

Effect of exercise rehabilitation on hemodynamic performance after carotid artery stenting: a numerical study

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A high in-stent restenosis rate and thrombosis have compromised clinical benefits after vascular stent placement. Exercise rehabilitation after stenting emerges as a promising and practical therapeutic strategy to improve the clinical performance of this therapy, although it remains controversial. The present study aimed to explore the impact of exercise training on hemodynamic performance after vascular stent implantation. Different 3-dimensional computational models based on the patient-specific carotids were constructed to calculate hemodynamic parameters, including flow velocity, time-averaged wall shear (TAWSS), oscillatory shear index (OSI) and relative residence time (RRT). The results demonstrated that exercise training increased TAWSS but decreased OSI and RRT in some cases after the intervention, and high-intensity exercise further suppressed the adverse blood flow. However, exercise training remarkably reduced TAWSS and elevated OSI and RRT in patients with mild stenosis at upstream of stented segment. Additionally, we discovered that the hemodynamic environment change induced by exercise training was not significant compared to the stent position in some cases. Exercise had a less beneficial impact on the disturbed blood flow after the distal common carotid artery (CCA) stenting. These findings highlighted that exercise-induced hemodynamic changes differ under different conditions. The exercise training for the intervention patients should only be performed after a comprehensive vascular function assessment.

Key words: exercise, postoperative treatment, carotid artery, numerical simulation, stenting

1. Introduction

Atherosclerosis is a prevalent cardiovascular disease manifested by abundant lipid deposition in the arterial intima, intimal thickening and intimal plaque formation. It leads to a reduced or completely blocked lumen, causing diseases such as heart failure, brain stroke and peripheral artery disease. Vascular stenting has been widely used as an effective therapy for stenosis or occlusion of the artery [2], [25]. However, the clinical benefits can be compromised by inevitable

shortcomings after stenting. According to clinical data, the in-stent restenosis rate after the intervention ranges between 10–20% [37], and stent thrombosis is a potentially fatal complication of stent implantation [14].

The evidence demonstrates that exercise rehabilitation can change the clinical outcomes after the intervention. Fu et al. [12] discovered that exercise training for the intervention group may reduce the late lumen loss of stented segments, and this group had low-risk in-stent restenosis. According to reports [26], [39], functional exercises after intervention decreased mortality and morbidity risk by improving physical func-

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tioning. Moreover, observational studies [7], [9], [15], [22], [28], [36] suggested that regular exercise could significantly benefit in preventing atherosclerotic progression, including improvement in the endothelial function, decreasing the inflammatory response, plaque size modulation, arterial wall remodeling and macrophage function. Hence, exercise rehabilitation training is a promising strategy for improving patients' preoperative outcomes of vascular stent implantation. However, the role of exercise in the intervened patients is controversial. Considering the evidence in intervention patients that stent thrombosis was associated with exercise training, some exercises might induce platelet aggregation and activation, triggering or enhancing stent thrombosis after the exercise [6], [43]. Olivier Ormezano et al. [34] suggested that exercise-induced platelet hyperactivation might trigger stent thrombosis. According to other studies, platelets were activated or induced activity, and platelet count was elevated from 10% to 40% after strenuous exercise [20]. They thought a strong relationship existed between stent thrombosis and vigorous or strenuous exercise, which probably played an important role in exercise-induced clinical events such as coronary ischemia. Moreover, exercise is the strongest independent factor related to stent fracture. Osamu Iida [16] indicated that patients who daily walked 5000 steps were more likely to develop stent fractures than sedentary patients. Therefore, it has been increasingly recognized as a potential noninvasive treatment for the treated patients, but the underlying mechanism of adverse exercise-induced impact must be elucidated.

The mechanisms involved in exercise-induced impacts are complex and multifactorial. Nevertheless, hemodynamics after training plays a critical role in normal physiological functions. It is considered a principal contributor for in-stent restenosis and thrombosis after the intervention, as evidenced by early studies. Adverse or disturbed local blood flow associated with these adverse events is featured by separation and low/oscillatory wall shear stress (WSS) flow around the protruding struts. It has been demonstrated that WSS, oscillating shear stress index (OSI) and relative residence time (RRT) are the quantitative evaluation indicators to describe the unfavorable flow. A low WSS and high RRT and OSI can lead to disturbed local mechanical conditions contributing to adverse events after stent implantation [4], [27], [28]. In the present study, we believe that exercise rehabilitation may change the hemodynamic performance after the intervention, hence suppressing or worsening the adverse events after stent implantation.

The important studies on exercise training focused on the correlation between exercise and outcome after

stenting. However, they failed to conduct a complete assessment of the patients before/after the various exercise training or rehabilitative strategies. The beneficial exercise strategy and best estimate for this strategy were not yet evident in the literature. Accordingly, the present work aimed to assess the potential role of exercise training in the host artery after stenting with 3D computational fluid dynamics models based on the human patient-specific carotid bifurcation. The exercise-induced hemodynamic changes of the host artery after stent implantation, such as changing velocity field, WSS, OSI, and RRT, were investigated using pulsatile and non-Newtonian behaviors of blood flow. The mild stenosis impact upstream of the stented segment and different stenting scenarios after exercise training on the hemodynamic changes of the treated artery were also discussed.

2. Materials and methods

2.1. Computational model

Carotid artery model

The imager (Siemens Medical Solutions, Forchheim, Germany) was employed to obtain the sequence carotid slices from heart to head. 3D carotid bifurcation (the internal carotid artery (ICA), the external carotid artery (ECA) and the common carotid artery (CCA)) model with stenosis was reconstructed based on these images, as performed by Zhenmin [10]. The centerline of carotid bifurcation and lumen profile were manually exacted from the other surrounding tissue by Mimics (Materialise N.V.). Subsequently, Geomagic studio software (Geomagic, 2013, North Carolina, USA) was applied to slightly smooth the initial rough model. The finally reconstructed carotid model was verified by watershed transform from markers [5], [23]. Two carotid bifurcation models were constructed with a side-branch narrowing, as shown in Fig. 1a. Severe stenosis (78%) at the proximal ICA was observed at Patient 1, while severe (76%) and mild stenosis (48%) is located at the middle and proximal of Patient 2 ICA. Each CCA length was not less than 87 mm to achieve fully development. 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 this study and signed an informed consent prior to their participation. Extensive details about the approaches of obtaining

medical images and 3D model reconstruction can be found in ref. [10].

The implanted stent

The stent for intervention presented here is the same as the commercially available one. The stent strut thickness was 0.087 mm and the outer diameter was 1.1 to 1.2 times larger than that of the healthy lumen [24], [29]. More accurate geometric information about the stent can be found in the early study [3].

Carotid artery model after intervention

Carotid artery model after intervention was finished in UG (Unigraphics NX). A model was constructed using an idealized cylinder with a diameter equal to the outer surface diameter of the stent and a length equal to that of the stent. The stent was then emplaced into this ideal cylinder to complete the construction of the model after stent implantation. The stent-artery component was placed along the centerline within the carotid artery, with totally covering the lesion. The lesion was subsequently removed based on the length of stent-artery component. After smoothing the junction between the stent and the artery, five models after the intervention were constructed in Fig. 1b. Based on clinical experience, surgical intervention is necessary for patients with severe (>75%) stenosis to prevent serious complications, while the

artery with mild ($\leq 50\%$) stenoses is left untreated. Hence, the patient may still have mild or moderate stenosis elsewhere after stenting. In order to explore exercise-induced influence of the upstream-mild stenosis on the hemodynamic performance, the upstream regions accompanied by no stenosis and 25% stenosis were constructed. In order to explore exercise-induced influence of different stenting scenarios on the hemodynamic performance, vascular stent was implanted in CCA, ICA and ECA, as shown in Fig. 1b.

2.2. Governing equation

The non-Newtonian behavior of blood flow is resumed in the present study [42]. The numerical work was carried out based on the incompressible Navier–Stokes equation and the conservation of mass:

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \nabla \cdot \boldsymbol{\tau}, \quad (1)$$

$$\nabla \cdot \mathbf{u} = 0, \quad (2)$$

where $\boldsymbol{\tau}$ and ρ ($\rho = 1050 \text{ kg/m}^3$) are respectively the stress tensor and the density. \mathbf{u} and p represent the three-dimensional velocity vector and pressure in the carotid artery, respectively.

$$\boldsymbol{\tau} = 2\mu(\dot{\gamma})\mathbf{S}, \quad (3)$$

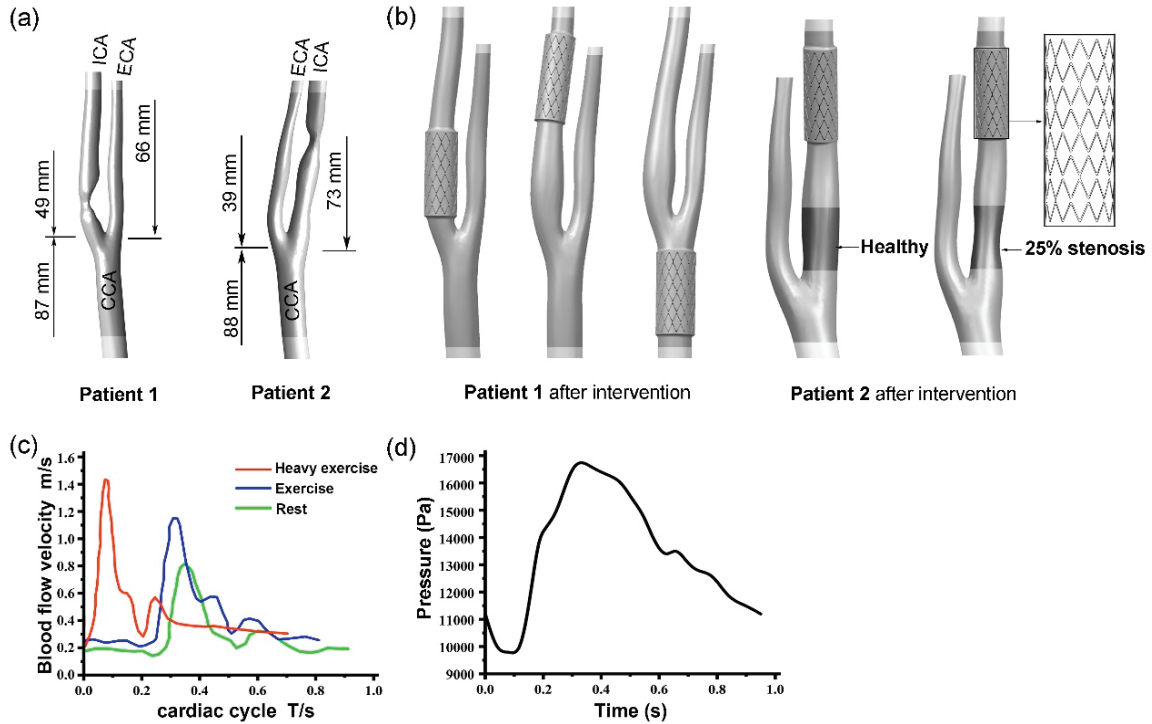


Fig. 1. (a) Image-based carotid artery models, (b) computational models after carotid stenting, (c), (d) flow velocity and pressure waveforms at inlet and outlet of the computational models

where \mathbf{S} and stand $\dot{\gamma}$, respectively, the rate of deformation tensor and the shear rate. The blood flow viscosity is described by Carreau model [41].

$$\mu(\dot{\gamma}) = \mu_{\infty} + (\mu_0 - \mu_{\infty}) [1 + (\lambda \dot{\gamma})^2]^{\frac{n-1}{2}}, \quad (4)$$

where μ_{∞} and μ_0 represent respectively the viscosity at infinite shear rate ($\mu_{\infty} = 0.00345$ kg/ms) and at zero shear rate ($\mu_0 = 0.056$ kg/ms), λ stands for the time constant ($\lambda = 3.31$ s) and n stands for the power law index ($n = 0.36$) [32].

2.3. Boundary condition

As shown in Fig. 1c, three different pulsating velocity waveforms of blood flow (rest, moderate-intensity and high-intensity exercise), which are from human in resting state [1], performed simple aerobic exercise [19] and heavy exercise [18], are respectively applied at the inlet (CCA). The unsteady pressure is applied at the outlet, as shown in Fig. 1d [8]. The artery wall and stent in the present study is regarded as non-slip rigid walls without movement and deformation [11], [31].

2.4. Computation procedures

All models presented here used Ansys ICEM (ANSYS, Inc., Canonsburg, PA, USA) for the hybrid grids meshing. The region of model close to the stent was constructed unstructured grids, while structured grids were created in other regions. The specially refined grids were used to obtain the sharp change in

near-wall blood flow. All the blood flow simulations in the present work were carried out by the commercial software Ansys CFX. A fixed time step was 0.005 s and with 200 iterations for each time-step, and the convergence criterion of the residual is set to 10^{-5} . Mesh independency test was performed to evaluate computations and denser cases, which was achieved at the WSS difference between two cases less than 3%. Five cardiac cycles were calculated for each case, while data analysis was only performed for the third one.

2.5. Data postprocessing

Since high OSI, low WSS and high RRT are the important index usually associated with adverse blood flow pattern in the early works, we focused on the change of these variables after exercise. The presence of low TAWSS values (<0.26), high OSI values (>0.31) and RRT values (>8.95) were identified as indicative of an unfavorable hemodynamic environment, which significantly increased the susceptibility to lesion formation [4], [27].

3. Results

3.1. Effect of exercise after vascular stenting

In Figure 2a, velocity streamlines of the intervened model at the peak systolic phase are shown (0.34 s for the resting state, 0.30 s for the simple aerobic exercise

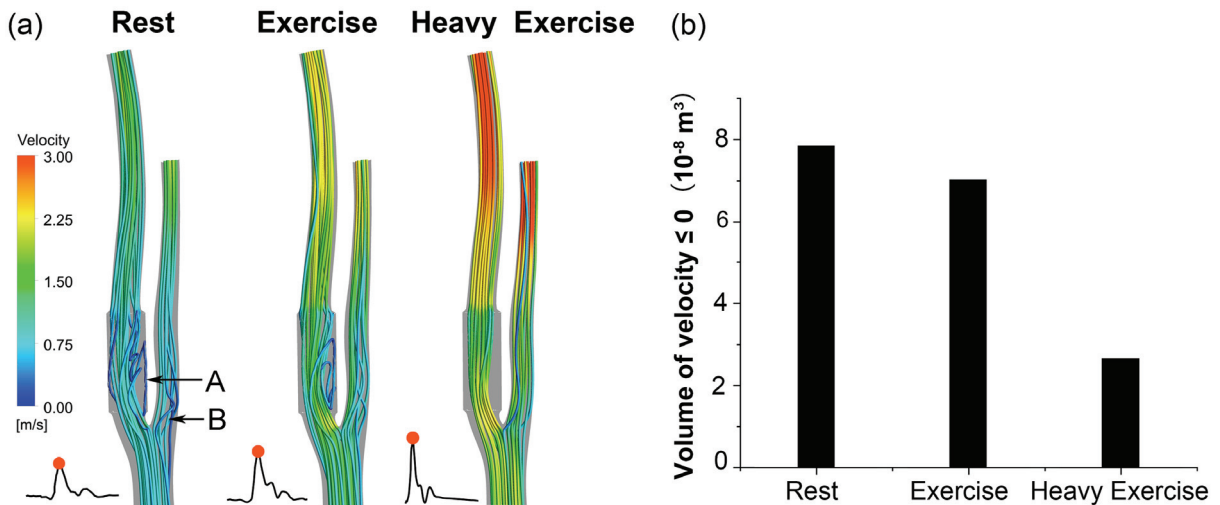


Fig. 2. (a) Velocity streamlines for intervened carotid artery at the peak systolic phase, (b) the reverse flow volume at the stented segment

and 0.07 s for the heavy exercise). As shown in the figure, disturbed blood flow is observed at the stented segment and the bifurcation near ECA, such as region A, B. The disturbed blood flow at these regions after exercise are significantly improved when compared with the resting state. Moreover, chaos flow is further suppressed in areas A and B as the exercise degree increases. Clearly, vortex characteristics and reflux areas can be noticed in area A at rest or after simple aerobic exercise, while these almost disappear after vigorous exercise. As shown in Fig. 2b, the reverse flow at the stented segment is also suppressed after exercise training, and the effect of exercise improvement is more evidently as the exercise degree increases. The volume of reverse flow after vigorous exercise is only 35% of the model at rest state.

In Figure 3a, carotid artery TAWSS contours after intervention under three conditions are compared. Carotid artery TAWSS values has greatly improved after exercise compared with the resting state. Moreover, the TAWSS values gradually increases as the exercise degree increases. However, a relatively low TAWSS area can be still found near stent struts and the bifurca-

tion close to the ECA, such as region A and B, while the low TAWSS area is decreased as the exercise degree increases, especially low TAWSS at region B, where low TAWSS area almost disappears after heavy exercise. In order to further quantify the TAWSS changes caused by exercise, we calculated the area of low TAWSS (<0.26 Pa). The low TAWSS area of the stented segment is markedly reduced as the exercise degree increases in Fig. 3d. The area of the low TAWSS after simple aerobic exercise is only 37.5% of the resting state, and the low TAWSS area after heavy exercise is 23.6% of the resting state.

OSI distributions, depicted in Fig. 3b, are rather similar in the three models under three different conditions, although the values are different. The high OSI is observed at the bifurcation near the ECA and the stented region, such as region A and B. Compared to the model at resting state, the high OSI area after the exercise state is slightly reduced. Nevertheless, there was no significant difference in the high OSI area after simple aerobic exercise and strenuous exercise. In order to further quantify the degree of high

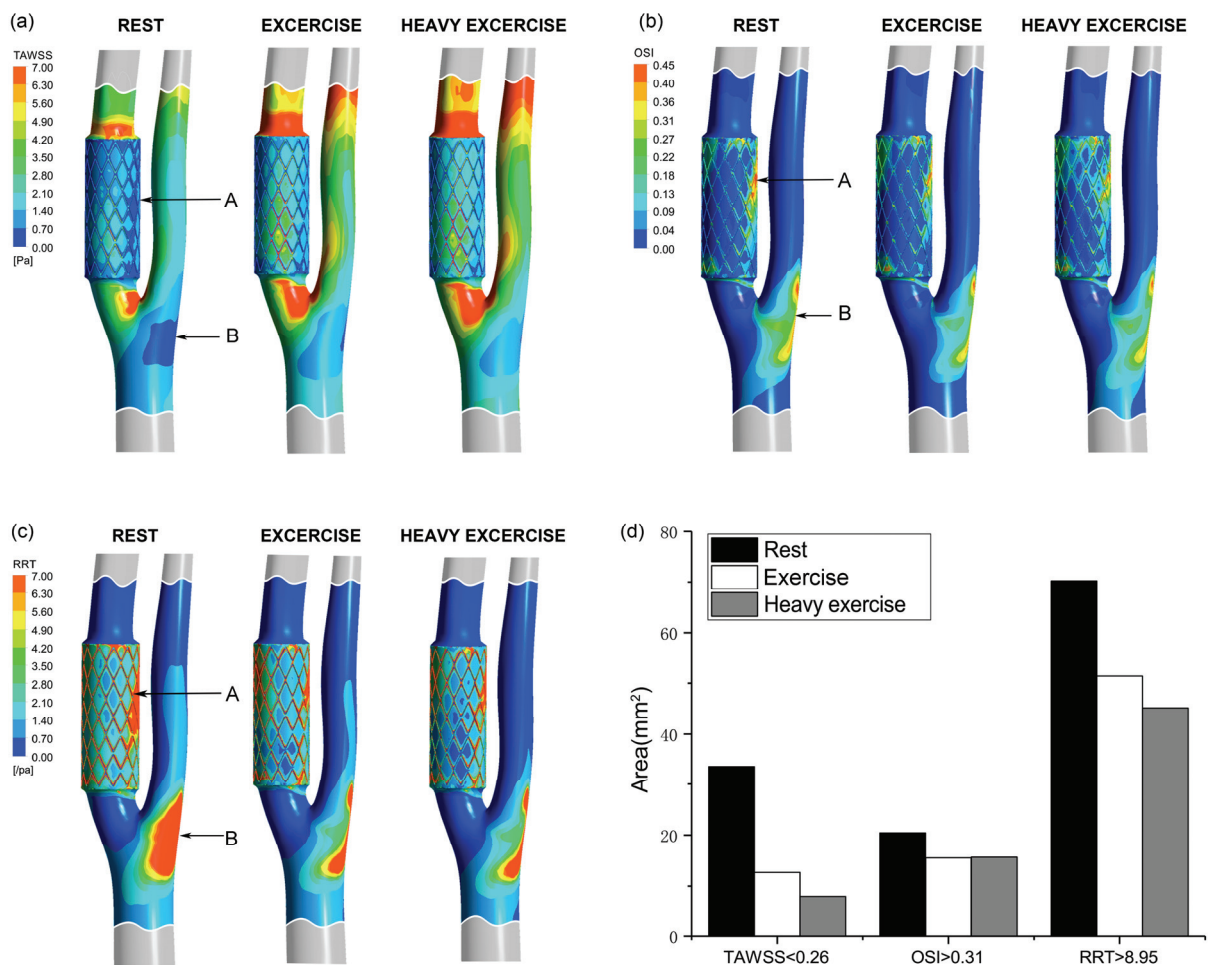


Fig. 3. The distribution of TAWSS (a), OSI (b), and RRT (c) of implanted carotid artery under three conditions (rest, moderate-intensity and high-intensity exercise), Area of abnormal blood flow (TAWSS (<0.26), RRT (>8.95), and OSI (>0.31)) on the stented artery (d)

OSI after exercise, we calculated the $OSI > 0.31$ area at the stented segment. As shown in Fig. 3d, the high OSI areas under simple aerobic and heavy exercise state are markedly reduced compared with resting state, and the high OSI area after exercise is about 0.76 times larger than that of resting state.

The high RRT (Fig. 3c) is located at the bifurcation near the ECA and the stented region, such as region A and B. Compared to the resting state, the high RRT area after exercise is decreased, and the high-intensity exercise further suppresses the high RRT area. In order to quantify the high RRT caused by exercise, $RRT > 8.95$ area is calculated. As shown in Fig. 3d, the high RRT area after moderate and high-intensity exercise are 73.2% and 64.3% of that of the resting state, respectively.

TAWSS between models with and without untreated stenosis upstream of the stented segment under

different exercise states was compared in Fig. 4a. The untreated stenosis model (25% stenosis) leads to low TAWSS area at downstream of narrow throat (such as region B), while this improved greatly after exercise. As shown in Fig. 4d, the low TAWSS (< 0.26 Pa) area is 1.19 times larger than that of the non-stenosis model, and these areas are 1.16 and 1.14 times larger than that of the non-stenosis model after moderate-intensity and high-intensity exercise.

It can be clearly seen in Fig. 4b that the mild stenosis (25% stenosis) may induce high OSI (severe disturbed flow) at the narrow throat downstream and the stented region (region B and C). Moreover, this does not improve greatly after exercise. Compared to the resting state, the model with 25% stenosis has a noticeable high OSI value at the stented segment after exercise, and the region further worsen with the exercise degree increases. As shown in Fig. 4e, the high OSI ($OSI >$

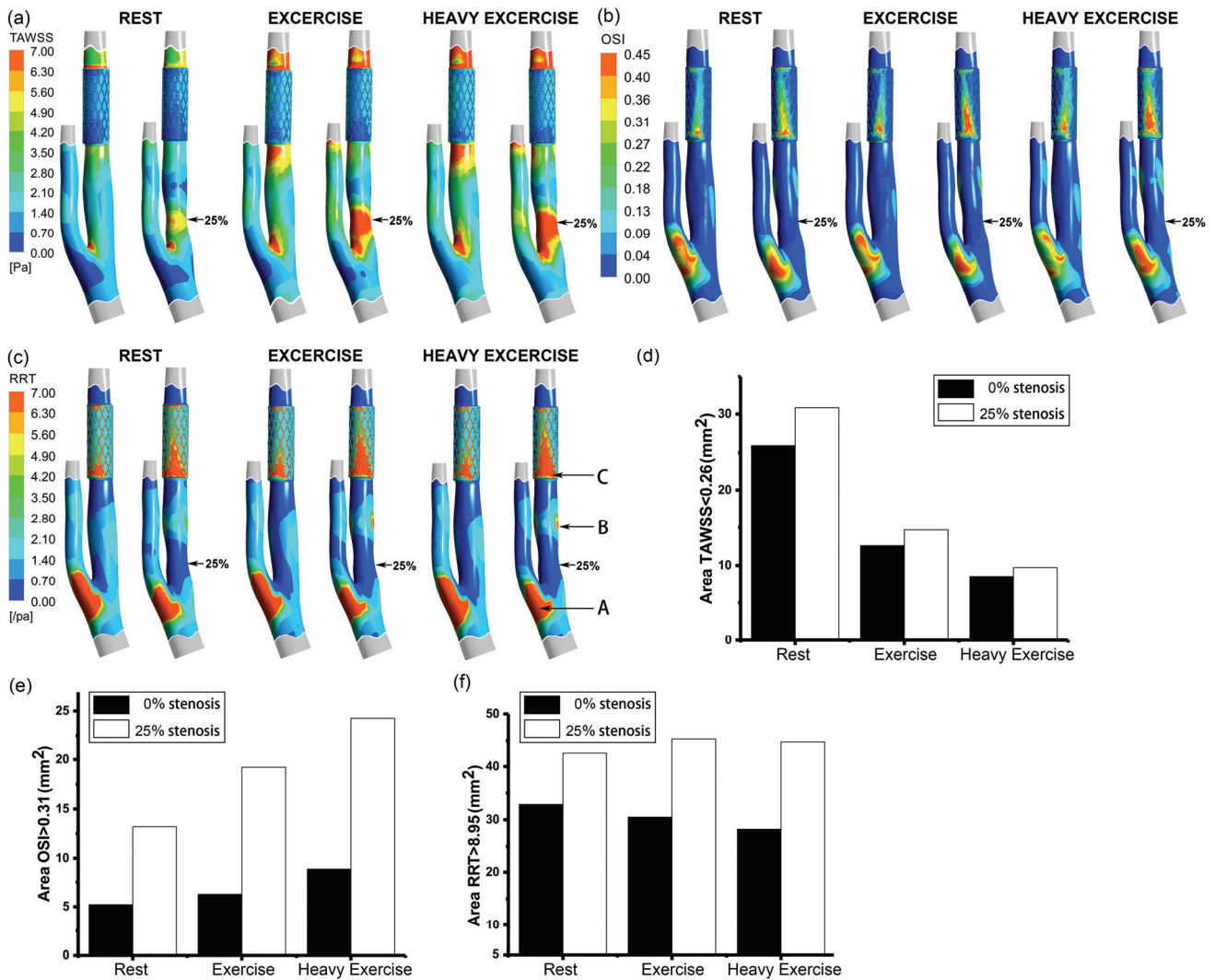


Fig. 4. The hemodynamic impact of mild stenosis on the vascular stenting (a)–(c). The distribution of TAWSS, OSI, and RRT of implanted carotid artery under three conditions (d)–(f). The histograms represent the area of the abnormal flow (TAWSS (< 0.26), RRT (> 8.95), and OSI (> 0.31)) after intervention on the stented artery

0.31) area is 3.8 times larger at the stented segment after moderate-intensity exercise than that of the non-stenosis model at rest, while the model after high-intensity exercise is as high as 4.8 times larger than that of the non-stenosis model at rest.

For the RRT distribution in Fig. 4c, it is roughly similar to that of OSI. The high RRT is observed at downstream of the narrow throat (region B) and the stented segment (region C), and this may worsen with the exercise degree increase. As shown in Fig. 4f, after quantitative analyzed of the high RRT area ($RRT > 8.95$), we found the areas for the mild stenosis after moderate and high intensity exercise were 1.29 and 1.49 times larger than that of the non-stenosis model at rest.

3.2. Effect of stenting scenarios on the treated artery

The TAWSS distribution on models with various stenting scenarios after exercise is shown in Fig. 5a.

For all stenting scenarios, the two end sides of stented segment and stent struts suffer from the low TAWSS, while the low TAWSS distribution in each segment differs remarkably. For the model treated a stent at the CCA or the middle ICA, TAWSS slowly increases from the proximal side of the stented segment, while the model treated at the proximal ICA exhibits a non-uniform spatial TAWSS distribution, which is manifested by the low value on the inside of the stented segment (region B). Moreover, the OSI distributions are similar after three different exercises, although the values are different. Under the same exercise, the stent implanted at the CCA may lead to noticeable low TAWSS at the stented segment, while this phenomenon does not show significant improvement after exercise training. As shown in Fig. 5b, the low TAWSS ($TAWSS < 0.26$ Pa) area after the distal ICA stenting under the resting state is 1.05 times larger than the proximal ICA stenting, while the area at the distal CCA stenting is even 2.51 times larger than the proximal ICA stenting. The low

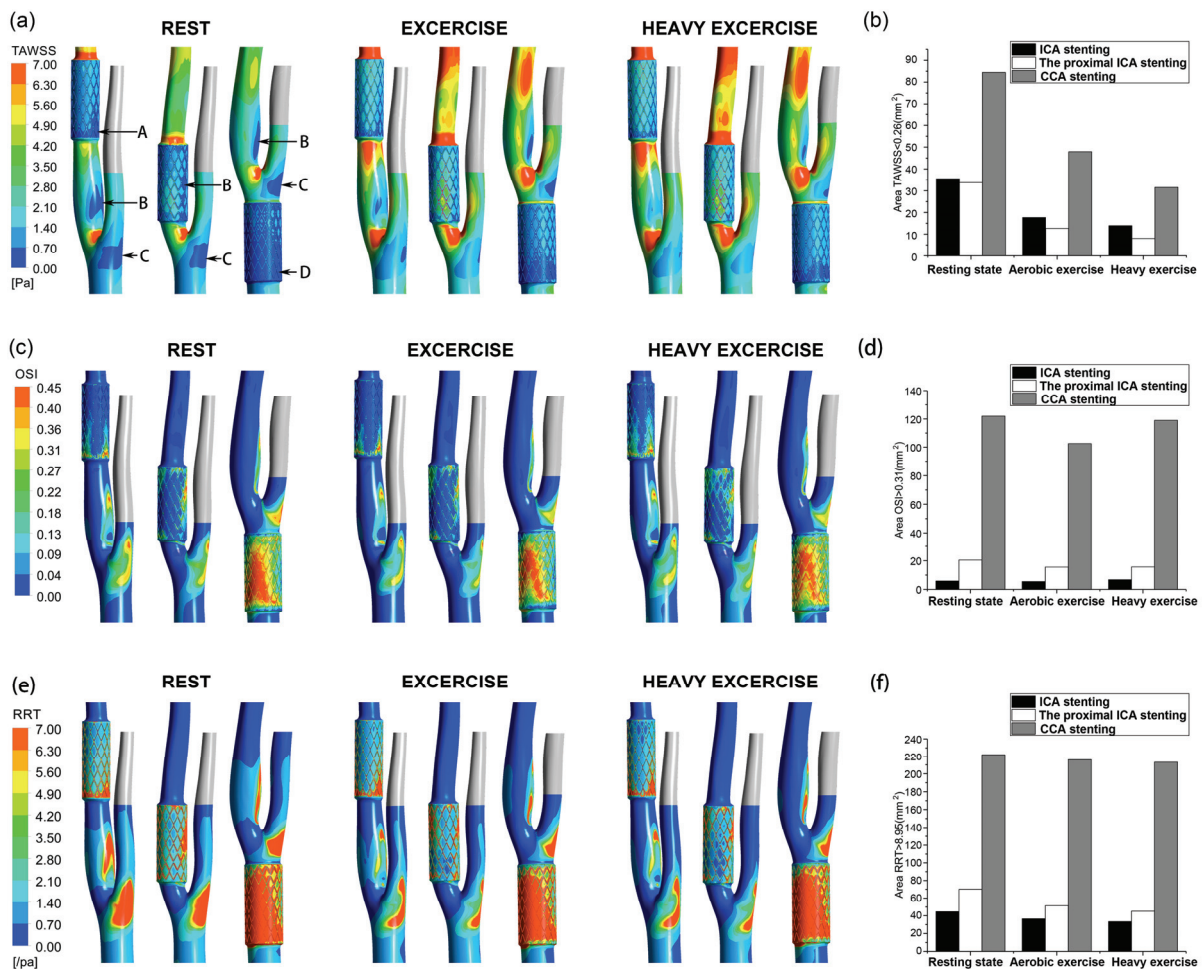


Fig. 5. The hemodynamic effect of different stenting scenarios. (a), (c), and (e) is the distribution of TAWSS, OSI, and RRT of implanted carotid artery under three conditions. (b), (d), and (f) The histograms represent the area of the abnormal flow ($TAWSS < 0.26$, $RRT > 8.95$, and $OSI > 0.31$) after intervention on the stented artery

TAWSS area of various stenting models after simple aerobic exercise is nearly half of all models at the resting state, and these areas further decreased to a third of all models after heavy exercise. Nevertheless, the low TAWSS area is obviously larger on the model stented at the distal CCA than others under the same exercise training.

As is evident from OSI distribution (Fig. 5c), there are remarkable differences between stenting scenarios. All models have an uneven OSI distribution at the stented segment, and it should be noted that very high OSI appears at the stented segment of distal CCA. In addition, the exercise training has less impact on OSI magnitude and spatial distribution for this model. As depicted in Fig. 5d, the high OSI ($OSI > 0.31$) area at the stented segment of distal CCA is more than fivefold than others, no matter what kind of training the patients performed. Similarly, extraordinarily large differences between three stenting scenarios can be observed in RRT distributions (Fig. 5e), while little difference exists between three exercise states. The implanted stent at the distal CCA induces a very high RRT, which even showed a limited improvement after different exercise training. As is evidenced in Fig. 5f, the high RRT ($RRT > 8.95$) area at the stented segment of distal CCA is sixfold more than others, no matter what kind of training the patients performed.

4. Discussion

The occurrence of restenosis or stent thrombosis is associated with adverse clinical outcomes after the intervention. Thus, some researchers strongly recommend rehabilitation exercise training to improve post-operative outcomes [12]. However, other researchers discovered that certain exercise programs might induce platelet activation leading to stent thrombosis [35]. This debate has existed for a long time on whether the rehabilitation exercise program is beneficial or harmful for patients after stenting and the role of an exercise program in this patient management has been controversial. The abnormal hemodynamic performance featured by low TAWSS (< 0.26), high OSI (> 0.31), and RRT (> 8.95) [27] after stenting is a crucial reason for these above adverse clinical outcomes. We focus on the hemodynamic characteristics after exercise in the present study. 3D computational fluid dynamics models based on human carotid bifurcation were constructed. The impact of other lesions without the stenting and different stenting scenarios after exercise training on

the hemodynamic performance in the host artery were also discussed.

This study revealed that exercise training could increase TAWSS but decrease RRT and OSI in Patient 1 after the intervention. These hemodynamic changes may be beneficial and are the underlying mechanisms for the significantly improved clinical outcomes for the intervened patients after the exercise training. Early studies [26] demonstrated a strong association between exercise training and death rate, with a two-third decrease in the exercise-training group. Kim [21] and Jaureguizar [17] discovered that patients who performed high-intensity interval training exercises after stenting performed better than the moderate continuous training group in peak oxygen uptake and 6-min walking distance, consistent with our results. These benefits may be caused by increased wall shear stress over the luminal surface of vascular endothelium after exercise training, which is an effective way of accelerating the generation of various pivotal regulators, such as growth factors, nitric oxide, and cytokines, which maintain vascular homeostasis. Nitric oxide (NO) can reduce endothelial permeability, inhibit the migration/proliferation of smooth muscle cells, suppress leukocyte chemotaxis and endothelial regeneration, inhibit the adhesion and aggregation of platelet, and prevent thrombosis, and it is mediated by WSS. The endothelial NO synthase activity increases with a certain degree of WSS [7], [33]. According to reports, exercise training programs up-regulated endothelial NO bioactivity, improving vascular endothelial functions and myocardial flow, stabilizing blood pressure, and demonstrating anti-thrombotic effects [15], [30], [44]. The above and our results suggested that the training-mediated changes in a term at hemodynamic parameters are advantageous for the patient emplaced stent. Nevertheless, these results are not suitable for all cases.

This study reported that exercise was harmful to the patients with mild stenosis upstream of the stented segment (Patient 2) due to the marked emergence of disturbed blood flow regions (low TAWSS, high OSI, and RRT). Moreover, heavy exercise training may impair the hemodynamic performance in the host artery, hence triggering or enhancing in-stent restenosis or stent thrombosis. These may be the key reason for the adverse clinical events response to exercise training [38]. In clinical practice, patients with severe vascular stenosis ($>75\%$) were commonly intervened with stents, whereas patients with mild stenosis received no treatment. This suggests that the patient may still have multiple mild stenoses in other locations after the intervention. This mild stenosis has a negligible effect

on blood flow, but it can affect the local flow dynamics in the stented segment, worsening as exercise intensity increases. We believe that patients with mild stenosis upstream of the stented segment are unsuitable for physical exercise, cumbersome exercise. This may be an important reason for the exercise controversy. These results imply that rehabilitation training for intervention patients should only be performed after a comprehensive vascular function assessment.

This study also discovered that the exercise effect on the hemodynamic environment was not compared with the stent position. Our results revealed a marked difference between the various stenting scenarios, with CCA stenting placement inducing increased adverse blood flow. The oscillations and chaos blood flow at the distal CCA stented segment may be more prone to adverse events than the ICA stenting. This does not improve even after different exercise training. A possible reason for these results can be that exercise-induced hemodynamic changes are limited. In this work, arterial geometry, stent struts, and blood flow demonstrate the local hemodynamic performance of the stented segment [40], while the bifurcation configuration exhibits low TAWSS but relatively high RRT and OSI on the inner luminal surface wall of ICA and the distal CCA, even in high inlet flow rates and different stentings. The exercise-induced hemodynamic changes significantly differ under various conditions, and determining the straightforward training effect for interventional patients remains difficult. Additional studies are warranted to evaluate the complex interplay between exercise and hemodynamic performance.

Although this study has reached some conclusions, it is a preliminary study in this area with inevitable limitations existing. The model used in this study only came from two specific patients, and more cases and perioperative related data should be constructed to support the conclusion of this study [13]. The stented segment in the present work was treated as idealized geometry, and we ignored vessel wall movement in order to simplify the numerical model. The process of exercise is highly intricate and its influence on blood flow is equally intricate. When engaging in physical activity, the configuration of blood vessels, particularly the carotid artery, may undergo modifications. The movement of the head, specifically the alterations in geometric properties, significantly affects blood flow. Furthermore, different exercises exert mechanical effects on the arterial wall, which play a crucial role in modifying blood flow. Consequently, further investigation is warranted in future research endeavors to comprehensively understand the impact of exercise.

5. Conclusions

This numerical study has demonstrated that the potential mechanism underlying exercise-induced hemodynamic effects in intervention patients is multifactorial. It has been observed that exercise training can enhance blood flow, thereby improving local hemodynamic performance by suppressing adverse blood flow (low TASS but high OSI and RRT) in certain cases. However, patients with mild stenosis upstream of the stented segment have exhibited an unfavorable hemodynamic environment following intense exercise. Therefore, we believe that rehabilitation training for these who had stenting should only be performed after a comprehensive vascular function assessment.

Authors' contributions

Zhenmin Fan: Conceptualization, Methodology, Software. Jiashuai Liu: Data curation, original draft preparation. Xiao Liu: Visualization, investigation. Xiao Xu: Visualization, original draft preparation. Mingyuan Liu: Software, data curation. Xia Ye: Writing-Reviewing and Editing. Xiaoyan Deng: Supervision.

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Declaration of conflicting interests

All authors declare no competing interests.

The ethical approval statement

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).

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