Quantitative assessment of changes in hemodynamics of the internal carotid artery after bypass surgery for moyamoya disease

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OBJECTIVE Although intracranial vessel remodeling has been observed in moyamoya disease, concerns remain regarding the effect of bypass surgery on hemodynamic changes within the internal carotid artery (ICA). The authors aimed to quantify the surgical effect of bypass surgery on bilateral ICAs in moyamoya disease and to estimate pressure drop (PD) along the length of the ICA to predict surgical outcomes.

METHODS Records of patients who underwent bypass surgery for treatment of moyamoya disease and in whom flow rates were obtained pre- and postsurgery by quantitative MR angiography were retrospectively reviewed. Quantitative MR angiography and computational fluid dynamics were applied to measure morphological and hemodynamic changes during pre- and postbypass procedures. The results for vessel diameter, volumetric flow, PD, and mean wall shear stress along the length of the ICA were analyzed. Subgroup analysis was performed for the circle of Willis (CoW) configurations.

RESULTS Twenty-three patients were included. The PD in ICAs on the surgical side (surgical ICAs) decreased by 21.18% (SD $\pm$ 30.1%) and increased by 11.75% (SD $\pm$ 28.6%) in ICAs on the nonsurgical side (contralateral ICAs) ($p = 0.001$). When the PD in contralateral ICAs was compared between patients with a complete or incomplete CoW, the authors found that the PDI in the former group decreased by 2.45% and increased by 20.88% in the latter ($p = 0.05$). Regression tests revealed that a greater postoperative decrease in PD corresponded to shrinking of ICAs ($R^2 = 0.22$, $p = 0.02$).

CONCLUSIONS PD may be used as a reliable biomechanical indicator for the assessment of surgical treatment outcomes. The vessel remodeling characteristics of contralateral ICA were related to CoW configurations.

<https://thejns.org/doi/abs/10.3171/2017.5.JNS163112>

KEY WORDS moyamoya disease; bypass; vessel remodeling; pressure drop; computational fluid dynamics; magnetic resonance angiography; vascular disorders

MOYAMOYA disease (MMD) is a progressive, occlusive disorder of the cerebral vasculature, with particular involvement of the circle of Willis (CoW). Outer-diameter narrowing of the involved arteries has been observed in patients with MMD.¹² Intimal thickening is a typical pathological change, leading to stenosis and/or occlusion of the terminal portion of the internal carotid artery (ICA), as well as the middle and anterior cerebral arteries. As a result, the collateral ves-

sels develop a hazy, film-like appearance, which is described as “moyamoya” on angiograms. MMD is thus regarded as a unique and dynamic cerebrovascular disease involving vascular flow from the IC to the external carotid (EC) system (which can develop transdural arterial recruitment), with the degree of involvement varying with the stages of MMD.⁶ Insufficiency of this IC-EC conversion system may result in cerebral ischemia, as well as intracranial hemorrhage from aneurysm development in

ABBREVIATIONS CFD = computational fluid dynamics; CoW = circle of Willis; EC = external carotid; ICA = internal carotid artery; MMD = moyamoya disease; NOVA = Noninvasive Optimal Vessel Analysis; PD = pressure drop; PDI = PD index; QMRA = quantitative MR angiography; WSS = wall shear stress.

SUBMITTED December 13, 2016. **ACCEPTED** May 8, 2017.

INCLUDE WHEN CITING Published online October 20, 2017; DOI: 10.3171/2017.5.JNS163112.

the collateral vascular networks, both of which contribute to the clinical presentation of MMD. Surgical revascularization by extracranial-intracranial bypass is thus the preferred procedure for treatment of MMD, complementing IC-EC conversion and thereby avoiding cerebral infarction and/or intracranial hemorrhage.⁶ Angiographic diminishment of moyamoya vessels, improvement in dilation of the anterior choroidal artery, and formation of collateral vascular networks from the EC system were observed following bypass surgery.^{10,11,15} However, the exact hemodynamic change of the IC system in MMD remains unknown.

One major view postulates the role of rising hemodynamic stress, caused by multiple stenotic changes in arteries at the base of the brain, in the development and progression of MMD. Reduction of hemodynamic stress on abnormal collaterals may be the core theoretical basis of revascularization treatment.⁹ Studies have yet to directly measure abnormalities in hemodynamic stress on the involved arteries. In our previous studies, we observed characteristic vessel remodeling in both the bypass graft and the ICA following bypass surgery. The changes in pressure drop (PD) along the ICA following bypass surgery were found to be a reliable hemodynamic parameter in the assessment of surgical treatment outcome.^{13,21,22}

In this study, we assessed the morphological and hemodynamic modifications in the ICA following bypass surgery, through the use of quantitative MR angiography (QMRA) and computational fluid dynamics (CFD) technology, to aid in exploration of the mechanisms for revascularization in surgery for the treatment of MMD. Subgroup analysis was performed according to differing configurations of the CoW.

Methods

Patient Selection

Following approval by the institutional review board, clinical data in all patients with MMD who underwent bypass surgeries at our institution between 2011 and 2012 were reviewed ($n = 120$). Among these patients, 68 had undergone QMRA, and bilateral ICA flow rates were measured in 23 patients by QMRA, both before and after bypass surgery. These 23 patients were selected to undergo CFD simulation. All operations in this case series were performed unilaterally. MMD was diagnosed according to the criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease).⁷ This study was approved by the ethical committees. Written informed consent was obtained from each patient.

Surgical Procedures

Surgical intervention for MMD was indicated after comprehensive evaluations of angiography images, clinical manifestations, brain perfusion or metabolic findings, and detailed surgical indications as described previously.^{11,19} Anterior and/or posterior branches of the superficial temporal artery were anastomosed end-to-side to the cortical branch of the middle cerebral artery. Encephaloduro-

myosynangiosis, the indirect bypass procedure involved, was described in our previous study.¹⁹

Blood Flow and Vessel Diameter Measurements

QMRA, which was implemented using Noninvasive Optimal Vessel Analysis (NOVA) software (VasSol, Inc.), was performed to measure the volumetric flow rate within the ICA.^{3,4} A 3D time-of-flight MRA scan (4 slabs, 40 slices per slab; TR 22 msec; TE 4.2 msec; flip angle 18°; matrix size 365 × 384; slice thickness 0.5 mm; field of view 181 × 200 mm²) was obtained with the 3.0-T MR Systems console (Verio, Siemens Medical Systems). Blood flow through the ICA was measured using commercially available NOVA software based on phase-contrast MRI, the accuracy of which has been validated both in vitro and in vivo.^{5,20}

CFD Modeling

3D geometries of the ICA were reconstructed and segmented through the use of MIMICS (Materialise' Interactive Medical Image Control System) to create domains for CFD computation.^{18,21} Mesh generation yielded elements ranging from 0.8 to 1.4 million. The conservation equations were solved through the use of ANSYS CFX 15.0, a finite volume-based CFD solver. Patient-specific inflow boundary conditions were measured using NOVA software based on MRA images. A zero static pressure was specified as an outlet boundary condition after extrusion of the outlet distally in a direction normal to the blood flow downstream to 30 times the size of the artery outlet. Blood flow was assumed as a laminar and Newtonian fluid with a density and dynamic viscosity of 1050 kg/m³ and 0.0032 Pa·sec, respectively.

PD Index

The PD index (PDI) was calculated as the ratio of difference in pressure reduction changes along the ICA and preoperative pressure reduction. The PDI can be calculated using the formula

$$PDI = \frac{\Delta P_f - \Delta P_p}{\Delta P_p} \times 100\% = \frac{(P_{if} - P_{of}) - (P_{ip} - P_{op})}{\Delta P_p} \times 100\% \quad (1)$$

where ΔP_f and ΔP_p are the calculated pressure reduction at follow-up and preoperatively, respectively; P_{if} and P_{of} are the follow-up pressure values calculated at the inlet and outlet sections, respectively; and P_{ip} and P_{op} are the preoperative pressure values calculated at the ICA inlet and outlet, respectively. The positions of both proximal (inlet) and distal (outlet) planes, where we measured the pressure values, are the same between preoperative and follow-up models. The pressure was measured in mm Hg. The mean wall shear stress (WSS) of ICA was calculated using formula (2), with the WSS measured in dyn/cm²

$$WSS = 10 \mu (\Delta V / \Delta y) \quad (2)$$

where μ (Pa·sec) is flow viscosity, ΔV (m/sec) is the velocity difference at the near vessel wall surface, and Δy (m) is the distance to the vessel surface.

Statistical Analysis

A 2-tailed, paired Student t-test was applied to compare the results of preoperative and follow-up parameters, both on the surgical side (surgical ICA) and the contralateral (nonsurgical) side (contralateral ICA) of the ICA. Regression analysis was used to assess the relationships between vessel diameter, PD, mean WSS, and volumetric flows before and after treatment. Statistical analysis was performed using SPSS version 17.0 software (IBM Corp.). Throughout the analysis, a significance level of $p \leq 0.05$ was assumed.

Results

Patient Characteristics

Ten male and 13 female patients with MMD were selected for this study. The mean age of patients was 35.3 ± 9.2 years, ranging from 16 to 50 years. Postoperative follow-up and observations were conducted for 3–11 months, with an average follow-up of 6.5 ± 3.1 months. Patient characteristics and subtypes of MMD are outlined in Table 1. All cases were classified into 2 groups according to the morphology of the CoW (with or without an intact arterial circle in bilateral ICAs) following analysis of the angiographic images: Group A (14 patients) had an incomplete CoW, and Group B (9 patients) had a complete CoW. There were no significant differences in baseline hemodynamic values between surgical and contralateral ICAs prior to surgery, including vessel diameter, volumetric flow, PD, or WSS.

Pressure Drop

The mean PD ($\pm$ standard deviation) in surgical ICAs was 6.5 ± 2.8 mm Hg before surgery, compared with that in contralateral ICAs (4.5 ± 2.9 mm Hg; $p = 0.09$). For all cases, the mean PDI ($\pm$ standard deviation) of surgical ICAs was $21.18\% \pm 30.1\%$, compared with that of contralateral ICAs ($-11.75\% \pm 28.6\%$; $p = 0.001$). When analyzed by group, the difference in PDI between surgical and contralateral ICAs was significant in Groups A and B ($p = 0.002$ and $p = 0.04$, respectively). The mean PDIs of the surgical ICA in Groups A and B were 20.75% and 21.86%, respectively ($p = 0.934$). However, the mean PDIs of the contralateral ICA in Groups A and B were 20.88% and 2.45%, respectively. This difference was significant ($p = 0.05$) (Fig. 1).

Of these 23 patients, 15 underwent midterm follow-up (< 6 months), and 8 underwent long-term follow-up (> 6 months). Interestingly, the mean PDI ($\pm$ standard deviation) of the surgical ICA in the group with short-term follow-up was $17.7\% \pm 8.3\%$, a significantly higher value compared with the PDI of the contralateral ICA of $-17.3\% \pm 5.8\%$ ($p = 0.002$). The PDIs of the surgical and contralateral ICA in the long-term follow-up group, however, were $25.6\% \pm 8.3\%$ and $-1.2\% \pm 13.1\%$, respectively ($p = 0.11$) (Supplemental Fig. 1).

Volumetric Flow Rate

The mean volumetric flow rate ($\pm$ standard deviation) in the surgical ICA decreased significantly from $159.65 \pm$

TABLE 1. Summary of patient characteristics, MMD features, surgical procedures, and baseline hemodynamic values

Variable	Value
No. of patients	23
Female, %	56.5
Mean age, yrs (range)	35.3 (16–50)
Ischemic presentation, %	65.2
MMD characteristics	
Suzuki stage, no. of hemispheres	
I	0
II	4
III	22
IV	14
V	6
VI	0
Surgery, no. (%)	
Lt side	14 (60.9)
Single anastomosis	20 (87.0)
Encephaloduromyosynangiosis	23 (100)
Morphology & hemodynamic baseline values, mean $\pm$ SD	
Vessel diameter, mm	
Surgical ICA	3.44 ± 0.84
Contralat ICA	3.59 ± 0.96
ICA flow, ml/min	
Surgical ICA	159.65 ± 71.48
Contralat ICA	165.20 ± 51.96
PD, mm Hg	
Surgical ICA	6.5 ± 2.8
Contralat ICA	4.5 ± 2.9
WSS, dyn/cm ²	
Surgical ICA	77.0 ± 28.1
Contralat ICA	64.3 ± 37.8

71.48 ml/min to 135.97 ± 68.89 ml/min ($p = 0.01$). However, in the contralateral ICA, volumetric flow rates underwent an insignificant increase (165.20 ± 51.96 ml/min preoperatively vs 174.97 ± 97.47 ml/min at follow-up; $p = 0.46$). The volumetric flow rate in the surgical ICA decreased by 14.83% compared with that in the contralateral ICA, which increased by 0.96% ($p = 0.17$). There were no significant differences in percentage changes for volumetric flow rates between surgical and contralateral ICAs in either Groups A or B (11.11% vs 17.48% and 9.40% vs -9.02% , respectively).

Wall Shear Stress

At follow-up observation, the mean WSS ($\pm$ standard deviation) in the surgical ICA decreased significantly from 64.88 ± 28.05 dyn/cm² to 55.55 ± 37.93 dyn/cm² ($p = 0.05$). In the contralateral ICA, however, the mean WSS also decreased significantly (64.33 ± 37.80 dyn/cm² preoperatively vs 49.94 ± 17.61 dyn/cm² at follow-up; $p = 0.01$).

FIG 1. The difference in the PDI between groups with incomplete and complete CoW. The error bar represents the standard error. S-ICA-I CoW indicates surgical ICA with incomplete CoW; C-ICA-I CoW indicates contralateral ICA with incomplete CoW; S-ICA-C CoW indicates surgical ICA with complete CoW; C-ICA-C CoW indicates contralateral ICA with complete CoW.

The percentage change in the mean WSS in the surgical ICA was 10.67%, which was not significantly different than the value found in the contralateral ICA (12.41%; $p = 0.87$). There were no significant differences in percentage changes in inflow rates between surgical and contralateral ICAs in Groups A and B (6.46% vs 13.69% and 17.21% vs 10.56%, respectively).

Predictors of Decreased PD After Bypass Surgery

Linear regression analysis revealed that neither the ages of patients ($p = 0.12$) nor Suzuki stages of MMD ($p = 0.54$) were significantly associated with a decreased PD (Table 2). A greater decrease in PD postoperatively corresponded to greater increases in the mean WSS ($R^2 = 0.23$, $p = 0.02$), decreases in volumetric flow ($R^2 = 0.51$, $p = 0.000$), and was significantly associated with a reduction in the luminal diameter of ICAs ($R^2 = 0.22$, $p = 0.02$) (Figs. 2 and 3, and Supplemental Fig. 2). Multivariate analysis, however, demonstrated that the decreases in volumetric flow ($p = 0.001$), but not increases in WSS ($p = 0.14$) nor reductions in diameter ($p = 0.29$), remained predictive of decreased PD in ICAs after surgery (Table 2).

Discussion

Several studies have demonstrated that bypass surgery can prevent ischemic and hemorrhagic stroke in patients with MMD by improving cerebral blood flow through ischemic brain via newly constructed vessel networks from the EC system, thereby lowering the hemodynamic stress

of an abnormal IC system.^{4,8,15} Improvements in anterior choroidal artery dilation and decreases in moyamoya vessels have been hypothesized to be relevant angiographic changes following bypass.^{11,15} Most researchers, however, focus on morphometric analysis of vessels through angiographic and clinical data, with little research done to analyze hemodynamic mechanisms. CFD may contribute to a greater understanding of hemodynamic stress, because it has been used to quantify blood flow patterns and PDs in aneurysms and their arteries of origin.¹⁶

In this study, CFD technology was used to measure the PD along the ICA pre- and postoperatively. In addition, the mean WSS and flow rate through the ICA were quantified. Flow rates and PDs in the surgical ICA declined significantly following surgery (Fig. 4). Flow rate in surgical ICAs decreased by 14.83%, while the PD decreased by 21.18%. This phenomenon correlates with the theory that MMD is a cerebrovascular disease underpinned by the IC-EC conversion system,⁶ with bypass surgery thereby

TABLE 2. Predictors of decreased PD in the ICA after surgery

Variable	Univariate Analysis		Multivariate Analysis
	R Value	p Value	p Value
Decreases in diameter	-0.467	0.025	0.288
Increases in mean WSS	0.474	0.022	0.144
Decreases in volumetric flow	0.712	0.000	0.001

FIG 2. Changes in volumetric flow versus PD after surgery. A greater decrease in PD postoperatively corresponded to a greater reduction in volumetric flow ($R^2 = 0.51$, $p = 0.000$).

FIG 3. Changes in vessel diameter versus PD after surgery. A greater decrease in PD postoperatively corresponded to the shrinking of ICAs ($R^2 = 0.22$, $p = 0.02$).

useful in helping to complete the process of IC-EC conversion. After new collaterals are built, the hemodynamic function of the ICA may be weakened, with reduced hemodynamic stress following functional revascularization surgery.

The CoW is an important structure in creating redundancies or collaterals in cerebral circulation.² The PDI in the contralateral ICA in the group with complete CoW decreased by 2.45% at follow-up, whereas the PDI in the group with incomplete CoW increased by 20.88%. This may have been due to blood flow into the contralateral ICA through an intact arterial circle in bilateral ICAs. PD in the surgical ICA following bypass surgery may be matched to the contralateral ICA due to the connection of bilateral ICAs through the CoW.

The WSS represents the force of blood against the vessel wall, which is applied mainly to the endothelium. This hemodynamic force has been identified as a critical determinant of vessel diameter and vascular remodeling through the proliferation of endothelial progenitor cells.¹⁶ In addition, the WSS is also regarded as an important physical force that is vital to inducing the remodeling of preexisting arterioarteriolar anastomoses, or arteriogenesis, which may contribute to the mechanisms underlying bypass surgery for treatment of MMD.¹⁷ More recently, Alaraj et al. demonstrated that WSS was a potential biomechanical factor for efficient treatment of arteriovenous malformations.¹ In the present study, the mean WSS of both surgical and nonsurgical ICAs decreased, with the difference in mean WSS between surgical and contralateral ICAs following surgery found to be not significant. Because multiple stenotic changes occur along the ICA, the mean WSS may not be a sensitive parameter in the measurement of hemodynamic changes following surgery for treatment of MMD.

Overall, our findings clarify the hemodynamics underlying MMD and quantify the effects of bypass surgery.

Findings from this study indicate that vessel remodeling occurs in surgical ICAs following bypass surgery, which is associated with reductions in vessel diameter, volumetric flow, PD, and mean WSS. This pattern of vessel remodeling correlates with the dynamic nature of MMD, otherwise termed IC-EC conversion. From a hemodynamic perspective, bypass surgery has been proven to help complete the IC-EC conversion process. More specifically, the PDI has been identified as a potential biomechanical factor that may be important in remodeling of the ICA over time and in the decline in hemodynamic stress in the IC system following bypass surgery. Configurations of the CoW will likewise influence the effect of bypass surgery on the contralateral ICA.

Possible limitations of this study include its retrospective design and small sample size. However, to our knowledge, this is currently the largest study cohort for hemodynamic analysis following bypass surgery in patients with MMD, through the use of patient-specific QMRA assessment and CFD technology. Moreover, exact flow measurements using QMRA ensured greater accuracy of CFD simulation results. Another plausible shortcoming of this study is that the follow-up may not have been long enough to monitor the vessel remodeling processes in the contralateral ICA, because MMD is a gradually progressive cerebrovascular disorder, with a mean period of progression of 12–34 months.¹⁴

Conclusions

Our results confirm the occurrence of IC-EC conversion following bypass surgery, indicating the role of vessel remodeling in the ICA after bypass surgery in reducing PD and associated decreases in vessel diameter and volumetric flow. Moreover, configurations of the CoW will influence the effect of bypass surgery on the contralateral ICA. CFD may be a useful tool for virtually estimating

FIG 4. Illustrative case. **A:** Pre- and postoperative QMRA images showing the effects of bypass surgery in the left hemisphere (L). The volumetric flow of the ICA decreased from 145 ml/min to 110 ml/min, with more than two-thirds of the middle cerebral artery area of distribution supplied by newly constructed vessel networks from the EC system. On left panel, arrows indicate direction of the flow; on right panel, A indicates anterior view. **B:** Corresponding pressure contours showing that the PD decreased in bilateral ICAs.

the outcome of bypass surgery for treatment of MMD. Continuous long-term hemodynamic monitoring is recommended for the contralateral hemisphere in the event of disease progression.

Acknowledgments

This study was sponsored by Australian Research Council Discovery Project (DP1112985) (Qian, Morgan), National Key Technology R&D Program of the Ministry of Science and Technology of China (no. 2011BAI08B06) (Mao), Key Medical Project of Shanghai Science and Technology Commission (no. 13411950200) (Mao), The Foundation of National Natural Science Fund, China (no. 81401136 and 81171082) (Zhu, Mao), and Project of Shanghai Science and Technology Commission (no. 16495800300) (Tian).

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Qian, F Zhu, Xu, Gu, Mao, Morgan. Acquisition of data: Qian, F Zhu, Gu, Karunanithi, W Zhu, Chen, Mao. Analysis and interpretation of data: Qian, F Zhu, Xu, Karunanithi, W Zhu, Morgan. Drafting the article: Qian, F Zhu, Xu, Gu, W Zhu, Chen, Mao. Critically revising the article: Qian, F Zhu, Mao. Reviewed submitted version of manuscript: Qian, F Zhu, Karunanithi, Chen, Mao, Morgan. Approved the final version of the manuscript on behalf of all authors: Qian. Statistical analysis: Qian, F Zhu. Administrative/technical/material support: Qian, Mao. Study supervision: Qian, Mao, Morgan.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Figures 1 and 2. <https://thejns.org/doi/suppl/10.3171/2017.5.JNS163112>.

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