. The findings strengthen the need for standardized methodology for baseline physiological assessment, in order to correctly assess its relation to clinical outcome. Of note, OCT imaging follow-up was scheduled for all patients in the BIFSORB pilot study. Analysis of neointimal tissue coverage and thrombus formation will be performed in the future and correlated with baseline physiological parameters. All these efforts are crucial before embarking on further major studies.

Study Limitations
This study is limited by its small sample size, so selection bias cannot be excluded, although a large number of portions were analyzed per vessel because of the high resolution used in the SS analysis.

In order to compare the hemodynamic effects of implanting BRS with thinner struts, we used a virtual BRS model for the analysis. That might be different from actual BRS after implantation. Nevertheless, we created the virtual BRS model by shrinking the reconstructed stent at the inner side so that the apposition of the struts was the same as the reconstructed struts. In addition, by using the same luminal geometry and flow boundary conditions in the CFD analysis, we were able to compare the hemodynamic effects that were actually influenced by strut thickness. Only 1 type of BRS was studied. Hence, the results of this study may not be applicable to other types of BRS with different structure or thickness.

Conclusion
In vivo reconstruction of a BRS in a natural tortuous course after implantation in a coronary bifurcation is feasible. Neglecting the influence of the BRS on computational analysis led to significant difference in SS assessment, and underestimated the heterogeneity of local flow distribution, which was more pronounced at the SB ostia. Thinner BRS struts resulted in less SS heterogeneity. The relation between SS as assessed by this novel approach and stent healing warrants further investigation.

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Conflicts of Interest
Y.L. is an employee of Medis with a research appointment at the Leiden University Medical Center. J.H.C.R. is the CEO of Medis, and has a part-time appointment at Leiden University Medical Center as Professor of Medical Imaging. N.R.H. has received speaker fees from St. Jude Medical, Biotronik and Terumo, and institutional research grants from St. Jude Medical, Terumo, Boston Scientific, Medtronic, Biotronik, Medis and Cordis. S.T. received research grants from Medis. All other authors declare that they have no conflicts of interest.

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Supplementary Files

Supplementary File 1

Figure S1. Subsegment analysis method.

Figure S2. Histogram of frequencies showing the TASS difference between the 2 models (TM-BRS–TM).

Please find supplementary file(s): http://dx.doi.org/10.1253/circ.CJ-17-1332