NITRIC OXIDE TRANSPORT IN CAROTID BIFURCATION AFTER DIFFERENT STENT INTERVENTIONS: A NUMERICAL STUDY

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Abstract. Stent restenosis and late thrombosis compromise endovascular stent implantation clinical benefit, and the mechanism is unclear. Since nitric oxide (NO) plays a pivotal role in maintaining vascular homeostasis, we believe that stenting can affect NO concentration in the host artery, thereby contributing to postoperative adverse events. We numerically investigated NO concentration after stenting based on the patient-specific carotid to verify this hypothesis. The simulation revealed that stent implantation caused blood flow disturbance, a low wall shear stress, and a significant decrease in NO on the luminal surface, especially in the region of the stented segment. Moreover, severe damage to the artery wall or low blood flow, leading to a low NO generation rate, would induce relatively low NO level in the stented segment. Additionally, we demonstrated that NO distribution might be affected by the combination of stent struts and carotid bifurcation geometry, while the host arterial configuration might play a leading role in the distribution of NO concentration. In conclusion, the carotid artery had a relatively low NO concentration level near stent struts, especially at the severely injured artery, low blood flow, long stenting, and complex host artery which might lead to a genesis/development of adverse events after that intervention.

Mathematics Subject Classification.

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1. Introduction

Carotid artery stenting (CAS) is an effective strategy for revascularization of stenosis, but the relatively high rate of in-stent restenosis (ISR) and stent thrombosis (ST) have compromised its clinical benefit. According to clinical data, the ISR incidence after CAS ranged from 5% to 12% [1, 2]. The stent thrombosis occurrence is low, but complication of stent thrombosis is serious and often fatal. Stent thrombosis was associated with a 90% disability and mortality rate [3, 4]. These adverse events impose a severe financial and psychological burden on patients and their families after the intervention.

Keywords and phrases: Carotid artery, stent intervention, hemodynamics, nitric oxide.

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The precise mechanisms responsible for the onset and progression of stent restenosis and thrombosis remain incompletely elucidated. However, studies have proved that the adverse event may be closely related to nitric oxide (NO). Vascular endothelial cells are responsible for the production of nitric oxide (NO). It prevents the leukocyte adhesion on vascular endothelial cells and their migration in the arterial wall, inhibits the excessive migration and proliferation of smooth muscle cells, and regulates endothelial cell repair and vasodilation. Importantly, NO can suppress platelet adhesion and aggregation on the luminal surface, inhibiting thrombus formation [5, 6]. A study conducted on animals demonstrated that NO has the ability to inhibit the formation of blood clots within blood vessels in rats over a period of six months [7]. Furthermore, the presence of high levels of NO induced by exercise in rats was found to decrease the aggregation of platelets following vascular injury [8]. Moreover, it was observed that catalytically produced NO could accelerate the repair of damaged endothelial cells and significantly inhibit thrombus formation in bypass grafts [9]. Consequently, NO within the vascular system plays a crucial role in regulating vascular tone and significantly impacts the availability of NO, thereby inhibiting inflammation, in-stent restenosis, and stent thrombosis.

NO distribution in the host artery may be changed after the stent implantation. First, the generation rate of NO may drop dramatically. The implemented stent damages the endothelial cells, resulting in endothelial dysfunction, and hence changing the NO release and synthesis from endothelial cells [10, 11]. Second, the disturbed flow induced by protruded stent strut would change NO release and transport. NO is released from endothelial cells, and its generation rate is strongly associated with wall shear stress [12, 13]. Evidence demonstrated that NO release would increase with the increasing wall shear stress, and decrease with decreasing wall shear stress within a certain range [14].

The transcription of the eNOS gene is regulated by hemodynamics, whereby exposure of endothelial cells to a laminar flow environment leads to increased eNOS expression and enhanced release of NO [15]. Consequently, the release and transportation of NO are likely to be altered as a result of the disrupted flow caused by protruding stent struts. The blood flow has been demonstrated to have strong relationship with the mass transport of the drug-eluting stents, leading to high drug concentration near struts. Our early works also revealed that disturbed flow caused by the loss of lumen size would inhibit NO transport [16-18]. The implanted stent induced abnormal local blood flow in the stented segment, leading to stagnation flow and flow separation around the struts [19]. This abnormal regional blood flow after the intervention makes different the NO release and transport, changing the NO distribution in the host artery.

Many theoretical studies have been performed to simulate and analyze the NO transport and distribution in the vascular system. However, these works have only focused on small arteries, where atherosclerosis and aneurysms rarely occur. The link between shear stress and NO generation rate has been assumed constant [20-22]. Early studies [23, 24] applied shear-dependent NO production rates in their simulations, but they neglected the convective term of NO. Qian et al. [25] simulated the spatiotemporal distribution of NO in patient-specific carotid bifurcations using MRI and convective diffusion models but did not consider the effect of stent implantation. Liu et al. [18] investigated the effect of stent deployment and design on NO transport and distribution in stented arteries, but their model only used a simple two-dimensional ideal model.

In this study, it was hypothesized that the implantation of various stentings and configuration could lead to a different NO distribution within the host artery, thereby promoting the occurrence of in-stent restenosis and thrombosis. The computational models after intervention were constructed based on the patient-specific carotid bifurcation. The stent implantation effect on blood flow and NO transport was analyzed to test this hypothesis. The synergistic impact of endothelial injury, blood flow, stenting scenarios, and the host artery geometry on the NO distribution was also discussion.

2. Method
2.1. Image-based computational model
Carotid artery model. The imager (Siemens Medical Solutions, Forchheim, Germany) was employed to obtain the sequence carotid slices from heart to head. The 3D carotid bifurcation model (the internal carotid artery (ICA),
Figure 1. (A) Geometry of the carotid bifurcation model after stent implantation. (B) View for the orientation of the presentation slice from the host artery. (C) Carotid artery inlet velocity waveform is used for this numerical simulation.

The external carotid artery (ECA), and the common carotid artery (CCA) with stenosis was reconstructed based on these images, as performed by our early study [19]. The carotid lumen profile was manually exacted from the other surrounding tissue of human by Mimics (Materialise N.V.), and the centerline of the lumen was generated based on the profile. Subsequently, Geomagic studio software (Geomagic, 2013, North Carolina, USA) was slightly smoothed the initial rough model. The finally reconstructed carotid model was verified by the automated artery segmentation approach [26, 27]. Each CCA length is not less than 81mm to achieve fully developed. The present study obtained the local ethics committee approval from the Ethics Committee of Beijing Friendship Hospital (Beijing, China), and all participated volunteers were provided the information about the study and signed an informed consent agreement prior to their participation. Extensive details about the approaches of images acquired and 3D model reconstruction can be found in Ref [19]. The arterial wall was constructed by dilating the lumen surface outward by 0.5 mm which was the average thickness of carotid artery.

The implanted stent. The stent used in the intervention is identical to the commercially available one. The stent strut thickness is 0.087 mm, and the outer diameter is 1.0 to 1.2 times larger than the healthy lumen [28, 29]. More accurate geometric information of the stent can be found in early study [30].

Carotid artery model after intervention is constructed in UG (Unigraphics NX). The stent is implanted in the host artery along the centerline of the lumen, totally covering the lesion. After smoothing the junction between the stent and the artery, models after stent intervention (Fig. 1) were constructed.

To study the effect of stent length on the distribution of NO concentration, stents lengths are 18.4 mm, 24.8 mm, and 31.2 mm, respectively.
2.2. Governing equation

2.2.1. Fluid dynamics

Blood was a homogeneous and incompressible non-Newtonian blood fluid in this work. The deformation of the arterial wall was neglected. The simulations were performed under transient flow conditions. 3D dimensional Navier-Stokes equations were applied to calculated the flow within the host artery wall.

\[
\rho_l \left( \frac{\partial \mathbf{u}_l}{\partial t} + \mathbf{u}_l \cdot \nabla \mathbf{u}_l \right) = -\nabla p_l + \nabla \cdot \tau \tag{2.1}
\]

\[
\nabla \cdot \mathbf{u}_l = 0 \tag{2.2}
\]

where \(\tau\) and \(\rho_l (\rho_l = 1050 \text{ kg m}^{-3})\) are respectively the stress tensor and the density \([31]\). \(\mathbf{u}_l\) is the three-dimensional velocity vector, and the pressure in the carotid artery is represented by \(p_l\).

\[
\tau = 2\eta(\dot{\gamma}) \mathbf{S} \tag{2.3}
\]

where \(\dot{\gamma}\) and \(\mathbf{S}\), respectively, is the rate of deformation tensor and the shear rate. To simulate the chaos flow around the stent strut and pulsatile flows, the blood flow viscosity was described by Carreau model \([32]\).

\[
\eta(\dot{\gamma}) = \eta_\infty + (\eta_0 - \eta_\infty) \left[ 1 + (\lambda \dot{\gamma})^2 \right]^{\frac{n-1}{2}} \tag{2.4}
\]

where \(\mu_\infty\) and \(\mu_0\) represent respectively the viscosity at infinite shear rate (\(\mu_\infty = 0.00345 \text{ kg (ms)}^{-1}\)) and at zero shear rate (\(\mu_0 = 0.056 \text{ kg (ms)}^{-1}\)), \(\lambda\) stands for the time constant (\(\lambda = 3.31 \text{ s}\)) and \(n\) stands for the power law index (\(n = 0.36\)).

2.2.2. Solute dynamics

(a) Lumen

The advection–diffusion–reaction equation was used for describing the mass transport of NO in the host artery fluid.

\[
\mathbf{u}_l \cdot \nabla c_l - D_l \Delta c_l + \dot{V}_l = 0 \tag{2.5}
\]

where \(c_l\) represents the NO concentration in lumen, \(\dot{V}_l\) is the consumed NO concentration due to the reactions, and \(D_l\) is NO diffusion coefficient in the fluid (\(D_l = 3.3 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}\)) \([21]\). The reaction in the host artery lumen was decided by the consumption by erythrocytes and the oxidation by oxygen, which is described by the following:

\[
\dot{V}_l = k_e c_l^2 - k_o c_l \tag{2.6}
\]

where \(k_e\) and \(k_o\) were taken to be 2.3 s\(^{-1}\) and 7.56\(\times 10^{-6}\) nM\(^{-1}\) s\(^{-1}\), respectively \([33]\).

(b) Endothelium

The generation rate (\(R_{NO}\)) of NO from endothelium cells is an important index for simulating the NO transport. \(R_{NO}\) was measured by Andrews and be described by the following \([34]\):

\[
R_{NO} = R_b - R_{max} \frac{|\tau_w|}{|\tau_w| + x} \tag{2.7}
\]
where \( R_b = 2.13 \text{ nM s}^{-1} \), \( \beta = 3.5 \text{ Pa} \), \( R_{\text{max}} = 457.5 \text{ nM s}^{-1} \). To investigate the effect of vascular damage on nitric oxide distribution, we made 60% (mild damage), 50% (moderate damage), and 40% (severe damage) NO production rate from the endothelium, respectively.

(c) Arterial wall
The following equation was used for NO transport in the arterial wall:

\[
D_w \Delta c_w - u_w \cdot \nabla c_w - \dot{V}_w = 0
\]  
(2.8)

where \( c_w \) stands for the NO in the host artery wall, \( \dot{V}_w \) is the NO reaction rate, and \( D_w \) is NO diffusivity in the host artery wall \((D_w = 8.48 \times 10^{-10} \text{ m}^2\text{s}^{-1})\) [35]. The NO reaction rate is described by [36]

\[
\dot{V}_w = k_w c_w
\]  
(2.9)

where \( k_w \) is 0.01 s\(^{-1}\) and stands for the consumption rate.

(c) Stent
Since the stent is an exogenous substance, we assume that it does not produce NO and no transport in the stent-zone.

2.3. Boundary conditions

Boundary condition for blood flow. The inlet flow rate was chosen from a cardiac cycle [37]. The determination of the flow ratio between ICA and external ECA is imperative due to the discrepancy in outlet resistance. The outflow ratio is set to 0.56 for ECA to ICA [38]. The luminal surface of endothelium was assumed to be slip-free.

Boundary condition for NO Transport. The NO concentration is 0 nM at the inlet (the proximal CCA) and the surface of stent. The concentration NO continuity was maintained at outlets, while the mass flux across the artery wall and lumen interface was described by the following:

\[
c_l = c_w \quad (2.10)
\]

\[
N_l \cdot n_l - N_w \cdot n_l = R_{\text{NO}} H \quad (2.11)
\]

\[
N_l = -D_l \nabla c_l + c_l u_l; N_w = -D_w \nabla c_w + c_w u_w \quad (2.12)
\]

where \( N_l, n_l \) represents the NO mass flux from the endothelial cells to the host artery wall, while \( N_w, n_l \) stands for the NO mass flux from the endothelium cells to the host artery lumen. \( H \) is the endothelium thickness, and it is 2 \( \mu \text{m} \) in this work. The concentration gradient was taken zero in the boundary normal direction for other boundaries.

2.4. Computation procedures

The governing equations were calculated numerically by ANSYS Fluent with a user-defined function, which was preformed to solve the mass transport of NO in the host artery. Hexahedral and tetrahedral grids were be created for the health artery and the stented segment in this computational study, and refined grids were was used near the host artery wall to obtain steep spatial and temporal variation of NO. To ensure mesh independence, a criterion was established whereby the discrepancy between the meshes employed for calculations and denser meshes was maintained below 3\%. The convergence criterion was taken to \( 10^{-5} \), and the third heart cycle numerical results were performed for data-processing and presentation.
3. Result

3.1. Hemodynamics may modulate the NO concentration distribution after intervention

Figure 2A shows velocity streamlines of the model after intervention. Disturbed flow is observed near the stent-treated ICA and the proximal ECA at different moments of a cardiac cycle. t3 has relative high level but presents more chaos flow than other moment, while disturbed flow significantly improves at t2. As shown in Figure 2B, as the velocity increases, the shear stress also increases; conversely, as the velocity decreases, the shear stress decreases. WSS at t1 and t3 is much lower than t2. At t2, and the low WSS is located at the stent struts and two end sides of the stented segment. It is also worth to mention that WSS distributed unevenly on the stent-treated ICA wall at t1 and t2.

Figure 2C compares NO distribution at different moments after the intervention. Substantial differences in NO concentration were observed at various moments during the cardiac cycle. Specifically, the NO concentration was found to be lowest at t1, highest at t2, and slightly elevated at t3, which aligns with the distribution of velocity and WSS. However, the stent-treated segment in the three models is exposed to a relatively low level of NO than other regions. At t2, the highest NO concentration at the stent-treated artery wall was 1.41 nM, approximately 20% for t1, and 33% for t3. We calculated the NO concentration distribution on the stented arterial wall to facilitate observation at different moments. Figure 2D presents that NO concentration on most regions of the stent-treated luminal surface is below 0.4 nM at t1, and the area below 0.2 represents up to 68%
Figure 3. Uneven NO concentration distribution in the carotid bifurcation after stent placement. (A) NO concentration distribution on the luminal surface and the media/adventitia interface. (B) NO distribution in representative carotid slices. (C) Location of representative cells in the stent segment. (D) Area-weighted average NO concentrations in circumferential cells. (E) Distribution of NO concentrations in the axial cells.

of the stent-treated segment. The NO concentration is improved at t3, although most regions (96%) remain below 0.6. There is a significant increase on the stented segment at t2. NO concentration on most region (84%) is higher than 0.6 nM, and most region (55%) at t2 on the stented segment distributes from 0.8 to 1 nM.

Figure 3 demonstrates the NO distribution on the stent-treated carotid bifurcation. Figure 3A indicates that NO concentration on the stented segment distributes significantly nonuniform, with the low NO concentration at the distal of CCA and the stented segment. The luminal surface of the host artery wall near stent struts suffers from very low NO concentration. Additionally, the outer arterial wall exhibited a lower distribution of NO compared to the inner wall. NO concentration ranges from 0.05 to 2.43 nM on the luminal interface with a mean of 1.37, while it ranges from 0.03 to 0.87 nM with a mean of 0.3 NM on the media/adventitia interface. Stent implantation caused a further decrease on the media/adventitia interface, where NO concentration was 0.3 nM on the healthy artery but close to 0 nM at the stented segment. The implantation causes a significant NO alternation on the luminal surface, and only one-fourth of NO is observed on the stented segment compared with other regions. Figure 3B illustrates that NO concentration is evidently lower at the stent segment (Slice 1) than at other locations (Slice 2 and Slice 3). Additionally, three slices display that the NO concentration in the host artery is relatively low in the lumen due to consumption-convection-diffusion.

Moreover, NO concentration is observed to be uneven at the segment where the stent is placed. The relative low NO concentration was observed near the stent struts and both end sides of the stented segment. Besides, the stented segment’s posterior lateral wall has a low-level NO concentration. The area-weighted average NO concentration circumferential distribution was calculated on the luminal surface of the stent segment (Fig. 3C, D). The highest area-weighted average concentration was 0.71 nM, located on the inner arterial wall (on S5), while the lowest value (0.18) was approximately one-fourth of the highest situated on the outer arterial wall (on S9). Hence, the axial area-weighted average concentration was analyzed along the inner and outer artery wall. Figure 3E displays that NO concentration on the inner artery wall gradually decreases from the proximal to the distal of the stented segment while increasing progressively along the outer arterial wall. The concentration eventually tended to be similar at the end of the stented segment, with the largest difference located at the beginning.
3.2. Endothelial damage due to intervention may change NO distribution

Figure 4 depicts the distribution of NO concentration on the luminal surface of the artery wall following different types of endothelial injuries caused by the stent. Despite variations in the numerical values, the NO distributions near the stented segment remain similar across different types of injuries, but with a significant decrease in NO levels observed after severe injury. The posterior lateral wall of the stented segment has an increased low NO concentration area on the luminal surface near the strut and both end sides of the stent after severe damage to the arterial wall. The area-weighted NO concentration in the stented segment after the mild injury was 0.47 nM, which is 79% and 61% after moderate and severe injury. We calculated the area of NO concentration in different intervals to study various injuries impact (Fig. 4B). More areas of low NO concentration may be generated as the endothelium damage increases. The area below 0.4 nM accounted 41% of the total area stented segment after mild damage, while 63% and 81% after moderate and severe damage, respectively. Furthermore, the low NO concentration (less than 0.2 nM) area after severe damage is approximately threefold larger than the moderate damage and even sixfold larger than the mild case.

3.3. Effect of stent length on the NO distribution

Figure 5 displays the distribution of NO concentrations on the luminal surface of the stent-treated arterial wall after different interventions. The NO concentration (Fig. 5A) is significantly low near the struts, the two
stented artery end sides, and the posterior lateral of the stented segment after implanting different stents. The area of the low NO concentration is largely same on the posterior lateral of the stented segment, while the long stent induced an increased low NO concentration due to the increased stent struts. We present the NO concentration on the stented arterial wall in different intervals to facilitate observation in Fig. 5B. Although long stent led to a slightly high NO concentration (>1 nM), these areas are less than 1% of the stented segment, and the long stent induces an increased low NO concentration at the stented segment. The area of NO concentration below 0.4 nM is 1.69 cm$^2$ after implanted a long stent, while it is 0.9 cm$^2$ for the short stents.

4. Discussion

Vascular stent implantation is a crucial and efficacious intervention for cardiovascular conditions; however, it still encounters clinical challenges such as in-stent restenosis and thrombosis subsequent to the procedure. NO, as a key endothelial-derived substance, has many functions, including preventing smooth muscle cell proliferation/migration, inhibiting leukocyte chemotaxis, and suppressing platelet aggregation and adhesion. It is also an important regulator for numerous vital activities affecting the vasculature and plays a significant role in in-stent restenosis and stent late thrombosis development. In this work, we numerically investigated the effect of stent placement on NO concentration based on the patient-based carotid artery model. Effects of various factors, such as velocity, endothelial injury, stent deployment, and vessel geometry on NO distribution were also discussed.

The alteration of the local blood flow environment induced by the deployed stent would damage the host artery. The stent intervention restores the blood flow and leads to dramatic changes by the protruded stent struts. These changes alter the local blood flow environment and cause abnormal wall shear stress (WSS) after implantation, which may damage the arterial wall, thereby making certain areas of the host artery susceptible to adverse events, such as neointimal hyperplasia and restenosis. Jimenez et al. [39] suggested that disturbance flow was found at both ends side of stent struts, which agrees with this numerical simulation results. Our results found that WSS, blood velocity, and NO concentration were lower at the stented segment than elsewhere in the host artery, even near struts. The flow disruption and separation caused by protruding struts suppress the NO concentration near struts and influence its distribution, resulting in uneven NO concentration, especially for both sides of the stent struts. However, it is worth noting that the distribution of the carotid bifurcation in the healthy segment without stent implantation exhibits a relatively uniform pattern, with significantly higher values compared to the stent segment examined in this study [25]. This phenomenon could be attributed to the influence of local blood flow on the diminished levels of NO in the stent segment, as well as the potential enhancement of NO release by endothelial cells due to high shear force. Additionally, the presence of locally generated or transferred NO, originating from the upstream, can also contribute to the alteration of blood flow at the bifurcation, thereby exacerbating the uneven distribution of NO within the stent segment. These results supported preliminary findings on the effect of stent implantation on NO distribution by Liu et al. [18]. Low NO concentration near the struts after the intervention may be a critical reason for vascular remodeling and thrombosis in the stented segment, and increasing local NO concentration may be a practical and effective treatment strategy for the improved postoperative performance.

This study indicated a relatively large difference in NO concentration distribution within a cardiac cycle. NO concentration was significantly increased at the peak systolic phase, while it was low at other low flow velocities. This result is consistent with the findings that evidence that increased blood flow velocity would elevate NO concentration in the circulatory system [17]. Since the dependence between wall shear stress and NO, a certain degree of high blood flow led to the high WSS, enhancing NO generation, while the low blood flow lessened NO production and blood flow controlled NO transport. Additionally, when the Reynolds number rises from 50 to 700, there is a gradual augmentation in concentration within the stenosis artery model, peaking at a maximum value of 16 nM [16]. This concentration is considerably greater than the concentration of NO observed in the stent segment investigated in this study. Animal studies suggested that significantly increased blood flow contributed to NO production [8]. Hence, the present study indicated that high blood flow would improve the NO concentration to a certain degree.
The interaction between the stent and the artery after radial stent expansion caused vascular damage. This event triggered the subsequent adverse events, beginning inflammatory response from the intima tear and endothelial cell denudation/damage. Afterward, endothelial damage and demudation due to the stent-induced disturbance flow led to platelet accumulation, fibrin deposition, cytoplasmolysis, inflammatory cells attachment, contributing the neointima and early thrombosis regulated by the various proteins and vasoactive factor expressions, such as vasodilators (NO), adhesion molecules (ICAM-1), growth factors (PDGF), which are involved in mediating various physiological and pathological processes after stenting. The present study revealed that varying degrees of endothelium damage caused by the implanted stent led to disparate patterns of NO concentration transport and distribution. NO concentration at the stented segment was mainly determined by the endothelial cells in that region, while upstream and downstream endothelial cells had little or no effect on NO concentration magnitude and distribution. Additionally, this study revealed that the degree of endothelium damage had inverse correlations with NO concentration, and severely damaged endothelium induced greater than 50% reductions at the stent segment, contributing to subsequent adverse events. Consequently, it is advisable to minimize excessive stent damage during expansion procedures. Instead, a strategy of repeated mild expansion interventions is recommended to mitigate stent-induced damage and enhance the postoperative efficacy of the intervention. However, the damage is an inevitably measure to ensure this treatment works, especially in complex situations, such as the artery with occlusion or severe stenosis and the bifurcation lesion.

Notably, the concentration of NO is contingent upon the condition of the endothelium affected by stent-induced damage, thereby implying that the implantation of longer stents may result in the emergence of augmented regions with low NO levels. Relevant evidence was provided here. We found that NO concentration was associated with the implanted stent length. The long one would trigger increased low NO concentration regions on the artery wall due to the increased struts despite similar NO distribution at the stented segment. Therefore, the long stent intervention is unfavorable regarding NO transport and distribution, consistent with clinical findings, and may be the significant cause for a long stent-induced high probability of adverse events [40–42]. Although some studies believed stent struts might penetrate the soft lipid pool after the intervention, causing the significant increased local stress in the vessel wall [43, 44], leading to acute events, Yano et al. [45] illustrated that a long enough stent covering the lesion is the best interventional strategy.

Our results indicated that NO concentration distribution might be strongly associated with vessel configuration. In the present study, there is uneven NO distribution after the carotid bifurcation stenting, as evidenced by the lateral posterior of the intervened arterial segment bearing relatively low NO concentration, which does not improve greatly even with different stent length, endothelium damage degree, and cardiac cycle moments. This suggests that NO concentration distribution after implanted may still be primarily driven by the macroscopic blood flow environment induced by the host artery configuration. Nevertheless, low NO concentration around stent struts is affected by the local blood flow environment due to the protruding struts. In this study, we conducted a comparison of hemodynamic performance and distribution of NO by constructing various ideal vessel configurations. Our aim was to quantify the influence of macroscopic and local blood flow on the distribution of NO. The geometrical parameters and boundary conditions of these numerical models were supplied at Additional information.

Figure 6 presents the uniform NO distribution and WSS in different ideal models. These results revealed a significant positive relationship between NO concentration and WSS, and a decrease in NO concentration was observed as WSS decreased. Low NO concentration and WSS were observed on the straight artery near the stent struts and gradually decreases at downstream of the stent segment, the WSS results were similar to the early findings [46]. These results suggested that low NO and WSS near the struts, especially for the one at the distal of the stented segment, might be susceptible to adverse events, which might be one reason for the lumen narrowing at the stent ends [40]. Besides, the low level of WSS and NO were identified on the curved artery model, while the distribution changed compared to the straight artery, with a large low WSS and NO concentration area on the proximal-out stented segment. Moreover, the uneven NO concentration distribution exacerbated as curvature increased, and the high curvature (90°) vessel caused the uneven distribution and very low WSS and NO concentration. Therefore, NO distribution for the straight artery is mainly affected by the
local blood flow due to the geometric abruptness caused by protruding stent struts, decreasing NO gradually from the proximal to the distal side, while NO concentration distribution on the curved artery would change both governed by local blood flow around struts and macroscopic hemodynamics induced by vessel geometric configuration. Consequently, we anticipate that the postoperative outcomes will vary for different vessel geometric configurations. The intervention for the complex configurations, such as vessel curves and bifurcates, is prone to initiate some regions with very low WSS and NO concentration. Therefore, we assert that it is imperative to design a patient-specific stent tailored to the specific lesion, such as reducing the thickness of stent struts in regions with low NO concentration or implementing a device to mitigate unfavorable microscopic flow.

**Limitation**

In the present study, it was observed that the configuration of the carotid bifurcation exerts a substantial influence on the distribution of NO within the stent segment. However, it is important to note that only data from a single patient’s bifurcation was utilized in this investigation, and it is possible that the reconstructed bifurcation may deviate from its in vivo counterpart during the three-dimensional reconstruction procedure. This discrepancy arises due to the inherent limitations of the technology employed in the modeling process, which introduces inaccuracies in the reconstruction of the geometrically sensitive and clinically significant bifurcation carina and side branch. Consequently, the accuracy of NO distribution in this study is directly affected. However, the observed decline in NO and non-uniformity of the stent segment following stenting is not significantly influenced by this. In order to obtain precise findings, additional detection techniques may be necessary to collectively rectify the geometric configuration of the reconstruction. In this work, the deformation and motion from artery wall were ignored, which may affect the accuracy of NO concentration. The generation rate model for NO used in the present work came from experimental measurements within a few minutes, which might lead to an overestimation of the NO generation rate at high WSS. Consequently, the NO distribution may be overestimated at the high WSS region, while it may be reasonable at the low WSS region.

**5. Conclusions**

Stent implantation leads to blood flow disturbance, low WSS, and significantly decreased NO bioavailability on the luminal surface and the media/adventitia interface, contributing to the pathologic process of in-stent...
restenosis and thrombosis. Moreover, NO concentration after intervention might be multifactorial and regul-
ated by the degree of endothelial injury, blood flow, stent placement strategy, and the host arterial geometry
configuration.

Additional information

The ideal artery models based on the human coronary artery had a length of 104.8 mm, an internal diameter
of 4 mm, and a wall thickness of 0.5 mm. The three ideal models had 180°, 135°, and 90° vessel curvature,
and each model was respectively emplaced a stent at middle of the model. The models exhibited curvature at
the central part, with angles of 180°, 135°, and 90° between the two ends of the artery. In the 135° and 90°
curved models, circular arcs with radii of 3 and 4 m were employed to smoothly connect the centerlines of both
ends. The stent is like the commercially available one and has 0.081 mm strut thickness. The pulsating velocity
was applied at the inlet [47], and the other boundary conditions for the artery and the stent were same as 2.3 Boundary
conditions.

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Conflicts of interest. All authors declare no competing interests.

Data availability statement. The data used to support the findings of this study are included within the article.

Ethical approval. This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University
(approval no. 2022-P2-210-01). The study conformed to provisions of the Declaration of Helsinki (as revised in 2013).

REFERENCES


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