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Flow Patterns at Stented Coronary Bifurcations: Computational Fluid Dynamics Analysis

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Short title: Flow Patterns at Stented Coronary Bifurcations

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Abstract

Objectives To assess hemodynamic parameters known to affect the risk of restenosis and thrombosis at coronary bifurcations following various single and double stenting techniques.

Background The ideal bifurcation stenting technique is not established and data on the hemodynamic characteristics at stented bifurcations are limited.

Methods and Results We employed computational fluid dynamics analysis to assess the distributions and surface integrals of the time averaged wall shear stress (TAWSS), oscillatory shear index (OSI) and relative residence time (t_r). Single main branch stenting without side branch balloon angioplasty or stenting provided the most favourable hemodynamic results (integrated values of TAWSS= $4.13 \cdot 10^{-4}$ N, OSI= $7.52 \cdot 10^{-6}$ m², $t_r=5.57 \cdot 10^{-4}$ m²/Pa) with bifurcational area subjected to OSI values >0.25 , >0.35 , and >0.45 calculated as 0.36mm², 0.04mm², and 0 mm², respectively. Extended bifurcation areas subjected to these OSI values were seen after T-stenting: 0.61mm², 0.18mm², and 0.02mm², respectively. Among the considered double stenting techniques, crush stenting (integrated values of TAWSS= $1.18 \cdot 10^{-4}$ N, OSI= $7.75 \cdot 10^{-6}$ m², $t_r=6.16 \cdot 10^{-4}$ m²/Pa) gave the most favourable results compared to T-stenting (TAWSS= $0.78 \cdot 10^{-4}$ N, OSI= $10.40 \cdot 10^{-6}$ m², $t_r=6.87 \cdot 10^{-4}$ m²/Pa) or the culotte technique (TAWSS= $1.30 \cdot 10^{-4}$ N, OSI= $9.87 \cdot 10^{-6}$ m², $t_r=8.78 \cdot 10^{-4}$ m²/Pa).

Conclusions Stenting of the main branch with or without balloon angioplasty of the side branch offers hemodynamic advantages over double stenting. When double stenting is considered, the crush technique with the use of a thin strut stent results in improved hemodynamics compared to culotte or T stenting.

Keywords: angioplasty, stents, hemodynamics

Introduction

Coronary bifurcations remain one of the most challenging lesion subsets, even in the era of drug eluting stents (DES). Single stent implantation in the main vessel with provisional stenting to the side branch vessel has been found superior to double stenting^{1, 2} and is considered the default approach in most coronary bifurcation lesions.³ However, in true bifurcation lesions, this provisional approach may leave significant residual stenosis of the side branch vessel after PCI, and in recent randomized study, double stenting reduced target vessel revascularization without affecting major adverse coronary events compared to provisional side branch stenting.⁴ Thus, operators may opt for double stenting in the presence of a big side branch. Still, the ideal stenting technique is not established in this respect.

Several methods for deployment of two stents at bifurcations have been proposed, but their impact on clinical outcomes such as restenosis and, especially, stent thrombosis and iatrogenic myocardial infarction, still a reason for concern with DES,⁵ is not known. Stenting at the site of bifurcation inevitable affects coronary flow patterns that have been associated with restenosis rates and stent thrombosis.⁶ Indeed, altered geometry and associated blood flow disturbances induced by stenting can influence restenosis.^{7, 8} Disturbed flow may also facilitate the accumulation of platelets and other blood thrombogenic factors close to the wall.^{9, 10} 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.^{11, 12} Luminal dimensions and flow patterns are theoretically restored after PCI, but bifurcation stenting is associated with geometric deformation of both the main and side branch and, most importantly, introduction of stents struts into the coronary artery, with frequent protrusion into the lumen, that alter the original flow environment. Stent struts alter flow conditions both close to the vessel wall and inside the vessel lumen.¹³ Thus, each stenting technique has a distinct and possibly significant effect on the flow patterns at the

bifurcation region. The disturbances that the various bifurcation stenting techniques impose on post-PCI coronary flow have not been studied.

In the present study, we employed computational fluid dynamics (CFD) analysis to assess hemodynamic conditions and flow patterns at stented coronary bifurcations by simulating single and double stenting techniques that are commonly used in clinical practice. Such as analysis may define the predisposition of each stenting technique to restenosis and thrombus formation and may guide clinical decisions for optimum therapy in this challenging setting.

Materials

Creation of an idealized coronary bifurcation model

The model represents a typical left anterior descending – diagonal bifurcation which are coronary bifurcations frequently affected by atherosclerosis (Figure 1).¹⁴ The diameter of the proximal main branch (PMB) of the model is 3.5mm and the diameter of the side branch (SB) is 2.5mm, since usually only side branches with diameters greater than 2.25mm are considered for stenting.¹⁵ The diameter of the distal main branch (DMB) is calculated from the diameters of the PMB and SB by the scaling law of Finet: $PMB = (DMB + SB) \times 0.678$.¹⁶ The bifurcation angle, defined as the angle between the axis of the main vessel and the axis of the side-branch at its origin, is 50° which is the median value of 538 coronary bifurcation lesions with a side branch >2mm.¹⁷ The dimensions of simulated stents were 16mm/3.5mm at the MB and 7mm/2.5mm at the SB, thus stent implantation caused enlargement of the DMB. At the cases that there was residual stenosis at the SB, the lesion shape was considered cosinus-shaped in the longitudinal view and circular-shaped in the cross-sectional view.

Stent simulation and incorporation at the bifurcation model

The simulated coronary stent closely resembles the strut design and linkage pattern of a third generation, everolimus-eluting stent (PROMUS Element, Boston Scientific). The struts are

particularly thin compared to other available stents (0.081-0.086 mm depending on stent diameter) and widened at the crown to redirect the strain of expansion to the longitudinal portion.¹⁸ The cross-section of the simulated stent struts was considered square with thickness of 0.081mm, while the struts were slightly widened at the crowns to capture the design of the actual stent. In order to reproduce the linkage pattern of the stent, a 24mm/2.5mm PROMUS Element DES was inflated at 12atm to its nominal diameter. After balloon extraction the stent was macro-photographed with a 14MP digital camera. The digital image was imported to a QCA computer-based system (QCA-CMS 6.0, Medis) and the geometric features of the strut linkage pattern were extracted after image calibration. Computer Aided Design (CAD) software was used in order to reproduce the stented geometry as accurate as possible (SolidWorks 2009, SolidWorks Corp., Concord, MA). The first step involved the creation of the solid model of the bifurcation geometry and the second step involved the creation of the actual expanded stent geometry. A hollow tube with outer diameter equal with the nominal expanded diameter of the actual stent and thickness equal with the thickness of the stent was created. A 2-dimensional sketch with the strut dimensions of the stent was propagated and wrapped around that tube. Then a cutout was performed thus obtaining 1 ring of the stent. That ring was propagated axially in order to create the full length expanded stent solid representation. The last step involves the modification and the “virtual implantation” of the solid stent model inside the bifurcation geometry. The stent solid model is placed in the proper position of the bifurcation model. At this point, depending on the case, material removal (i.e. struts removal from the SB entrance) or flex deformation (i.e. to simulate “Culotte” or “Crush” double stenting techniques) was applied. Finally, by using Boolean operation, the modified solid stent model is subtracted from the solid bifurcation model in order to obtain the final geometry. Those steps are repeated for each stent that is to be “virtually implanted”.

Considered stenting techniques

Six bifurcation stenting techniques were considered, three single stenting techniques and three double stenting techniques:

(1) Stenting of the MB only

In this case of provisional stenting, one stent is implanted at the MB without any intervention at the SB (Figure 2-1). Stenting of the MB results to introduction of a stent inside the bifurcation lumen at the orifice of the SB. At the SB, we considered a symmetrical ostial diameter stenosis of 75% affecting both the outer vessel wall and the flow divider.

(2) Stenting of the MB followed by balloon angioplasty of the SB

In this case of provisional stenting, one stent is implanted at the MB and then a balloon is inflated at the SB through the struts of the MB stent (Figure 2-2). Balloon inflation removes the stent struts from the orifice of the SB, thus there are no struts inside the lumen at the bifurcation site. At the SB we considered a residual diameter stenosis of 30% since angiographic success is frequently defined as achievement of <50% residual stenosis by any percutaneous method.¹⁹

(3) Balloon angioplasty of the SB followed by stenting of the MB

Balloon angioplasty of the SB precedes stenting of the MB (Figure 2-3). After balloon inflation and stent implantation there is usually a residual stenosis at the SB (considered 50%) due to the combined effect of plaque shifting from the proximal segment of the MB, and displacement of the flow divider by the expanded stent struts. Since stenting of the MB follows balloon angioplasty of the SB, at the bifurcation site there are stent struts inside the lumen at the orifice of the SB.

(4) “Culotte” stenting

“Culotte” or “trousers” stenting consists of implanting a first stent from the proximal to the distal segment of the MB. A second stent is then placed from the proximal MB towards the

SB through the struts of the first stent (Figure 2-4). Culotte stenting results in a double layer of struts in the proximal part of the MB and presence of struts in the lumen of the MB at the bifurcation site.²⁰ We assumed that after stent implantation there is no residual narrowing at the MB or SB.

(5) “Crush” stenting

“Crush” stenting consists of advancing two stents simultaneously into both the MB and SB. The proximal segment of the SB stent is first deployed in the MB and then it is crushed to the main vessel wall during deployment of the MB stent (Figure 2-5). Crush stenting results in a triple layer of struts in the proximal MB wall towards the branching vessel, and a double layer of struts (from the MB stent and the crushed SB stent) at the orifice of the SB.²⁰ We assumed that after stent implantation there is no residual narrowing to either the MB or SB.

(6) Ideal T-stenting

This hypothetical stenting technique simulates an “idealized” T-stenting method in which one stent is implanted at the MB and one stent at the SB while there is no strut overlap at any site of the bifurcation and additionally the struts at the orifice of the SB have been intentionally removed (Figure 2-6). This model was included in order to consider it as the “gold standard” of bifurcation scaffolding.

CFD methodology and evaluation of simulations results

The simulations were conducted using the commercial software ANSYS FLUENT 12.1 (by Fluent Inc.) The numerical grid for the simulation was created from the constructed geometries using ANSYS Meshing 12.1 (by Fluent Inc.). The grid density was greatly enhanced in the region around the stents. The total number of elements varied for the cases examined from 2.7 to 4.5 million elements approximately. The following assumptions were made:

- Blood was considered a Newtonian fluid with viscosity 3.5 cP and density 1.06 g/ml

- The artery walls are assumed rigid and no deformation is taken into account
- The simulation was transient covering 2 complete cardiac cycles. Results are presented for the 2nd cycle. A total of 102 time steps per cardiac cycles were simulated
- At the inlet, a pre-described pulse of the blood flow rate and pressure has been assumed²¹
- Mass flow exit boundary conditions were used for the 2 branches. The flow was assumed to split proportionally to the (3/2) power of the bifurcation vessel's normal diameters

The hemodynamic parameters that were assessed at stented coronary bifurcations through CFD simulations were the time averaged wall shear stress (TAWSS), the oscillatory shear index (OSI) and the relative residence time (t_r). **TAWSS** expresses the frictional force per unit area that is exerted by the flowing blood to the vascular wall due to the viscous properties of blood.²² **OSI** is a dimensionless parameter that accounts for the degree of deviation of WSS from the antegrade flow direction. Small OSI values (close to 0) indicate small variations of the WSS vector during the cardiac cycle. Conversely, OSI values close to 0.5 indicate that WSS vector is subject to large variations and WSS can be very small or change direction at parts of the cardiac cycle, which means that at those time instances flow is stopped or reversed.²³ Although OSI can identify regions of flow reversal, it is insensitive to shear magnitude thus it has been suggested that OSI should be employed in combination with other shear measures.²⁴ A relevant suitable index of flow is the **relative residence time** derived from TAWSS and OSI by the equation $t_r \approx [(1 - 2 \cdot OSI) \cdot (|TAWSS|)]^{-1}$.²⁴ Studies at stented coronary segments have shown that neointimal growth is located at regions of low WSS and high temporal oscillations in WSS quantified by high OSI.²⁵ The atherosclerotic process is also enhanced at areas at which the solutes and formed elements of blood have high residence times in the neighborhood of the vascular endothelium.²⁶ Hemodynamic parameters have also

impact on many processes involved in thrombus formation, including platelet recruitment to the vessel wall, platelet adhesion activation and aggregation.¹⁰ Thrombus formation is enhanced at areas of slow and reversed flow characterized by high OSI and high residence times since these conditions enhance platelet aggregation.⁹ In this study the bifurcation stenting techniques were comparatively evaluated in terms of the induced flow alterations at the region of the bifurcation. Although we cannot directly link hemodynamic disturbances and the risk of restenosis and thrombosis, it is plausible that the risk of restenosis and thrombosis would be higher if regions of the bifurcation are continuously exposed to low WSS or high OSI and t_r . Thus, high TAWSS, low OSI and low t_r values were considered hemodynamically favorable regarding the predisposition of each technique to restenosis and thrombosis. TAWSS, OSI and t_r were calculated as previously described.^{11, 24}

Results

Figures 3, 4 and 5 give the TAWSS, OSI and t_r distributions for the six considered stenting techniques. These figures clearly demonstrate that each stenting technique has a distinct impact to the flow patterns that is reflected both at the distribution and the magnitude of the calculated flow indices to the bifurcation region.

Single stenting

At the three single stenting techniques (left panel of Figures 3-5) there is residual stenosis at the SB through which flow is accelerated resulting to high flow velocities and thus WSS values at this vessel. At the MB the distributions of WSS, OSI and t_r are identical for the three single stenting techniques, with a region of low WSS and high OSI and t_r values at the distal MB, downstream the bifurcation. At the SB the distributions of WSS differ; at the cases of tight residual stenosis high WSS values are seen at the whole stenotic region whereas when the stenosis becomes less tight high WSS values are localized only close at the throat of the stenosis. OSI and t_r are identical among cases, particularly for the vessel segments close

to the bifurcation, indicating that due to the flow acceleration there is no stagnation or reversal of flow at this site. We can thus derive that in single stenting, flow patterns are governed by the degree of the residual stenosis, whereas the existence or absence of stent struts at the orifice of the SB do not impose any significant flow alterations.

Double stenting

With double stenting techniques (right panel of Figures 3-5), WSS, OSI and t_r distributions exhibit pronounced differences among cases. Culotte stenting results at low WSS regions at both the proximal and the distal MB whereas with the other two double stenting techniques, low WSS regions are confined to the distal MB. Regarding the SB, culotte stenting results at an extended region of low WSS opposite the flow divider. With T-stenting the low WSS region is considerably smaller, whereas with crush stenting there are no low WSS regions at the SB. The distributions of OSI and t_r also differ among stenting techniques; with culotte and T-stenting, ‘hot spots’ of OSI are seen at the proximal SB, opposite the flow divider, whereas with crush stenting the OSI distribution at the SB is smooth. At all cases small regions of high OSI are seen at the distal MB which coincide with the regions of low WSS. Regarding t_r , more distinct differences among cases are seen; in culotte stenting there are ‘hot spots’ both at the SB opposite the flow divider and at the proximal MB. At T-stenting there are ‘hot spots’ at both the SB and the distal MB whereas at crush stenting ‘hot spots’ are confined to the SB and occupy considerably less area.

Comparison of techniques

In order to compare findings, we calculated the surface integrals of TAWSS, OSI and t_r at a subregion of bifurcation site (Figure 1). The integral of each index was normalized to that of the stenting technique that provided the most hemodynamically favorable results, eg highest TAWSS, and lowest OSI and t_r (Table 1). The ranking of the stenting techniques in Table 1 follows a descending order, starting with the technique that gives the optimum results. From

Table 1 we can derive that single stenting techniques and particularly stenting of the MB only and balloon angioplasty of the SB followed by stenting of the MB, give better overall results compared to the double stenting techniques. Among the double stenting techniques, crush stenting gives the most favorable results while its overall ranking follows the two optimum single stenting techniques.

Additionally, we calculated for each stenting technique the total area of the bifurcation region that is subjected to OSI values greater than specific predefined thresholds (Table 2). As previously noted, OSI values close to 0.5 indicate arterial segments of flow stagnation or flow reversal. The results shown in Table 2 indicate that single stenting techniques result in smaller arterial segments at which flow is stopped or reversed. Crush stenting gives the optimum results among the double stenting techniques, which are comparable to those of single stenting techniques.

Discussion

Our results indicate that double stenting in bifurcations is associated with disturbed hemodynamics. They also indicate that double stenting techniques do not produce similar hemodynamic disturbances at bifurcations. Plaque and neointimal hyperplasia tend to form in bifurcations within the coronary arteries where normal patterns of blood flow are disturbed.²⁷ Even when proliferative responses to these altered hemodynamics are completely blocked by drug-eluting stents, abnormal flow patterns can be a possible cause of thrombosis.²⁸ A number of computational studies have assessed hemodynamic alterations produced by stent implantation at non-bifurcated vessel segments: LaDisa et al¹³ studied WSS alterations after a slotted-tube coronary stent and found that flow stagnation zones are localized around the stent struts and minimum WSS decreased by 77% in stented compared to non-stented vessels. Faik et al²⁹ validated the existence of secondary flow in the near wall region of the stented coronary segment and also demonstrated that secondary flow is more pronounced in the areas

following struts that are perpendicular to the main flow direction. Data regarding flow alterations caused by stent implantation at bifurcation lesion is limited. A computational study by Williams et al⁶ assessed hemodynamic changes after main branch stenting and side branch balloon angioplasty in a coronary bifurcation and indicated that this commonly used interventional strategy causes abnormal local hemodynamic conditions.

Our study, is the first one to investigate flow patterns following different stenting techniques at bifurcation sites. Although the findings of the study refer to the hemodynamic disturbances imposed by stenting which cannot be directly linked to the clinical outcome, it is plausible that the risk of restenosis and thrombosis would be higher at regions of the bifurcation that are continuously exposed to unfavorable hemodynamic conditions. In a recent study at specimens of stented bifurcations of patients dying of severe coronary artery disease, Nakazawa et al³⁰ reported that neointimal formation is significantly less at the flow divider compared with the lateral wall and that late stent thrombosis has a higher prevalence at flow divider sites due to uncovered struts and disturbed flow at the carina region. Our computational findings are in part in keeping with these observations since in all simulated stenting techniques, regions of low WSS and high OSI which are both associated to neointimal formation, are confined at the lateral arterial walls. Regarding stent thrombosis, our results indicate that the bifurcation regions at higher risk of thrombosis generally coincide with the regions of neointimal formation and are located opposite the flow divider. This difference is probably due to the fact that our study did not consider strut coverage by neointimal formation. Thus, considering the results of both studies, one might speculate that the risk of acute stent thrombosis is higher at sites opposite the flow divider whereas the risk of late thrombosis is higher at the carina region.

Regarding the comparison of single and double stenting techniques, our findings are in keeping with the results of large clinical trials which documented that single stenting of the

main vessel is preferable in the great majority of bifurcation lesions.^{1, 2} A recent clinical trial comparing double kissing (DK) crush with provisional stenting for the treatment of bifurcation lesions demonstrated that DK crush is associated with significant reduction of target lesion and target vessel revascularization, whereas there was not significant difference in major adverse cardiac events.⁴ Interestingly, in our study crush stenting was associated with the most favorable hemodynamic conditions among double stenting techniques which were in some cases comparable to those imposed by single stenting. Surprisingly, the considered ‘ideal’ T-stenting evaluated in the study which theoretically provides optimum bifurcation scaffolding since it covers the bifurcation region without strut overlap or strut protrusion into the vessel lumen produced overall the worst results from a hemodynamic perspective. However, in clinical practice, the NORDIC investigators failed to detect any difference between the culotte and crush techniques using a Cypher Select+ stent (Johnson and Johnson).³¹ Whether this can be attributed to the thicker struts of this stent cannot be deduced from our data. In theory, arterial segments covered with double layers of stents are less prone to stent recoil due to the increased exerted radial force which counteracts more effectively any recoil of the elastic vessel wall.³² In our study, the only stenting technique in which part of the bifurcation is circumferentially covered with double layers of stents is the “Culotte” technique which was however not associated with favourable hemodynamic results. Nevertheless, both phenomena of restenosis and thrombosis are complex and multifactorial and the effect of stent recoil cannot be neglected.

Study limitations

The considered model represents an idealized coronary bifurcation with vessel dimensions and bifurcation angle of a typical left anterior – diagonal branch bifurcation. At the SB we considered an ostial symmetrical stenosis, affecting both the outer vessel wall and the flow divider although the shape of an actual coronary lesion is seldom symmetrical either axially

or radially. However, although early atherosclerosis is localized at sites of low wall shear stress (WSS) such as the outer walls of vessel bifurcations,³³ at advanced to severe atherosclerosis, plaques grow circumferentially from the low WSS region into the high WSS flow divider,³⁴ thus severe ostial stenoses become circumferentially symmetric. Additionally, ostial stenoses of side branches are commonly aggravated after MB stent implantation due to the combined effect of plaque shifting from the proximal segment of the MB into the SB ostium³⁵ and displacement of the flow divider by the expanded stent struts (carina displacement between the two diverging branches).³⁶ The MB and SB were considered straight, non-compliant and stationary although coronary vessels are curved, compliant and attached to the beating myocardium. Studies have shown that myocardial motion has only a minor effect on flow distribution within the arterial tree relative to the effect of the blood pressure pulse³⁷ and stent implantation causes straightening of the vessel and reduces its regional compliance.³⁸ Regarding the assumptions of the flow simulation, the boundary conditions were similar to most relevant studies and included realistic pulsatile flow and pressure, whereas blood was considered Newtonian, and this is not applicable to all flow conditions. However, this assumption has been shown to have minor effect on the distribution of the flow parameters assessed in this study.³⁹

Acknowledging these limitations, our data indicate that single stenting of the main branch with or without balloon angioplasty of the side branch ostium, offers better hemodynamic patterns than double stenting. When double stenting is considered necessary, the crush technique with the use of a thin strut stent is preferable to culotte or T stenting. Whether these theoretical advantages translate into improved clinical outcomes cannot be deduced from our study.

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References

1. Behan MW, Holm NR, Curzen NP, Erglis A, Stables RH, de Belder AJ, Niemela M, Cooter N, Chew DP, Steigen TK, Oldroyd KG, Jensen JS, Lassen JF, Thuesen L, Hildick-Smith D. Simple or complex stenting for bifurcation coronary lesions: A patient-level pooled-analysis of the nordic bifurcation study and the british bifurcation coronary study. *Circulation*. 2011;4:57-64
2. Katritsis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: A meta-analysis. *Circulation*. 2009;2:409-415
3. Latib A, Colombo A, Sangiorgi GM. Bifurcation stenting: Current strategies and new devices. *Heart (British Cardiac Society)*. 2009;95:495-504
4. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ, Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions results from the dkcrush-ii (double kissing crush versus provisional stenting technique for treatment of coronary bifurcation lesions) trial. *Journal of the American College of Cardiology*. 2011;57:914-920
5. Onuma Y, Serruys PW. Bioresorbable scaffold: The advent of a new era in percutaneous coronary and peripheral revascularization? *Circulation*. 2011;123:779-797
6. Williams AR, Koo BK, Gundert TJ, Fitzgerald PJ, Ladisa J, Jr. Local hemodynamic changes caused by main branch stent implantation and virtual side branch balloon angioplasty in a representative coronary bifurcation. *J Appl Physiol*. 2010;109:532-540

7. Garasic JM, Edelman ER, Squire JC, Seifert P, Williams MS, Rogers C. Stent and artery geometry determine intimal thickening independent of arterial injury. *Circulation*. 2000;101:812-818
8. Kastrati A, Mehilli J, Dirschinger J, Pache J, Ulm K, Schuhlen H, Seyfarth M, Schmitt C, Blasini R, Neumann FJ, Schomig A. Restenosis after coronary placement of various stent types. *The American journal of cardiology*. 2001;87:34-39
9. Bluestein D, Gutierrez C, Londono M, Schoepfoerster RT. Vortex shedding in steady flow through a model of an arterial stenosis and its relevance to mural platelet deposition. *Annals of biomedical engineering*. 1999;27:763-773
10. Nesbitt WS, Mangin P, Salem HH, Jackson SP. The impact of blood rheology on the molecular and cellular events underlying arterial thrombosis. *Journal of molecular medicine (Berlin, Germany)*. 2006;84:989-995
11. Katritsis DG, Theodorakakos A, Pantos I, Andriotis A, Efstathopoulos EP, Siontis G, Karcanias N, Redwood S, Gavaises M. Vortex formation and recirculation zones in left anterior descending artery stenoses: Computational fluid dynamics analysis. *Physics in medicine and biology*. 2010;55:1395-1411
12. Moore JE, Jr., Timmins LH, Ladisa JF, Jr. Coronary artery bifurcation biomechanics and implications for interventional strategies. *Catheter Cardiovasc Interv*. 2010;76:836-843
13. LaDisa JF, Jr., Guler I, Olson LE, Hettrick DA, Kersten JR, Warltier DC, Pagel PS. Three-dimensional computational fluid dynamics modeling of alterations in coronary wall shear stress produced by stent implantation. *Annals of biomedical engineering*. 2003;31:972-980

14. Lefevre T, Louvard Y, Morice MC, Dumas P, Loubeyre C, Benslimane A, Premchand RK, Guillard N, Piechaud JF. Stenting of bifurcation lesions: Classification, treatments, and results. *Catheter Cardiovasc Interv.* 2000;49:274-283
15. Di Mario C, Morici N, Godino C, Goktekin O, Tamburino C, Barbagallo R, Antoniucci D, Grube E, Airolidi F, Zoccai GB, Colombo A, Sangiorgi GM. Predictors of restenosis after treatment of bifurcational lesions with paclitaxel eluting stents: A multicenter prospective registry of 150 consecutive patients. *Catheter Cardiovasc Interv.* 2007;69:416-424
16. Finet G, Gilard M, Perrenot B, Rioufol G, Motreff P, Gavit L, Prost R. Fractal geometry of arterial coronary bifurcations: A quantitative coronary angiography and intravascular ultrasound analysis. *EuroIntervention.* 2008;3:490-498
17. Dzavik V, Kharbanda R, Ivanov J, Ing DJ, Bui S, Mackie K, Ramsamujh R, Barolet A, Schwartz L, Seidelin PH. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: Importance of the bifurcation angle. *American heart journal.* 2006;152:762-769
18. Wilson GJ, Huibregtse BA, Stejskal EA, Crary J, Starzyk RM, Dawkins KD, Barry JJ. Vascular response to a third generation everolimus-eluting stent. *EuroIntervention.* 2010;6:512-519
19. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR, Jr., Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation.* 2004;109:1244-1249
20. Louvard Y, Lefevre T, Morice MC. Percutaneous coronary intervention for bifurcation coronary disease. *Heart (British Cardiac Society).* 2004;90:713-722
21. Berne RM, Levy MN. *Cardiovascular physiology*. St. Louis, USA: Mosby Inc; 2001.

22. Katritsis D, Kaiktsis L, Chaniotis A, Pantos J, Efstathopoulos EP, Marmarelis V. Wall shear stress: Theoretical considerations and methods of measurement. *Progress in cardiovascular diseases*. 2007;49:307-329
23. He X, Ku DN. Pulsatile flow in the human left coronary artery bifurcation: Average conditions. *Journal of biomechanical engineering*. 1996;118:74-82
24. Himburg HA, Grzybowski DM, Hazel AL, LaMack JA, Li XM, Friedman MH. Spatial comparison between wall shear stress measures and porcine arterial endothelial permeability. *American journal of physiology*. 2004;286:H1916-1922
25. Wentzel JJ, Gijzen FJ, Schuurbiers JC, van der Steen AF, Serruys PW. The influence of shear stress on in-stent restenosis and thrombosis. *EuroIntervention*. 2008;4 Suppl C:C27-32
26. Moore JE, Jr., Ku DN, Zarins CK, Glagov S. Pulsatile flow visualization in the abdominal aorta under differing physiologic conditions: Implications for increased susceptibility to atherosclerosis. *Journal of biomechanical engineering*. 1992;114:391-397
27. Stone PH, Coskun AU, Kinlay S, Clark ME, Sonka M, Wahle A, Ilegbusi OJ, Yeghiazarians Y, Popma JJ, Orav J, Kuntz RE, Feldman CL. Effect of endothelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans: In vivo 6-month follow-up study. *Circulation*. 2003;108:438-444
28. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: Molecular, cellular, and vascular behavior. *Journal of the American College of Cardiology*. 2007;49:2379-2393

29. Faik I, Mongrain R, Leask RL, Rodes-Cabau J, Larose E, Bertrand O. Time-dependent 3d simulations of the hemodynamics in a stented coronary artery. *Biomedical materials (Bristol, England)*. 2007;2:S28-37
30. Nakazawa G, Yazdani SK, Finn AV, Vorpahl M, Kolodgie FD, Virmani R. Pathological findings at bifurcation lesions: The impact of flow distribution on atherosclerosis and arterial healing after stent implantation. *Journal of the American College of Cardiology*. 2010;55:1679-1687
31. Erglis A, Kumsars I, Niemela M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galloe A, Narbutė I, Sondore D, Makikallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvanne M, Helqvist S, Kjell N, Wiseth R, Aaroe J, Puhakka M, Thuesen L. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: The nordic stent technique study. *Circulation*. 2009;2:27-34
32. Williams PD, Appleby CE, Chowdhary S, Fraser DG. Double stenting: A method for treating acute stent recoil and luminal filling defects. *EuroIntervention*.6:846-853
33. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *Jama*. 1999;282:2035-2042
34. van der Giessen AG, Wentzel JJ, Meijboom WB, Mollet NR, van der Steen AF, van de Vosse FN, de Feyter PJ, Gijzen FJ. Plaque and shear stress distribution in human coronary bifurcations: A multislice computed tomography study. *EuroIntervention*. 2009;4:654-661
35. Koo BK, Waseda K, Kang HJ, Kim HS, Nam CW, Hur SH, Kim JS, Choi D, Jang Y, Hahn JY, Gwon HC, Yoon MH, Tahk SJ, Chung WY, Cho YS, Choi DJ, Hasegawa T, Kataoka T, Oh SJ, Honda Y, Fitzgerald PJ, Fearon WF. Anatomic and functional

- evaluation of bifurcation lesions undergoing percutaneous coronary intervention.
Circulation. 2010;3:113-119
36. Vassilev D, Gil R. Clinical verification of a theory for predicting side branch stenosis after main vessel stenting in coronary bifurcation lesions. *Journal of interventional cardiology*. 2008;21:493-503
 37. Theodorakakos A, Gavaises M, Andriotis A, Zifan A, Liatsis P, Pantos I, Efsthopoulos EP, Katritsis D. Simulation of cardiac motion on non-newtonian, pulsating flow development in the human left anterior descending coronary artery. *Physics in medicine and biology*. 2008;53:4875-4892
 38. LaDisa JF, Jr., Hettrick DA, Olson LE, Guler I, Gross ER, Kress TT, Kersten JR, Warltier DC, Pagel PS. Stent implantation alters coronary artery hemodynamics and wall shear stress during maximal vasodilation. *J Appl Physiol*. 2002;93:1939-1946
 39. Johnston BM, Johnston PR, Corney S, Kilpatrick D. Non-newtonian blood flow in human right coronary arteries: Transient simulations. *Journal of biomechanics*. 2006;39:1116-1128

Figures

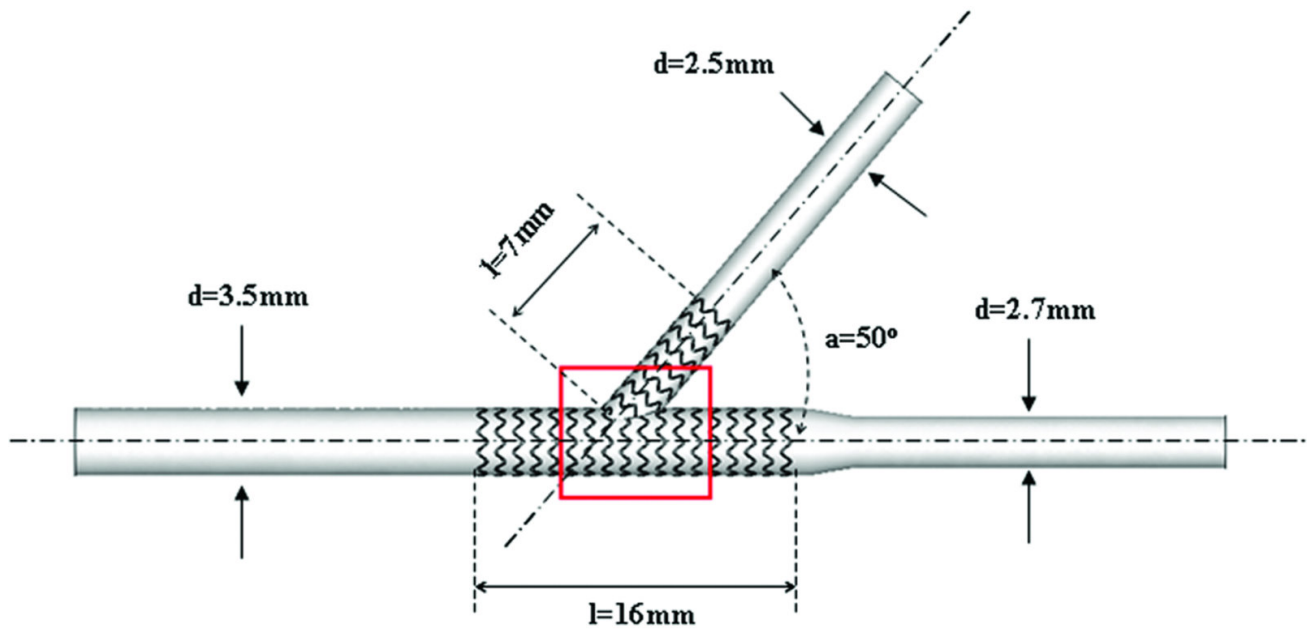


Figure 1. The considered model of a typical left anterior descending – diagonal bifurcation. The rectangle denotes the bifurcation subregion at which the surface integrals of the flow indices were calculated.

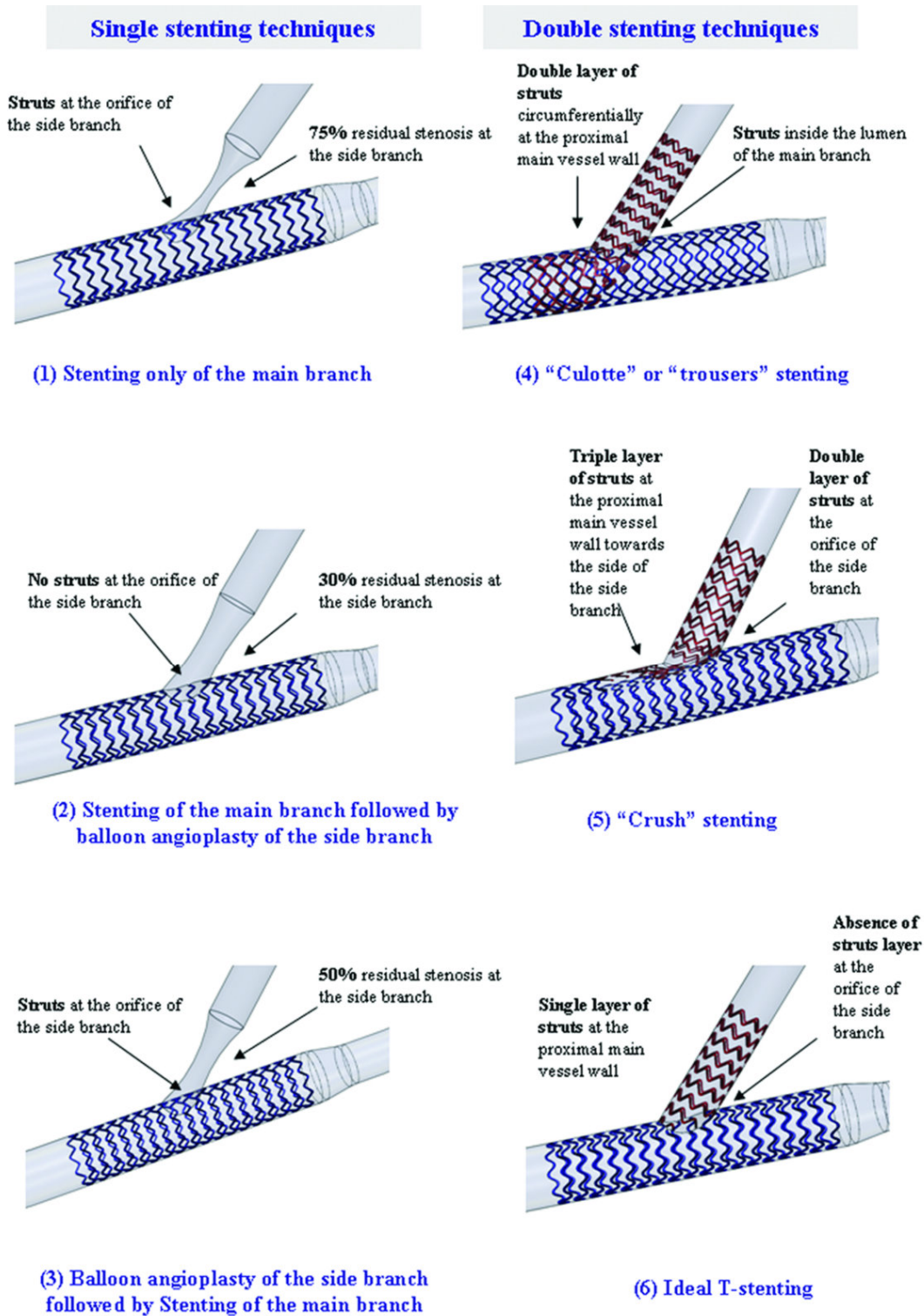


Figure 2. Considered bifurcation stenting techniques and they effect on stent strut distribution on the vessel wall and vessel lumen. The left panel illustrates the single stenting techniques and the right panel the double stenting techniques.

Time Averaged Wall Shear Stress (TAWSS)

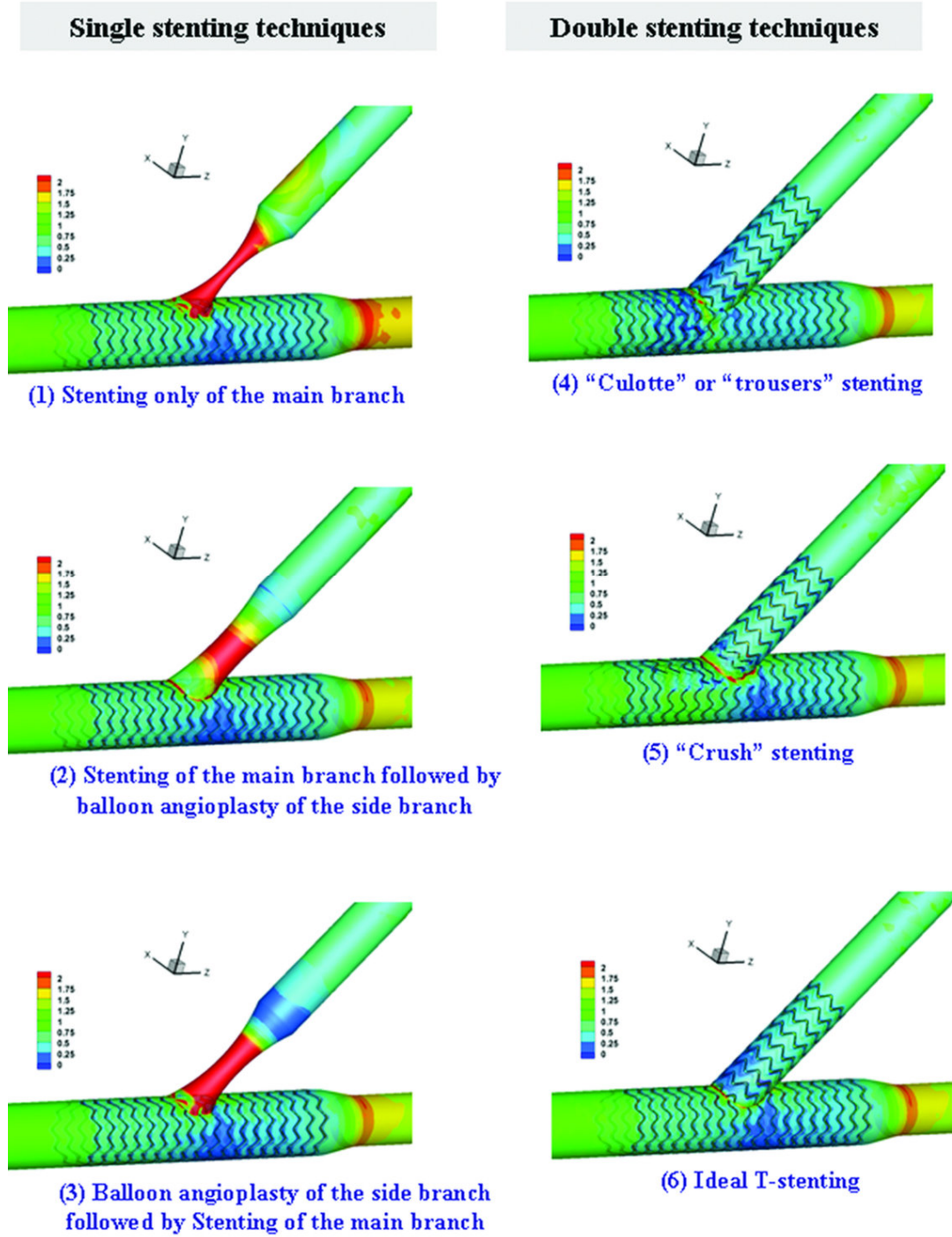


Figure 3. Time averaged wall shear stress (TAWSS) distribution at the bifurcation for the considered bifurcation stenting techniques.

Oscillatory Shear Index (OSI)

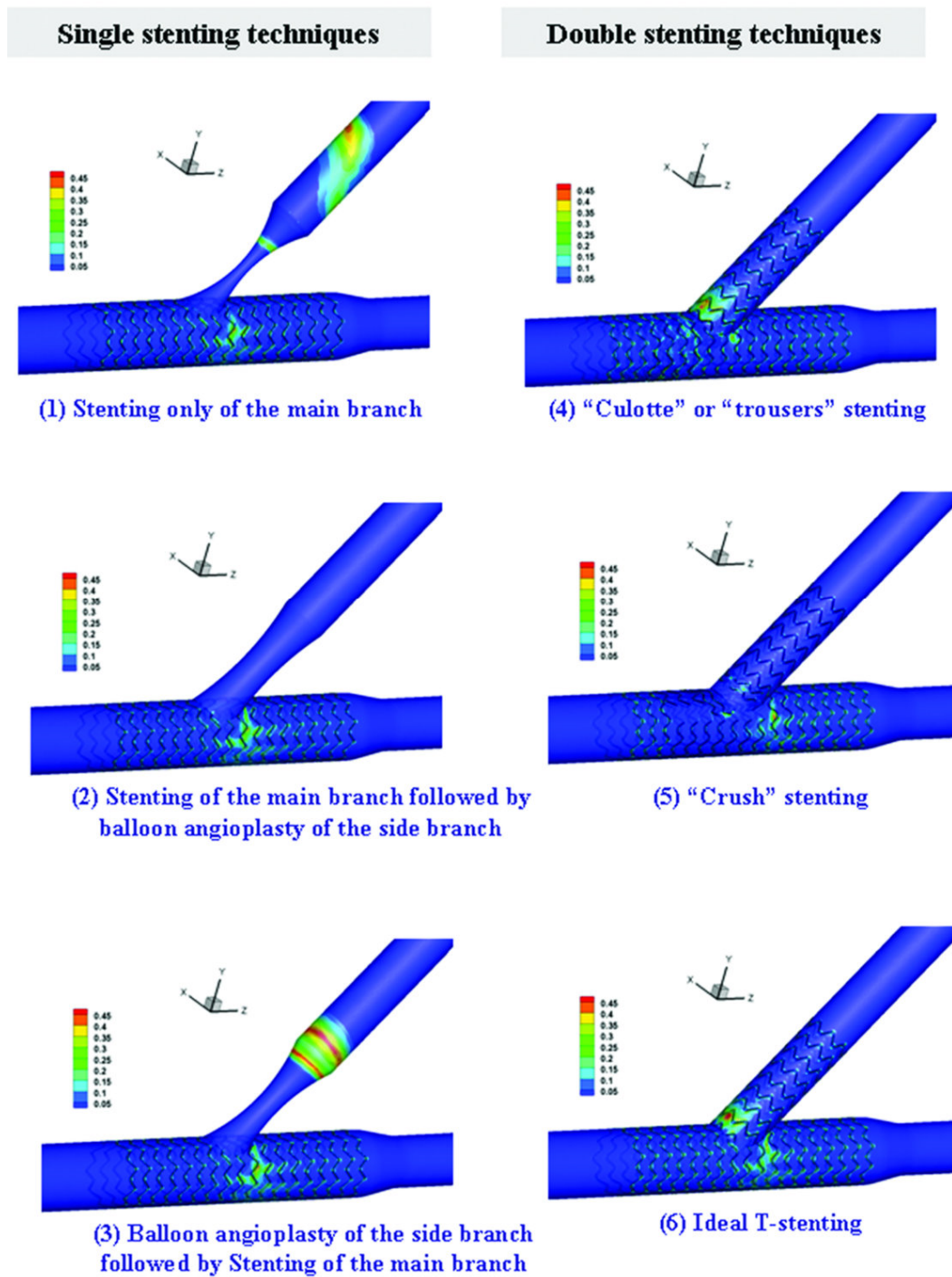


Figure 4. Oscillatory shear index (OSI) distribution at the bifurcation for the considered bifurcation stenting techniques.

Relative residence time (t_r)

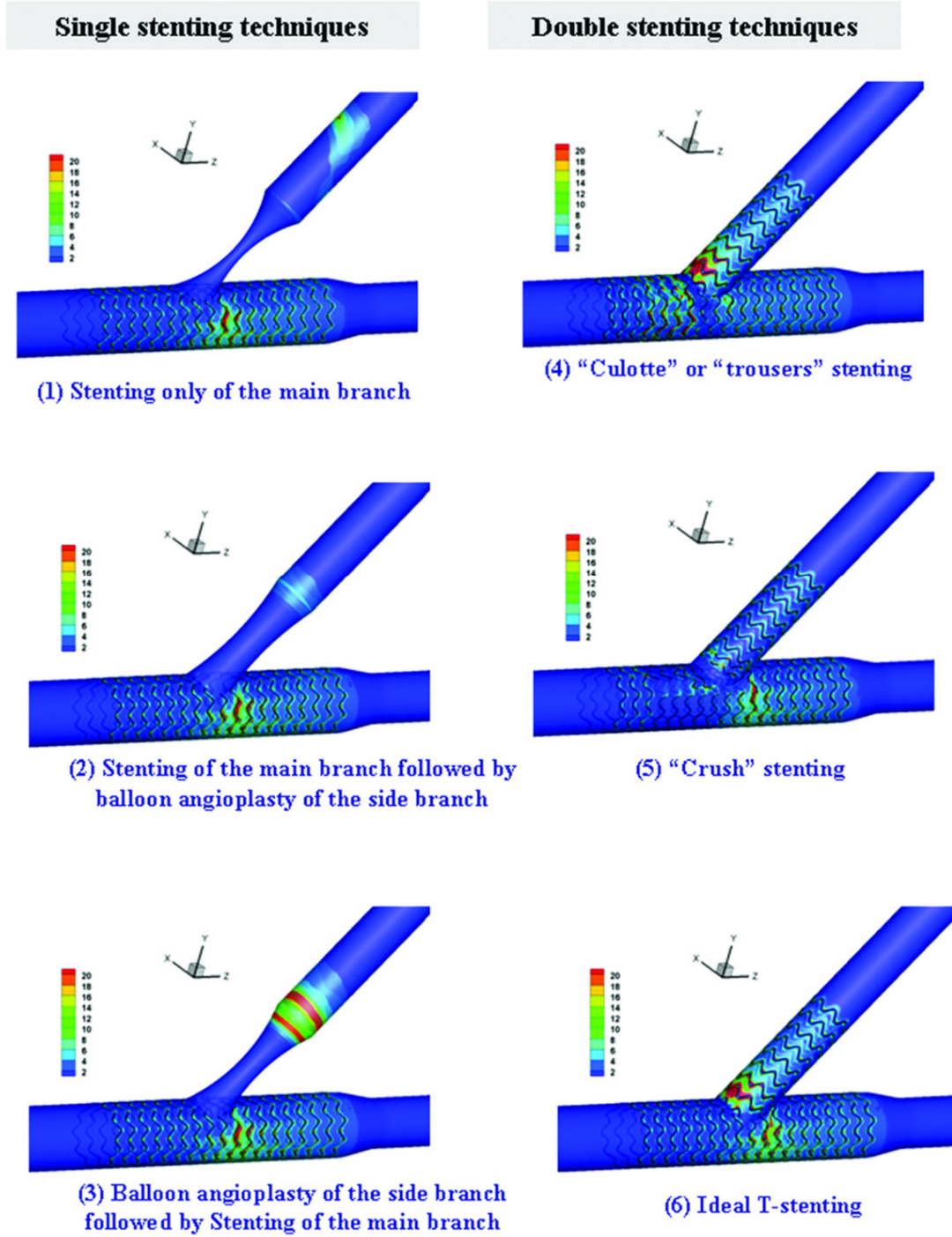


Figure 5. Relative residence time (t_r) distribution at the bifurcation for the considered bifurcation stenting techniques.

Table 1. Surface integrals of the flow indices for the six considered stenting techniques and normalized integrals to the technique that provided optimum result.

Stenting technique	TAWSS * ($\times 10^{-4}$ N)	Normalized TAWSS
Stenting of the MB § only	4.13	1.00
Balloon angioplasty of the SB followed by stenting of the MB	1.54	0.37
Culotte stenting	1.30	0.31
Crush stenting	1.18	0.29
Ideal T-stenting	0.78	0.19
Stenting of the MB followed by balloon angioplasty of the SB	0.15	0.04
	OSI † ($\times 10^{-6}$ m ²)	Normalized OSI
Stenting of the MB only	7.52	1.00
Crush stenting	7.75	1.03
Stenting of the MB followed by balloon angioplasty of the SB	8.07	1.07
Balloon angioplasty of the SB followed by stenting of the MB	8.20	1.09
Culotte stenting	9.87	1.31
Ideal T-stenting	10.4	1.38
	t_r ‡ ($\times 10^{-4}$ m ² /Pa)	Normalized t_r
Balloon angioplasty of the SB followed by stenting of the MB	5.57	1.00
Stenting of the MB followed by balloon angioplasty of the SB	5.59	1.00
Stenting of the MB only	5.77	1.04
Crush stenting	6.16	1.11
Ideal T-stenting	6.87	1.23
Culotte stenting	8.78	1.58

*TAWSS: Time averaged wall shear stress, †OSI: Oscillatory shear index, ‡ t_r : relative

residence time, §MB: main branch, |SB: side branch

Table 2. Bifurcation total area in which OSI exhibits values greater than specific thresholds.

Stenting technique	Bifurcation area (mm ²)		
	OSI * > 0.25	OSI > 0.35	OSI > 0.45
Stenting of the MB † only	0.29	0.01	0.00
Balloon angioplasty of the SB ‡ followed by stenting of the MB	0.37	0.03	0.00
Stenting of the MB followed by balloon angioplasty of the SB	0.36	0.04	0.00
Crush stenting	0.34	0.06	0.00
Culotte stenting	0.71	0.17	0.00
Ideal T-stenting	0.61	0.18	0.02

*OSI: Oscillatory shear index, †MB: main branch, ‡SB: side branch