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Assessment of the Cerebral Hemodynamic Benefits of Carotid Artery Stenting for Patients with Preoperative Hemodynamic Impairment Using Cerebral Single Photon Emission Computed Tomography (SPECT) and Carbon Dioxide Inhalation

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to evaluate the effects of carotid artery angioplasty and carotid artery stenting (CAS) on cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) in patients with preoperative cerebrovascular hemodynamic impairment.


Material/Methods: Seventeen patients with unilateral severe internal carotid artery (ICA) stenosis and ipsilateral CVR impairment underwent CAS. CBF and CVR were measured by single photon emission computed tomography (SPECT) with inhalation of carbon dioxide (CO₂) one week before and three months after CAS. Sixty-eight ROIs in the middle cerebral artery (MCA) territory were analyzed in 17 patients.

Results: Before CAS, CVR was impaired in all ROIs. CBF was impaired in 16 ROIs (23.5%). The percentage of ROIs with impaired CBF was significantly increased in patients with ≥90% carotid artery stenosis (p=0.047) without collateral flow through the circle of Willis (p=0.005). CAS significantly increased CVR in ROIs with a normal preoperative CBF and impaired CVR, indicating mild hemodynamic impairment (0.9±6.7% vs. 4.9±8.6%) (p=0.014). CAS significantly increased CBF in ROIs with preoperative impaired CBF and impaired CVR, indicating severe hemodynamic impairment (79.1±7.5% vs. 86.7±10.0%) (p<0.001). Following CAS, ROIs with normal CBF and impaired CVR had a significantly increased percentage of improved CVR (p=0.047); ROIs with impaired CBF and impaired CVR had a significantly increased percentage of improved CBF (p=0.027).

Conclusions: The severity of preoperative hemodynamic impairment, which is related to the degree of carotid artery stenosis and cerebral collateral flow, may influence hemodynamic benefits by CAS.

MeSH Keywords: **Carbon Dioxide • Carotid Stenosis • Cerebrovascular Circulation**

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Background

Carotid artery stenosis is an important cause of ischemic stroke [1]. The predominant pathophysiological mechanism for ischemia usually follows a thromboembolic event, but narrowing of the lumen of the carotid artery and its intracerebral branches can also result in cerebral hypoperfusion and may even potentiate the effects of distal embolization [2]. Cerebral blood flow (CBF) and cerebrovascular reactivity (CVR), which represent the change of CBF in response to vasoactive stimulation, are two important intracranial hemodynamic parameters [2,3]. Previously published studies have shown that resting CBF and CVR may predict future ischemic stroke in patients with carotid artery stenosis or occlusion [4–10].

Direct surgical revascularization techniques, such as carotid endarterectomy, have been shown to increase cerebral blood flow in ipsilateral cerebral territories or hemispheres for the patients with carotid artery stenosis [11]. During the last decades, driven by advancements in interventional technology and the accumulation of procedural expertise, carotid angioplasty and carotid artery stenting (CAS) have become therapeutic alternatives to carotid endarterectomy and can reduce mortality from carotid artery stenosis and stroke [12,13].

However, the intracranial changes in CBF and CVR that follow CAS are still unclear. Several factors, including the degree of vascular stenosis [14,15], tandem stenosis [16], the presence of unilateral or bilateral lesions [17,18], the degree of cerebral collateral circulation [19,20], symptomatic presentation [21], and preoperative cerebral hemodynamic impairment [22–25], may influence the benefits to CBF and CVR following CAS. Because preoperative cerebral hemodynamic status is associated with the degree of vascular stenosis [23,26,27], cerebral collateral circulation [2,28], and symptomatic presentation [4–10], we hypothesize that preoperative intracranial hemodynamic impairment might be the most important factor for CAS to benefit the CBF and CVR.

Therefore, the aim of this study was to evaluate the effects of CAS on CBF and CVR in patients with preoperative cerebrovascular hemodynamic impairment. In this study, patients were selected with unilateral severe internal carotid artery (ICA) stenosis and ipsilateral CVR who underwent stenting, and measured the intracranial resting CBF and CVR in the ipsilateral middle cerebral artery (MCA) territory by single photon emission computed tomography (SPECT) with inhalation of carbon dioxide (CO₂) before and after CAS, using a previously described model [29].

Material and Methods

Patients included in the study

Patients who underwent carotid artery stenting (CAS) at the General Hospital of the Air Force of the Chinese Peoples' Liberation Army, Beijing, China between October 2014 and December 2015 were invited to participate in this study. Patients provided written informed consent to participate in the study, which was approved by the Institutional Review Committee of the General Hospital of the Air Force of the Chinese Peoples' Liberation Army, China.

Eligibility criteria included the following: unilateral, severe (70–99%) stenosis of the internal carotid artery (ICA); the occurrence of transient ischemic attacks (TIAs) or moderately disabling ischemic stroke, as defined by the National Institute of Health Stroke Scale (NIHSS) ≤ 3 , attributable to ICA stenosis within the previous three months; no or ≤ 15 mm infarction in the territory of the middle cerebral artery (MCA) and cerebellum on computed tomography (CT) or magnetic resonance imaging (MRI); preoperative impairment of cerebrovascular reactivity (CVR) in the ipsilateral MCA territory.

Study exclusion criteria included the following: occlusion of the ICA; stenosis ($\geq 50\%$) or occlusion of other major cerebral arteries; ICA stenosis caused by diseases other than atherosclerosis, such as autoimmune disorders, and vasculitis; contraindications for CAS, such as allergy to iodine contrast agents; a previous endovascular stent, carotid artery endarterectomy, or extracranial-intracranial (EC-IC) bypass surgery; an embryonic posterior cerebral artery; severe cardiac, pulmonary, or renal disease; contraindications for single photon emission computed tomography (SPECT) and carbon dioxide (CO₂) inhalation.

Patient clinical assessment

Patient demographic details, including age and gender, were recorded. Vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking were recorded. The degree of stenosis of the ICA and cerebral collateral flow through the Circle of Willis were assessed by digital subtraction angiography (DSA), according to the method of North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET), and the degree of stenosis was divided into low-grade severe stenosis (LGSS) of $< 90\%$ and high-grade severe stenosis (HGSS) of $\geq 90\%$ [15].

Single photon emission computed tomography (SPECT) measurements

Resting and CO₂-challenged ethylcysteinate dimer (^{99m}Tc-ECD) (China Institute of Atomic Energy, China) SPECT brain scans were

carried out in a dark and quiet environment using a two-day protocol, according to the method in our previously published study [29]. On the first day, the resting brain perfusion examination was performed with an intravenous injection of 925 MBq of ^{99m}Tc -ECD into the antecubital vein. The images were obtained using the Infinia Hawkeye SPECT scanner (General Electric Company, USA) after one hour. The images were taken at every 6° during rotation of 360° and at a rate of 35 seconds per frame. The data were acquired on a 128×128 matrix.

On the second day, CO₂-challenged brain perfusion examination was carried out in a dark and quiet environment by inhalation of 5% CO₂ and 95% O₂ (carbogen). Patients wore a face mask with a one-way valve, which was connected to a 2-L steel 10-KPa carbogen bottle. The pressure of end-tidal CO₂ (Pet CO₂) was measured and hypercapnia (Pet CO₂=50 mmHg) was maintained for 60 seconds before intravenous infusion of ^{99m}Tc -ECD. SPECT brain scans were performed one week before CAS and three months (mean, 89±7 days) after CAS. All the complications associated with the procedures in this model, including restenosis (≥30% stenosis in the stents) were recorded during follow-up.

Selection of the region of interest (ROI) and data analysis

Selection of the region of interest (ROI) and data analysis was performed, as previously described [30]. The NeuroMatch Software package (GE Medical Systems, Segami Corporation, Columbia, MD, USA) was used to select the ROIs. Four imaging slices of cerebral hemisphere were selected on the orbitomeatal line (OML) +55 mm, +58 mm, +61 mm, and +64 mm. Six pairs of sphenoid mirrored ROIs over the cortical gray matter were drawn at each slice of the cerebral hemisphere (Figure 1). Four middle ROIs corresponding to the ipsilateral MCA territory of stenosis of the ICA stenosis were selected, and the mean value of the four slices in each ROI was calculated for data analysis. However, mirrored ROIs were also drawn in one slice of the cerebellar hemisphere (OML + 15 mm) for normalization of cerebral hemodynamic parameters. The ratio of radioactive counting obtained from the ROI on the cerebral hemisphere to those from the ROI on the ipsilateral cerebellar hemisphere was calculated automatically by computer analysis for the cerebral hemodynamic normalization.

Assessment of cerebral blood flow (CBF) and cerebrovascular reactivity (CVR)

In contrast with CBF and CVR in the whole middle cerebral artery (MCA) territory, CBF and CVR in each ROI was considered to be regional CBF (rCBF) and regional CVR (rCVR) [14,17]. rCBF was defined by normalization of cerebral radioactive counting. The impaired rCBF was defined as $\text{rCBF}_{\text{stenosis}}/\text{rCBF}_{\text{mirror}} \leq 90\%$. Normal rCBF was defined as $\text{rCBF}_{\text{stenosis}}/\text{rCBF}_{\text{mirror}} > 90\%$. The rCVR

was evaluated by the following formula: $\text{rCVR} (\%) = [(\text{rCBF}_{\text{CO}_2\text{-challenged}} - \text{rCBF}_{\text{basal}}) / \text{rCBF}_{\text{basal}}] \times 100\%$. The impaired rCVR was defined as ≤10%, and normal rCVR was defined as >10%. Patients with CVR impairment were defined as patients whose four ROIs in the ipsilateral MCA territory all had impaired rCVR. The improvement in rCBF following CAS was defined as $\text{rCBF}_{\text{after CAS}} > \text{rCBF}_{\text{before CAS}}$. The improvement in rCVR following CAS was defined as $\text{rCVR}_{\text{after CAS}} > \text{rCVR}_{\text{before CAS}}$.

Statistical analysis

Continuous variables were presented as the mean and standard deviation (SD). Categorical variables were reported as the percentage of patients in the subgroup. The paired t-test and the Student's t-test were used for comparisons of continuous variables. The chi-squared (χ^2) test was used for the comparisons of categorical variables. The statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS version 16.0 software (IBM, Amon, New York, USA).

Results

Seventeen patients were included in the study and underwent and performed single photon emission computed tomography (SPECT) brain scans before and after carotid artery stenting (CAS). The clinical characteristics of the patients included in the study are shown in Table 1. All 17 patients obtained the procedural success from CAS, and there were no complications during the peri-operative period or follow-up.

There were a total of 17×4=68 regions of interest (ROIs) for data analysis. Before CAS, the regional cerebral blood flow (CBF) (rCBF) and regional cerebrovascular reactivity (CVR) (rCVR) in the ROIs were 87.2±10.3% (range, 66.0–114.8%) and -0.7±6.4% (range, -16.0–9.0%), respectively. The rCVR was impaired in all the ROIs, but the rCBF was impaired in only 16 ROIs (23.5%). There were increased percentages of ROIs with impaired rCBF in the patients with high-grade severe stenosis (HGSS) (≥90%) and no collateral flow through the Circle of Willis (Table 2).

After CAS, the rCBF was 89.5±9.2% (range, 69.8–106.3%), which was significantly increased when compared with the rCBF before CAS ($p=0.017$). We further divided the whole sample into two groups, according to the preoperative hemodynamic status: the ROIs with a normal rCBF and impaired rCVR and the ROIs with impaired rCBF and impaired rCVR. However, rCBF after CAS was significantly increased when compared with before CAS only in the ROIs with impaired rCBF and impaired rCVR (79.1±7.5% vs. 86.7±10.0%) ($p < 0.001$). A higher percentage of the ROIs with preoperative impaired rCBF and impaired rCVR showed improvement in the rCBF after CAS compared with the ROIs with preoperative normal rCBF and impaired rCVR (81.3%

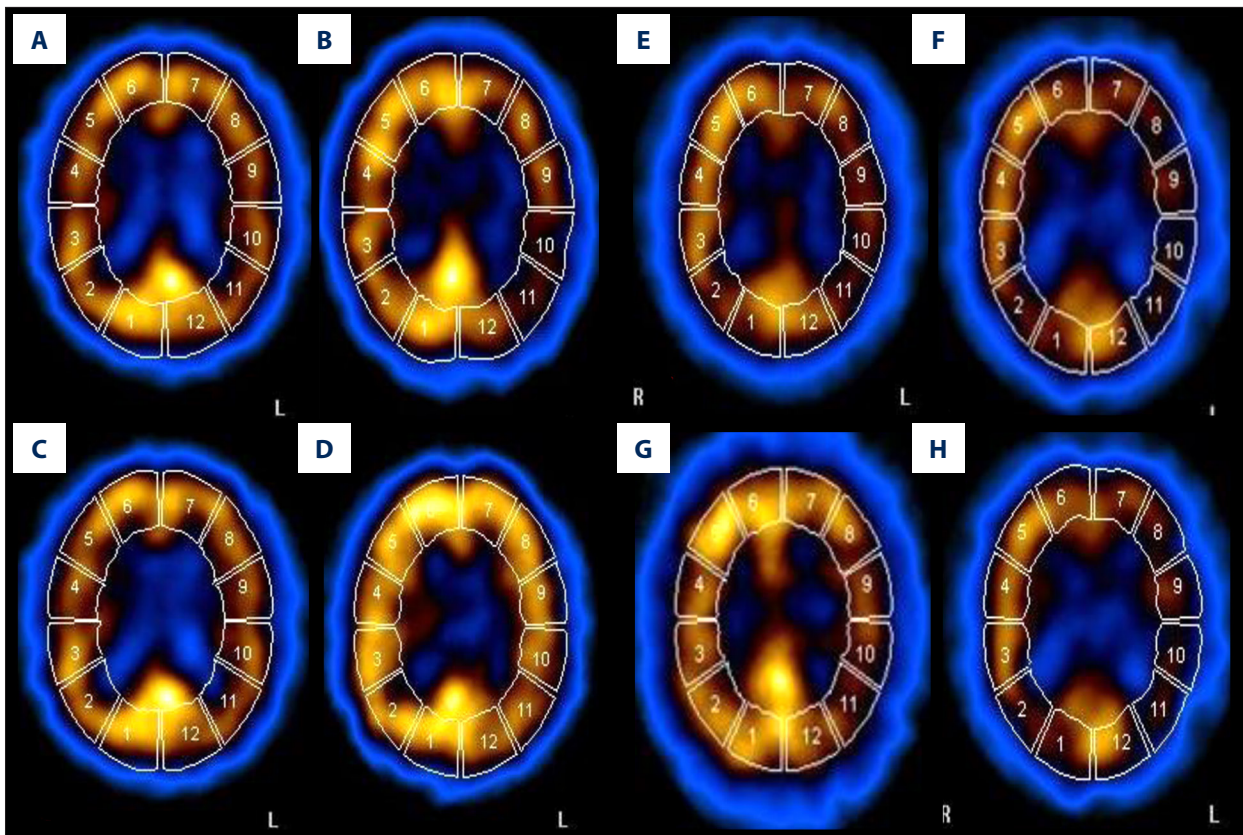


Figure 1. The effect of the different preoperative hemodynamic impairment on the model of the region of interest (ROI) cerebral blood flow (rCBF) and cerebrovascular reactivity (rCVR) improvement following carotid artery stenting (CAS). (A–D) Single photon emission computed tomography (SPECT) images show that the regions of interest (ROIs) (8–11) with normal cerebral blood flow (rCBF) and impaired cerebrovascular reactivity (rCVR) before treatment showed improved rCVR and unimproved rCBF after carotid artery stenting (CAS). (A) Baseline, before CAS, shows that that 8–11 ROIs have normal rCBF (equal tracer uptake compared to mirror). (B) The carbon dioxide (CO₂) challenge before CAS, shows that these ROIs have impaired rCVR, with decreased tracer uptake compared with A. after CO₂ inhibition. (C) Baseline, after CAS, shows that the normal rCBF was unchanged by CAS, with tracer uptake similar to A. (D) The CO₂ challenge after CAS shows that the impaired rCVR improved after CAS, with increased tracer uptake compared to B, after CO₂ inhibition. (E–H) SPECT images show that the ROIs (8–11) with impaired rCBF and impaired rCVR before treatment showed improvement of the rCBF but not the rCVR following CAS. (E) Baseline, before CAS, shows that 8–11 ROIs show impaired rCBF, with decreased tracer uptake compared to mirror. (F) The CO₂ challenge before CAS shows that the ROIs show impaired rCVR, with decreased tracer uptake compared to E, after CO₂ inhibition. (G) Baseline, after CAS, shows that the impaired rCBF improved by CAS, with increased tracer uptake compared to E. (H) The CO₂ challenge after CAS shows that the impaired rCVR was unchanged after CAS, with the tracer uptake still decreased and similar to F, after CO₂ inhibition.

vs. 50%) ($p=0.027$) (Figure 2). After CAS, the rCVR was $2.4\pm 8.0\%$ (range, -15.0 – 24.0%), which was significantly increased compared with the rCVR before CAS ($p=0.017$).

After stratification by preoperative hemodynamic status, the rCVR after CAS was significantly increased compared with that before CAS only in the ROIs with normal rCBF and impaired rCVR ($0.9\pm 6.7\%$ vs. $4.9\pm 8.6\%$) ($p=0.014$). A higher percentage of the ROIs with preoperative normal rCBF and impaired rCVR showed improvement in rCVR after CAS compared with the ROIs with preoperative impaired rCBF and impaired rCVR (59.6% vs. 31.3%) ($p=0.047$) (Figure 2).

Discussion

In this study, single photon emission computed tomography (SPECT) brain scans with inhalation of carbon dioxide (CO₂) were used to assess the cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) in regions of interest (ROI) (rCBF and rCVR) before and after carotid artery stenting (CAS) in patients with unilateral severe internal carotid artery (ICA) stenosis and ipsilateral CVR impairment. The findings were that rCBF was impaired only in the partial ROIs, and rCVR was impaired in all the ROIs. The patients with high-grade severe stenosis (HGSS) of $\geq 90\%$ and without collateral flow through

Table 1. Characteristics of patients with carotid stenosis.

Characteristics	Value
Age (years)	67.4±7.9 (49–78)
Gender (male)	11 (64.7%)
Hypertention(yes)	12 (70.6%)
Diabetes mellitus(yes)	11 (64.7%)
Hyperlipemia(yes)	12 (70.6%)
Smoking(yes)	7 (41.2%)
Stenosis location	
Left side	10 (58.8%)
Right side	7 (41.2%)
Preoperative stenosis degree (%)	85.7±9.8 (70–97)
Stenosis severity classifications	
<90%	9 (52.9%)
≥90%	8 (47.1%)
Collateral flow through CoW	
None	11 (64.7%)
Though AcomA only	2 (11.8%)
Though PcomA only	4 (23.5%)
Clinic symptoms	
Transient ischemic attack	6 (35.3%)
Cerebral infarction	11 (64.7%)
Postoperative stenosis degree (%)	6.2±5.2 (0–15)

CoW – Circle of Willis; AcomA – anterior communicating artery; PcomA – posterior communicating artery. Categorical variables are presented as number (percentage) and continuous variables are presented as means ± standard deviation (Range).

Table 2. Association of rCBF impairment in ROIs of ipsilateral MCA with stenosis severity and cerebral collateral flow in patients of carotid stenosis.

Characteristics	Normal rCBF (52 ROIs)	Impaired rCBF (16 ROIs)	p
Stenosis severity classifications			
<90%	86.1%	13.9%	0.047
≥90%	34.4%	65.6%	
Collateral flow through CoW			
None	65.9%	34.1%	0.005
Though AcomA/PcomA	95.8%	4.2%	

rCBF – regional cerebral blood flow; ROIs – region of interests; MCA – middle cerebral artery; CoW – circle of Willis; AcomA – Anterior communicating artery; PcomA – Posterior communicating artery.

Circle of Willis had a significantly increased percentage of the ROIs with impaired rCBF. CAS preferentially improved the rCVR in the ROIs with preoperative normal rCBF and impaired rCVR and improved the rCBF in the ROIs with preoperative impaired rCBF and impaired rCVR (Figure 1).

SPECT is the most readily available nuclear medicine technique for the assessment of cerebral hemodynamics [3]. Previously published studies have demonstrated that brain SPECT in conjunction with an acetazolamide challenge was a useful method to evaluate CVR in patients with vaso-occlusive disease [5,31]. However, because acetazolamide is associated with adverse effects, such as headache, nausea, dizziness, tinnitus, numbness of the extremities, and Stevens–Johnson syndrome [32], in this study brain SPECT with CO₂ inhalation was used to measure CVR. In a previously published study by our group, this approach was shown to be a reliable and useful model the assessment of CVR [29], and CO₂ inhalation has previously been shown to be both safe and tolerable [27].

When chronic arterial stenosis causes a progressive decrease in cerebral perfusion pressure (CPP), CVR decline occurs in the early stage of cerebral hemodynamic impairment and CBF decline occurs in the late stage of cerebral hemodynamic impairment [2,31]. Therefore, our study showed two kinds of cerebral hemodynamic status in the ROIs of the ipsilateral MCA territory: mild impairment (normal rCBF and impaired rCVR) and severe impairment (impaired rCBF and impaired rCVR). There were more ROIs of severe hemodynamic impairment in the patients with HGSS and without collateral flow through the Circle of Willis. This result supports the view that cerebral hemodynamics are determined not only by the degree of severity of carotid artery stenosis [23,26,27], but also by the cerebral collateral circulation [2,19,28].

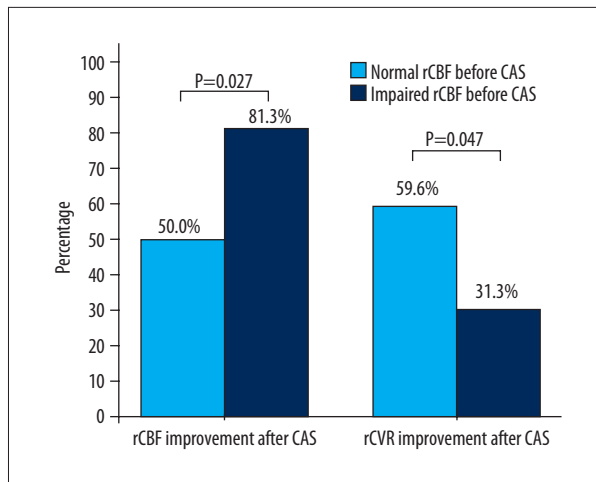


Figure 2. Comparison of the percentage improvement of the postoperative region of interest (ROI) cerebral blood flow (rCBF) and cerebrovascular reactivity (rCVR) following carotid artery stenting (CAS) between the different preoperative hemodynamic status groups. A higher percentage of regions of interest (ROIs) with preoperative impaired cerebral blood flow (rCBF) and impaired cerebrovascular reactivity (rCVR) show improvement in rCBF following carotid artery stenting (CAS), and a higher percentage of ROIs with preoperative normal rCBF and impaired rCVR show improvement in rCVR following CAS.

Previously published studies have shown that CAS could improve cerebral hemodynamic parameters by increasing the carotid artery lumen diameter and providing improved cerebral vascular perfusion [16,33,34]. However, some recent studies have shown that this improvement was often obtained only in patients with preoperative hemodynamic impairment, especially patients with preoperative CVR decline [14,15,22,23,25]. Our study also found that CAS increased the rCBF and rCVR in the ROIs in patients with preoperative rCVR impairment. Also, Goode et al. reported that carotid endarterectomy was able to provide the most benefit to patients with impaired preoperative CVR [24]. Therefore, preoperative hemodynamic impairment is an important and basic condition for hemodynamic benefit from CAS.

The findings of the present study further demonstrated that the severity of preoperative cerebral hemodynamic impairment determined the models of hemodynamic benefit by CAS. CAS preferentially improved the rCVR in the mildly hemodynamic impaired ROIs (normal rCBF and impaired rCVR) and improved the rCBF in the severely hemodynamic impaired ROIs (impaired rCBF and impaired rCVR). These results can be explained by the following mechanisms. In the mildly hemodynamic impaired ROIs, CAS might improve the CVR by preventing vasodilatation, and CAS benefits CBF little because CBF is not compromised at baseline [19]. In the severely hemodynamic impaired ROIs, the extreme vasodilatation with the exhaustion

of CVR due to chronic cerebral ischemia distal to the critical carotid artery stenosis can impact the elasticity and stiffness of the cerebral arterial system, and lead to the loss of normal vasoconstriction and the impairment of cerebrovascular autoregulation [22,25]. Therefore, CAS might increase the CBF through revascularization and the increase of CPP but not recover CVR in these ROIs. This view is supported by the findings of Oshida et al. who showed that preoperative exhausted CVR (with impaired rCBF) was associated with an increased risk of cerebral hyperperfusion, which greatly increased the ipsilateral CBF following the revascularization of carotid artery stenosis [35]. Although the findings of the present study support this phenomenon, it is not possible to exclude the fact that, in the long term, vasoconstriction and cerebrovascular autoregulatory mechanisms might recover following CAS, as has been shown by some previous studies [23,36].

This study had several limitations. First, the number of subjects included in this study was small, but this may not negate the importance of the study findings. In this study, we divided the territory of the middle cerebral artery (MCA) into four ROIs, which ensured that there were more ROIs corresponding to the detailed brain regions analyzed, and which, we believed, strengthened the statistical power of the analysis of the study findings. The study also excluded some conditions, which could confuse the cerebral hemodynamic benefits resulting from CAS, such as preoperative normal cerebral hemodynamics, bilateral carotid stenoses, and tandem stenosis, these exclusions might support the study findings. However, further studies with a larger patient sample size will be needed in future to confirm the findings of this study. The second main limitation of this study was that a relative value was used, that of normalized radioactive counting obtained in the ROIs of the MCA territory compared with the ipsilateral cerebellar hemispheres, instead of quantitative analysis. However, a recent study proposed that the use of this form of relative value might be a more sensitive biomarker than an absolute value in clinical applications as it minimizes inter-subject variations [37].

Conclusions

The findings of this study support that the preoperative hemodynamic status not only determines whether or not patients obtain cerebral hemodynamic benefit from carotid artery stenting (CAS) but has also described a model that demonstrates the clinical benefits of CAS. CAS might be a preferred treatment option to improve cerebrovascular reactivity (CVR) in patients with mild preoperative hemodynamic impairment, and to improve cerebral blood flow (CBF) in patients with severe hemodynamic impairment. Future studies should continue to be undertaken to evaluate cerebrovascular hemodynamic parameters before treatment with CAS.

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Conflict of interest

None.