Impact of blood pressure changes in cerebral blood perfusion of patients with ischemic Moyamoya disease evaluated by SPECT

Journal of Cerebral Blood Flow & Metabolism
2021, Vol. 41(6) 1472–1480
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DOI: 10.1177/0271678X20967458
journals.sagepub.com/home/jcbfm

Zhao Liming^{1,*}, Sun Weiliang^{1,*}, Jia Jia², Liang Hao¹, Liu Yang¹, Christopher Ludtka³, Behnam Rezai Jahromi¹ , Felix Goehre⁴, Ajmal Zemmar^{1,3}, Li Tianxiao¹, Juha Hernesniemi^{1,3}, Hugo Andrade-Barazarte^{1,3} and Li Chaoyue¹

Abstract

Our aim was to determine the impact of targeted blood pressure modifications on cerebral blood flow in ischemic moyamoya disease patients assessed by single-photon emission computed tomography (SPECT). From March to September 2018, we prospectively collected data of 154 moyamoya disease patients and selected 40 patients with ischemic moyamoya disease. All patients underwent in-hospital blood pressure monitoring to determine the mean arterial pressure baseline values. The study cohort was subdivided into two subgroups: (1) Group A or relative high blood pressure (RHBP) with an induced mean arterial pressure 10–20% higher than baseline and (2) Group B or relative low blood pressure (RLBP) including patients with mean arterial pressure 10–20% lower than baseline. All patients underwent initial SPECT study on admission-day, and on the following day, every subgroup underwent a second SPECT study under their respective targeted blood pressure values. In general, RHBP patients showed an increment in perfusion of 10.13% (SD 2.94%), whereas RLBP patients showed a reduction of perfusion of 12.19% (SD 2.68%). Cerebral blood flow of moyamoya disease patients is susceptible to small blood pressure changes, and cerebral autoregulation might be affected due to short dynamic blood pressure modifications.

Keywords

Cerebral blood flow, cerebral hemodynamics, moyamoya disease, brain imaging, blood pressure

Received 19 January 2020; Revised 11 June 2020; Accepted 16 September 2020

Introduction

Moyamoya disease (MMD) is a clinical entity characterized by chronic progressive stenosis or occlusion of the terminal internal carotid arteries, together with the development of collateral networks, which seem to provide an alternative route for cerebral perfusion.^{1,2} These neovascularization attempts to compensate for reduced cerebral perfusion often fail, leading to clinical symptoms and signs of the disease.^{1,3}

Digital subtraction angiography (DSA) remains the gold standard for the diagnosis of MMD and can provide perspective into the severity of the disease.⁴ However, there is often disparity between the angiographic findings and the clinical presentations of

¹Department of Neurosurgery, Cerebrovascular Disease Hospital, Henan Provincial People's Hospital; Zhengzhou University, Zhengzhou, China

²Department of Anesthesiology and Perioperative medicine, Henan Provincial People's Hospital; Zhengzhou, Zhengzhou, China

³"Juha Hernesniemi" International Center for Neurosurgery, Henan Provincial People's Hospital, Zhengzhou University, Zhengzhou, China

⁴Department of Neurosurgery, BG Klinikum Bergmannstrost Halle, Halle, Germany

*These authors contributed equally to this work.

Corresponding authors:

Andrade-Barazarte, Department of Neurosurgery, Cerebrovascular Disease Hospital, Henan Provincial People's Hospital; Zhengzhou University, Zhengzhou, China.
Email: hugoandrade2@yahoo.es

Li Chaoyue, Department of Neurosurgery, Cerebrovascular Disease Hospital, Henan Provincial People's Hospital; Zhengzhou University, Zhengzhou, China.
Email: lichaoyue1973@163.com

patients. Therefore, quantitative dynamic studies are necessary to evince cerebral perfusion and metabolism, which are important parameters in deciding further treatment modalities.¹

Quantitative hemodynamic imaging studies are able to demonstrate cerebral blood flow (CBF), cerebral blood volume, and cerebral vascular reactivity (CVR) under particular circumstances; such methods include: positron emission tomography (PET), single photon emission computed tomography (SPECT), dynamic perfusion computed tomography, MRI dynamic susceptibility contrast, and arterial spin labeling (ASL) and their respective functional tests with nitrous oxide and acetazolamide.^{1,5,6} Up to now, none of the previous tests have been performed under different controlled blood pressure (BP) targets, thus failing to provide information regarding CBF and its variations through BP modifications in patients with certain cerebrovascular pathologies. Thus, our aim was to determine the impact of targeted BP modifications on CBF in MMD patients, as assessed by SPECT imaging.

Methods

Study cohort

From March to September 2018, we prospectively collected data of 154 patients with MMD (diagnosis according to the Japanese guidelines of moyamoya disease)⁷ admitted to the neurosurgery department of Henan Provincial People's Hospital, who met the following inclusion criteria: (1) age within 18–65 years old; (2) symptomatic MMD patients presenting with transient ischemic attacks, headaches, dizziness, or with previous history of stroke—older than three months; (3) confirmed MMD diagnosis by DSA; (4) admission NIHSS score less than two points; (5) 24 h in-hospital BP monitoring to determine baseline BP values and that fluctuation range would not be higher than ± 10 –15% of the baseline value; (6) normal electrocardiogram and pulmonary function; (7) SPECT under targeted BP values.

Patients that failed to preclude under the given inclusion criteria and that had previous history of associated cerebrovascular diseases such as aneurysms or arteriovenous malformations as well as hemorrhagic (subarachnoid hemorrhage, intraventricular hemorrhage, and intracerebral hemorrhage) moyamoya disease presentation, endocrine and metabolic diseases, and respiratory and cardiovascular diseases (hypertension $\pm$ treatment) were also excluded from the study cohort. Additionally, patients that failed to reach the targeted BP value, with incomplete available data, were excluded as well (Figure 1). None of these

patients received any additional medical treatment or intravenous solutions before SPECT examinations.

MMD patients with other comorbidities and associated diseases which could affect CBF were excluded in order to ensure a study cohort affected only by ischemic MMD.

Patients were randomly assigned to each group following a strict simple method (1:1 ratio) during the targeted BP values until obtaining the total sample number and evaluations.

Baseline BP and initial SPECT imaging

All patients underwent 24 h in-hospital BP monitoring to identify baseline values based on mean arterial pressure (MAP) and BP fluctuations. On the next day, all the patients underwent an initial SPECT imaging as previously described by Juni et al.⁸ and according to the following protocol: (a) before examination, the patients should rest approximately 15 min in the waiting area; (b) following BP measurement and recording; (c) immediate intravenous administration of ⁹⁹TcM-ECD 925MBq; (d) SPECT imaging obtention; (e) return to the ward.

SPECT imaging under targeted BP

On the following day, BP values of all patients were remeasured to ensure that the MAP did not vary more than 5 mmHg. Then, the patients were subclassified in two subgroups: (1) Group A or relative high BP (RHBP) and (2) Group B or relative low BP (RLBP) patients. Then, a second SPECT study was performed under targeted BP parameters as follows: (1) Group A underwent light dynamic physical stimuli (stairs climbing) with continuous BP monitoring until achieving an increment of MAP 10–20% higher than the baseline value, then the contrast medium was administered immediately, and the SPECT study was performed. Patients who underwent 1–2 min of physical stimuli without achieving the targeted BP value continued the physical activity until the targeted BP was reached; however, when this was not possible after 10 min of exercise, the patient was excluded from the study; (2) Group B patients received a 10 mg sublingual single dose of Nifedipine, and the MAP was continuously monitored during 10–15 min until a 10–20% reduction of MAP was achieved, then the SPECT study was performed. Those patients in which a single dose of sublingual Nifedipine did not cause the desired BP reduction were as well excluded from the study sample.

⁹⁹TcM-ECD 925MBq is a radiopharmaceutical tracer with a long half-life that crosses the blood–brain barrier, and it distributes in the brain in proportion to blood flow. Therefore, after achieving the

Figure 1. Flow chart showing studied population and patient selection.

MAP: mean arterial pressure; BP: blood pressure; RHBP: relative high blood pressure; RLBP: relative low blood pressure; MMD: moyamoya disease; HPPH: Henan Provincial People's Hospital; SPECT: single-photon emission computed tomography.

required BP target and its immediate intravenous administration, BP measurement during the imaging acquisition was not considered necessary.

Image processing and analysis

All acquired images were assessed by two experienced nuclear medicine physicians (blinded to all patients' clinical history and subgroup division). Discrepancy between evaluations was resolved through discussion with an additional physician blinded to clinical information and group division as well. The frontal, parietal, temporal, and occipital cortices as well as basal ganglia, brainstem, and cerebellum were analyzed systematically. Abnormal brain SPECT findings were defined as heterogeneous regional cerebral blood flow (rCBF) with focal hypoperfusion or visible asymmetry in at least three consecutive slices. More than three consecutive cross-sectional radioactive sparse defect

areas were defined as ischemic lesions. Then, the most obvious region of radioactive sparse defect was selected, and the lesions were identified and counted.

Region of interest and CBF measurements

The reference blood flow area (Fr) of 55 ml 100/g/min (mean value of cerebellar blood flow in healthy people) was set up by using the Brain Lassen Correction post-processing software,⁹ which is included in the E.Cam equipment. The penetration coefficient (α) is 1.5. The symmetrical positions of bilateral frontal lobes, temporal lobes, parietal lobes, and bilateral basal ganglia on the cross-sectional images of resting and exercise load CBF perfusion imaging (region of interest (ROI)) were delineated by 12-point method as well as the ROI. The ratio defined as rCBF (obtained from the difference between the quantitative radioactivity count of the ROI in each vascular territory and the count of the

Table 1. Patients' demographics.

Demographic characteristics	RHBP	RLBP
Gender (male/female)	08/12	10/10
Age (median, range)	45.5 years (18–56 years)	43 years (23–55 years)
Symptoms		
TIA	12	8
Dizziness/headache	6	10
Asymptomatic	2	2
MAP baseline median (range)	92.67 mmHg (75.00–107.67)	99.75 mmHg (86.33–118.00)
MAP under target BP median (range)	103 mmHg (84.33–125.67)	87.8 mmHg (77.67–103.33)

MAP: mean arterial pressure; BP: blood pressure; RHBP: relative high blood pressure; RLBP: relative low blood pressure.

ROI in the cerebellum) was calculated as a normalized semi-quantitative parameter. Local rCBF values higher than 85% during baseline MAP were defined as normal perfusion, whether values below 85% were considered as hypoperfusion. Then the respective ROIs (normal and reduced) were recorded. After the second examination (BP targeted groups), the same planes were selected to record the rCBF values of each ROI.

ROI division

In order to simplify imaging analysis, the ROI were divided as follows: (1) Type A which included areas of perfusion defect (absence of contrast evidence on visual analysis) during the initial SPECT study at baseline MAP values; (2) Type B areas comprised ROI showing hypoperfusion during the SPECT study under targeted BP values; and (3) Type C which included areas that showed normal perfusion values. Additionally, it is important to mention that in our study, due the comparison between cerebellar blood flow rate (considered as normal) and supratentorial hemispheres, hyperperfusion areas were not identified.

Ethics and statistics

This study has the approval of the Henan Provincial People's Hospital Ethics Committee (HIRB-2019-329 Chinese moyamoya disease registry which follows the Declaration of Helsinki on Human Research Ethics). Written informed consent was acquired from involved patients. Data were analyzed with a commercial statistical software package (Graphpad prism 7 version for Windows). The variables were expressed as average, medians standard deviations, and quartiles when appropriate. They were correlated with the χ^2 test, Mann-Whitney U test, Pearson correlations, and linear regression when appropriate, with a P -value <0.01 considered statistically significant.

Results

Patients' demographics

This study comprised of 40 prospectively collected MMD patients (22 women and 18 men) with a median age at admission of 42 years (range 18–55 years). Patients were assigned following a 1:1 ratio to the different study groups (RHBP and RLBP). The patients' demographics are summarized in Table 1.

Effects of RHBP on cerebral perfusion

Of the total 20 patients in this subgroup, 240 ROI were identified and divided as follows: 21 Type A, 126 Type B, and 93 Type C based on the previously described division.

Among the Type A ROIs, the rCBF at initial SPECT (under baseline BP values) had a median of 37% (avg = 36.86%, SD 2.37%), whereas on the second SPECT examination (under targeted BP values), the rCBF had a median of 38% (avg = 38.05%, SD 2.33%). Among these ROIs, no significant perfusion increments or statistically significant difference was evident (Figure 2(a)) ($P > 0.01$). Regarding Type B ROIs, the rCBF under baseline BP values had a median of 78% (avg = 78.15% and SD 3.47%), whereas under RHBP values, the rCBF had a median of 86% (avg = 86.53% and SD 4.48%). After inducing RHBP values, a statistically significant perfusion increment existed between these ROIs (Figure 2(b)) ($P < 0.01$).

In Type C ROIs, the rCBF under baseline BP had a median of 87% (avg = 87.99%, SD 2.01%) and under RHBP values a median of 96% (avg = 96.15%, SD 1.98%) (Figure 2(c)). Among these ROIs, there was a statistically significant perfusion increment ($P < 0.01$) (Table 2). Exceptionally, within this subgroup, five regions showed not obvious local rCBF increment nor statistical significance ($P > 0.01$). Table 2 summarizes ROIs types and rCBF modifications, and

Figure 2. SPECT imaging demonstrating the different ROI under baseline blood pressure values and relative high blood pressure: (a) Type A ROI images at initial state during baseline BP and during relative high BP, demonstrating not significant changes in CBF perfusion; (b) Type B ROI images at initial state during baseline BP and during relative high BP, demonstrating significant increments in rCBF perfusion during the RHBP target; (c) Type C ROI at initial state during baseline BP and during relative high BP, demonstrating significant increments in rCBF perfusion during the RHBP target; (d) diagram showing cerebral blood perfusion deficit ratio under resting blood pressure and relative high blood pressure.

MAP: mean arterial pressure; SPECT: single-photon emission computed tomography; RHBP: relative high blood pressure.

Table 2. rCBF in ROI areas under baseline BP and RHBP.

Type	ROI	rCBF values (median, avg, SD) under resting BP	rCBF values (median, avg, SD) under RHBP	P-value Paired T test
A	21	37% (avg = 36.86%, SD 2.37)	38.05% (avg = 38.05, SD 2.33)	0.109
B	126	78% (avg = 78.15, SD 3.47)	86% (avg = 86.53, SD 4.48)	<0.01
C	93	87% (avg = 87.99, SD 2.01)	96% (avg = 96.15, SD 1.98)	<0.01

ROI: region of interest; BP: blood pressure; RHBP: relative high blood pressure.

Figure 2(d) demonstrates rCBF distribution under baseline BP and RHBP.

In general, under RHBP values in ROI Types B and C, the Δ rCBF% (change rate of rCBF) had a median increment of perfusion of 10.13% (SD 2.94%),

Effects of RLBP on cerebral perfusion

Among the RLBP group, a total of 240 ROI regions were selected and divided as follows: 16 Type A, 143 Type B, and 81 Type C ROIs.

Under baseline BP values, Type A ROIs had an rCBF median of 36% (avg = 36.13% and SD 1.09%), and under RLBP, a median of 35.5% (avg = 35.63%, SD 1.09%), showing no statistically significant perfusion decrease (Figure 3(a)) ($P > 0.01$).

Among Type B ROIs, the rCBF under baseline BP had a median of 79% (avg = 79.22% and SD 2.72%), whereas under RLBP values had a median of 70% (avg = 69.52% and SD 3.15%) (Figure 3(b)). Comparing these ROIs, images obtained during RLBP values showed a statistically significant perfusion reduction ($P < 0.01$).

Figure 3. SPECT imaging demonstrating the different regions of interest (ROI) under baseline blood pressure values and relative low blood pressure: (a) Type A ROI images at initial state during baseline BP and during relative low BP, demonstrating not significant changes in CBF perfusion; (b) Type B ROI images at initial state during baseline BP and during relative low BP, demonstrating significant reductions in rCBF perfusion during the RLBP target; (c) Type C ROI at initial state during baseline BP and during relative low BP, demonstrating significant reductions in rCBF perfusion during the RLBP target; (d) diagram showing cerebral blood perfusion deficit ratio under resting blood pressure and relative low blood pressure.

MAP: mean arterial pressure; SPECT: single-photon emission computed tomography; RLBP: relative low blood pressure.

Table 3. rCBF in ROI areas under baseline BP and relative low BP (RLBP).

Type	ROI	rCBF values (median, avg, SD) under resting BP	rCBF values (median, avg, SD) under RLBP	P value Paired T test
A	16	36% (avg = 36.13, SD 1.09)	35.5% (avg = 35.63, SD 1.09)	0.203
B	143	79% (avg = 79.22, SD 2.72)	70% (avg = 69.52, SD 3.15)	<0.01
C	81	88% (avg = 88.44, SD 2.85)	78% (avg = 77.72, SD 3.15)	<0.01

ROI: region of interest; BP: blood pressure; RLBP: relative low blood pressure; AVG: average; SD: standard deviation.

Under baseline BP values, type C ROIs had rCBF median of 88% (avg = 88.44%, SD 2.85%), whereas under RLBP values, the rCBF had a median of 78% (avg = 77.72%, SD 3.15%), demonstrating a statistically significant perfusion reduction ($P < 0.01$) (Figure 3(c)). Table 3 summarizes the ROIs distribution and characteristics, and Figure 3(d) demonstrates the rCBF distribution under baseline BP and RLBP.

In general, under RLBP values in ROI type B and C, the Δ rCBF% (change rate of rCBF) had a median reduction of perfusion of 12.19% (SD 2.68%).

Discussion

MMD is characterized by a chronic steno-occlusive and progressive vasculopathy affecting the terminal segment of the internal carotid arteries as well as the

development of pathological collateral networks to provide an alternative route for cerebral perfusion.^{2,3} Due to this imperfect and insufficient attempt to compensate for reduced cerebral perfusion, MMD patients are susceptible of presenting ischemic strokes or TIAs. In general, it is believed that MMD patients are more liable to BP changes than the general population, making them at risk of suffering additional lesions associated to hypoperfusion or hyperperfusion during the perioperative management. Moreover, the literature lacks studies demonstrating the direct relationship between BP changes and CBF/perfusion for MMD patients. Here, we present the first study regarding the impact of targeted BP changes on CBF in MMD patients as assessed by SPECT.

Benefits and limitations of SPECT in MMD

SPECT studies have been widely used in MMD patients to determine the presence of perfusion deficits, including the evaluation of the cerebrovascular reserve and postoperative assessments.^{1,7,10–12} This imaging technique provides quantitative or semiquantitative values of brain hemodynamics (CBF and CVR) based on whole brain images. Additionally, it is readily available and can be used at bedside and in children as well as adults.⁵

SPECT studies have poor spatial resolution, and rCBF values are generated through statistical comparisons from normal controls to represent areas of abnormal perfusion. In addition to these limitations, patients are exposed to radiation during the procedure.^{1,10–12} Despite these limitations, SPECT studies offer an advantage compared to PET or other hemodynamic evaluation methods since they detect misery perfusion with high sensitivity and have a high negative predictive value in MMD patients.¹³

Cerebral autoregulation changes

Cerebral autoregulation (CA) is thought to play an important role in CBF homeostasis. Per the classic description of Lassen in 1959, the CBF is maintained at a constant level across a wide range of mean arterial BP (60–150 mmHg).¹⁴ This classical concept of CA based on steady-state CBF and BP measurements (patients with hypertensive and hypotensive disorders) had dominated the medical consensus regarding CA and BP.¹⁵ However, during the last few decades, the concept of dynamic CA emerged based on high fidelity evaluations of CBF velocity and distribution. Dynamic CA loosely refers to the regulation of cerebrovascular resistance against dynamic changes in BP.^{16,17} Despite the development of new methods and models of dynamic CA quantification, the translation of these

findings into clinical practice has been limited.^{18–21} Therefore, our study is of clinical relevance to confirm the presence of dynamic, short changes on BP and its effects on CBF in a pathological cohort (i.e. MMD patients).

Exercise-induced BP changes and CBF in MMD patients

Exercise poses an important challenge for CA. During dynamic or resistance exercises, SBP or MAP can increase by 20–30%, combined with a slight decrease or no change in diastolic BP.²² However, despite these BP elevations, the CBF only increases by 15–25% and up to 70% of maximal oxygen uptake. Subsequently, CBF declines toward or below baseline during hyperventilatory-induced hypocapnia despite progressive increases in perfusion pressure.²³ These previous values are described for healthy populations. However, they are not in concordance with our findings in MMD patients, who showed an approximately 15% increase of perfusion when MAP values were 10–20% higher than RBP values. Therefore, this data leads to the possibility that dynamic CA is limited in MMD patients, and the possibility of suffering from hyperperfusion syndromes related to high BP is present.

Effects of hypotension in CBF of MMD patients

It is believed that short periods of hypotension do not cause brain dysfunction because compensatory CA prevents brain hypoperfusion from being activated.²⁴ However, several studies in elderly patients showed that CA does not necessarily protect the brain from chronic low BP and low cardiac output, something that could result in CBF insufficiency and its accompanying consequences.^{24–26} In our group of RLBP patients, there was a decrease in perfusion of previously affected areas of approximately 10–15% demonstrating the direct relationship between BP and CBF and the susceptibility of MMD patients in trying to maintain a normal compensatory CA.

Perioperative BP management

It is recommended by the Japanese guidelines for diagnosis and treatment of MMD⁷ to maintain a strict BP control, normocapnia, and adequate fluid balance during the perioperative period of MMD patients in order to prevent possible complications such as ischemia in the non-surgical site or hyperperfusion syndromes following revascularization procedures. This recommendation is in correlation to our findings, where MMD disease patients are liable or susceptible to small CBF variations during dynamic BP changes.

Limitations

The present study has certain some limitations. First, it is not a direct comparison of the impact of BP changes in CBF between a healthy control cohort and MMD patients, which is not possible to justify because of the unnecessary radiation exposure and imaging studies on healthy patients. Second, this study has no evaluation of the relationship between perfusion areas and treatment selection and patients' outcome. However, these parameters are out of the scope of this manuscript, as our primary intention was to elucidate the changes on CBF and perfusion based on targeted BP values. Additionally, the volume of previous stroke areas was not considered for analysis, which could reduce the sensitivity of SPECT studies in the presence of lacunar infarcts when evaluating hemispheres; however, our study cohort comprised only patients with NIH stroke scale less than 2; therefore, this cohort did not include severe volume strokes. Third, the use of physical exercise to increase MAP may induce hyperventilatory-hypocapnia, which could decrease the cerebral perfusion as a compensatory mechanism. However, in our cohort, increasing MAP values associated to increased CBF even at lower PCO₂ values, leading to the possible idea that BP (MAP) has a more direct correlation on cerebral perfusion than PCO₂. Fourth, measurements and results of SPECT studies tend to vary among the different cerebral regions (due to tracer uptake) and perfusion patterns even in healthy cohorts. In some circumstances, a small intersubject variability in quantitative analysis among healthy patients exists. On the contrary, visual analysis carries a considerable intersubject variability when comparing similar regions.²⁷ Therefore, in our study, we initially performed visual analysis for ROIs selection followed by semiquantitative analysis based on cerebellar blood flow rate in order to minimize the presence of intersubject variability.

Age decreases tracer perfusion patterns in several regions including the anterior and posterior cingulate cortices, medial temporal region, superior prefrontal region, and parietal cortex, which could lead to errors while comparing different cortices. Additionally, Tanaka et al.²⁷ demonstrated an increased cerebellum-to-cerebral cortex tracer uptake ratio with age and maybe related to the fact that cerebellar metabolic activity increased with age because of a greater decline in cerebral metabolic activity.²⁷ Based on this, the probability of underestimating the blood flow patterns along the different hemispheres exists when comparing to cerebellar blood flow in relationship to patient's age.

An additional limitation of our study is the absence of combined qualitative parameters to assess CBF as well as the inclusion of cerebral metabolism measurements (such as carbon dioxide in blood or expired air). However, our main idea was to demonstrate the different changes of CBF associated to minimal BP modifications and the previously known clinical susceptibility of MMD patients.

During our imagenological analysis, we did not consider symptomatic hemispheres to compare to the contralateral side, first of all because our patient cohort suffered bilateral MMD. Therefore, we considered more reasonable to compare the cerebellar blood flow (considered normal in healthy patient) with different hemispheres. However, for future studies requiring unilateral evaluation, it could be useful to evaluate first the symptomatic hemispheres when possible.

Conclusions

CBF of moyamoya disease patients is susceptible to small (± 10 –20% of MAP) BP changes. SPECT imaging is useful in observing CBF variations under targeted BP values. CA in moyamoya disease patients might be affected due to short, dynamic variations in BP. Therefore, in these patients, it is important to maintain a strict BP monitoring during the perioperative management to prevent further complications.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Conception and design: Zhao Liming, Sun Weiliang, Li Chaoyue, and Hugo Andrade-Barazarte. Analysis and interpretation of data: Zhao Liming, Sun Weiliang, Jia Jia, Liu Yang, Liang Hao, and Christopher Ludtka. Drafting the article: Zhao Liming, Sun Weiliang, Felix Goehre, Ajmal Zemmar. Critically revising the article: Zhao Liming, Sun Weiliang, Li Chaoyue, Hugo Andrade-Barazarte, Juha Hernesniemi, Behnam Rezai Jahromi, and Li Tianxiao. Reviewed submitted version of manuscript: Zhao Liming, Sun Weiliang, Li Chaoyue, Hugo Andrade-Barazarte, Behnam Rezai Jahromi, Jia Jia, Liu Yang, Liang Hao, Christopher Ludtka, Felix Goehre, Ajmal Zemmar, Juha Hernesniemi, and Li Tianxiao. Statistical analysis: Sun Weiliang. Study supervision: Hugo Andrade-Barazarte and Li Chaoyue.

ORCID iDs

Behnam Rezai Jahromi <https://orcid.org/0000-0003-3937-2816>

Hugo Andrade-Barazarte <https://orcid.org/0000-0001-6673-6369>

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