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The Significance of Cerebral Hemodynamics Imaging in Carotid Endarterectomy: A Brief Review

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Abstract

The indication of carotid endarterectomy (CEA) is principally determined by the presence or absence of symptoms and the degree of stenosis. However, the results of recent studies have implicated the usefulness of cerebral hemodynamics imaging for perioperative assessments. Many studies using single-photon emission computed tomography (SPECT) have demonstrated that cerebral hemodynamics imaging assessments are useful in the prediction and assessment of post-CEA hyperperfusion. In studies using transcranial Doppler ultrasonography, SPECT, or positron-emission tomography (PET), cerebral hemodynamic impairment is highly likely to increase the risk of cerebral infarction in patients with asymptomatic carotid artery stenosis. In other studies using the same modalities, cerebral hemodynamic impairment might be related to cognitive impairment in carotid artery stenosis, and this cognitive impairment might be improved with CEA. Nuclear medicine techniques involve the injection of radioactive tracers. Arterial spin labeling (ASL) is an emerging technique of perfusion magnetic resonance imaging (MRI) for the noninvasive measurement of cerebral perfusion. ASL could detect pathologic states such as hypoperfusion, impaired vasoreactivity, and postoperative hyperperfusion activities that are equivalent to SPECT. In addition, regional perfusion imaging visualizes cerebral perfusion territories by selective ASL. In conclusion, cerebral hemodynamic imaging would be useful for the perioperative assessment of CEA. However, there is a lack of sufficient scientific evidence to confirm the benefits, necessitating further study.

Key words: carotid endarterectomy, carotid stenosis, cerebral hemodynamics

Introduction

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are effective treatment methods for preventing cerebral infarction in carotid artery stenosis. The applicability of these therapies is principally determined by the presence or absence of symptoms and the degree of stenosis.[1–3] In this context, what is the meaning of assessing cerebral hemodynamics when performing CEA? Currently, the assessment of cerebral hemodynamics in the CEA perioperative period is considered to be significant for three reasons: (1) the prediction and assessment of hyperperfusion syndrome, (2) serving as a reference when determining the suitability of therapy, and (3) assessing the relationship between cognitive impairment and cerebral hemodynamic impairment. In the present article, these three points will be explored with examinations of cases and references to relevant literature.

Positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) are currently considered the standards for the assessment of cerebral hemodynamics. However, these nuclear medicine techniques involve the injection of radioactive tracers. Considering the noninvasive measurement of cerebral perfusion, a magnetic resonance imaging (MRI) technique known as arterial spin labeling (ASL) is particularly useful because it uses magnetically labeled blood as an endogenous tracer, which will also be discussed in connection with CEA briefly in the last section.

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I. Prediction and assessment of hyperperfusion syndrome

When considering the significance of cerebral hemodynamics assessment in CEA, the first issue to consider is the prediction and assessment of hyperperfusion syndrome. As a result of hyperperfusion following CEA, patients may develop the classic clinical triad which includes severe unilateral headache, face and eye pain, seizures, and intracerebral hemorrhage. However, many cases do not present with such dramatic symptoms.[4–7] SPECT, the most common imaging method for cerebral hemodynamics, can assess cerebral blood flow (CBF)

and cerebrovascular reactivity (CVR) quantitatively and three dimensionally, thus making it the optimal method for detecting hyperperfusion. Many studies have determined that hyperperfusion and hyperperfusion syndrome occur only when the CBF and CVR are reduced.[4,8,9] Accordingly, hyperperfusion can be predicted and diagnosed with SPECT. Fig. 1 shows typical SPECT findings of hyperperfusion syndrome cases.

In hyperperfusion syndrome, strict blood pressure control is required to prevent cerebral hemorrhage.[4,6,7,10] However, hyperperfusion does not necessarily occur when cerebral hemodynamics are impaired; rather, it also depends on when the control of blood pressure is started.[6,7,10] When assessing internal carotid artery (ICA) blood flow using a flowmeter during the CEA of 65 patients, a significant linear correlation was observed between the ICA flow increase after reconstruction and ipsilateral CBF increase on the first postoperative day as a percentage of the preoperative CBF, with the threshold defined as follows: CBF increase (%) = −12.1 + 0.41 × ICA flow increase (correlation coefficient r = 0.64, P = 0.0024), only in the reduced CVR group (Fig. 2, right panel) but not in the normal CVR group (Fig. 2, left panel).[4] If the formula is reversed, the 95% confidence interval (CI) associated with a predicted mean ICA flow increase for 100% CBF increase on the first postoperative day is 142–216 mL/min. In fact, postoperative hyperperfusion or hyperperfusion syndrome occurred only in cases with marked increases in the ICA blood flow after revascularization (Fig. 2, red circle) in the reduced CVR group. A marked increase in the ICA blood flow (100–200 mL) was also observed even in the normal CVR group. However, these patients with normal CVR never experienced postoperative hyperperfusion or hyperperfusion syndrome. Based on these findings,

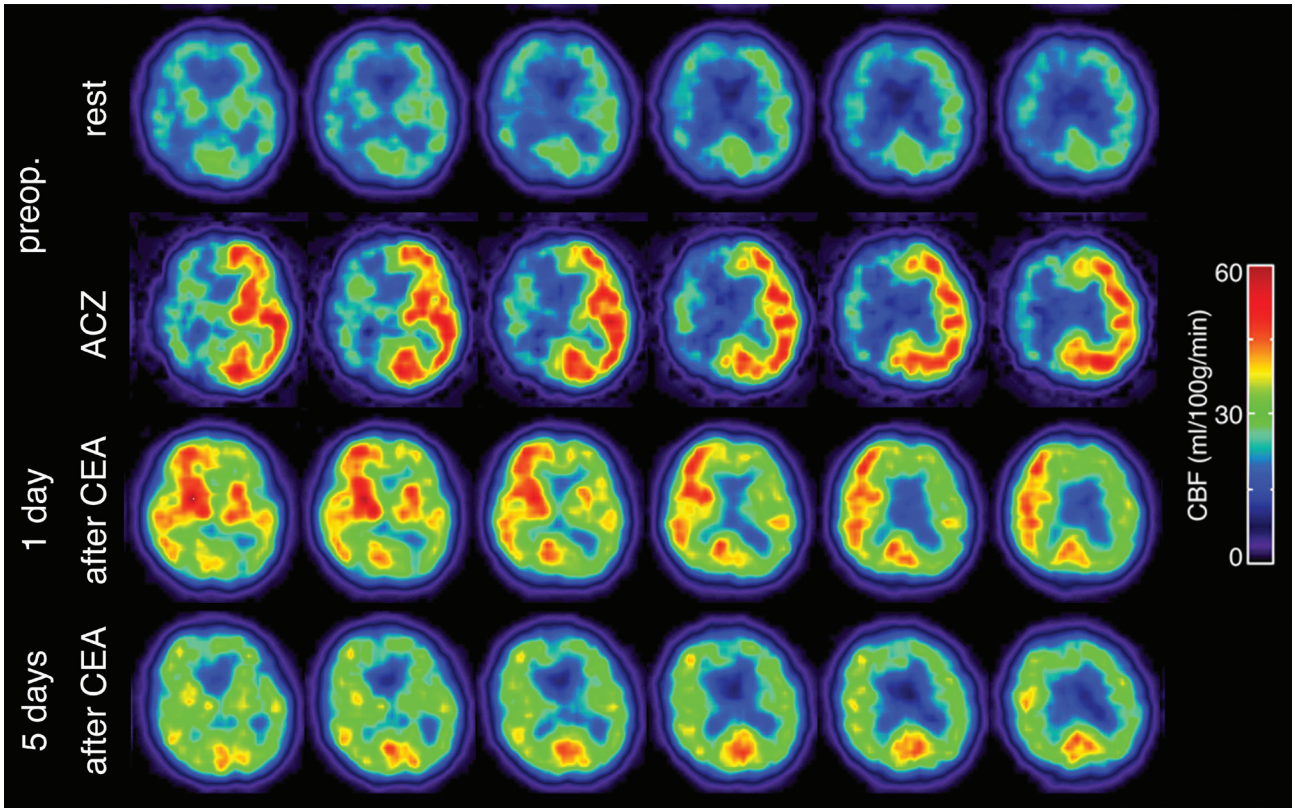

Fig. 1 A case of hyperperfusion with severe right carotid stenosis. *First row*: Preoperative resting SPECT. Moderate hypoperfusion is observed in the right ICA territory. *Second row*: Preoperative acetazolamide (ACZ)-challenge SPECT. Little CBF response to acetazolamide is observed in the same territory. *Third row*: SPECT on the first postoperative day clearly demonstrates hyperperfusion in the right ICA territory. A moderate CBF increase is also observed in the left ICA territory. *Fourth row*: SPECT 5 days after CEA. Preoperative hypoperfusion returns to almost normal, but a slight CBF increase is still observed in the right ICA territory. Rainbow displaying CBF from 0 mL/100 g to 60 mL/100 g per minute appears on the right. This patient had a right unilateral headache for a couple of days after CEA but eventually fully recovered after strict blood pressure control. CBF: cerebral blood flow, CEA: carotid endarterectomy, ICA: internal carotid artery, SPECT: single-photon emission computed tomography.

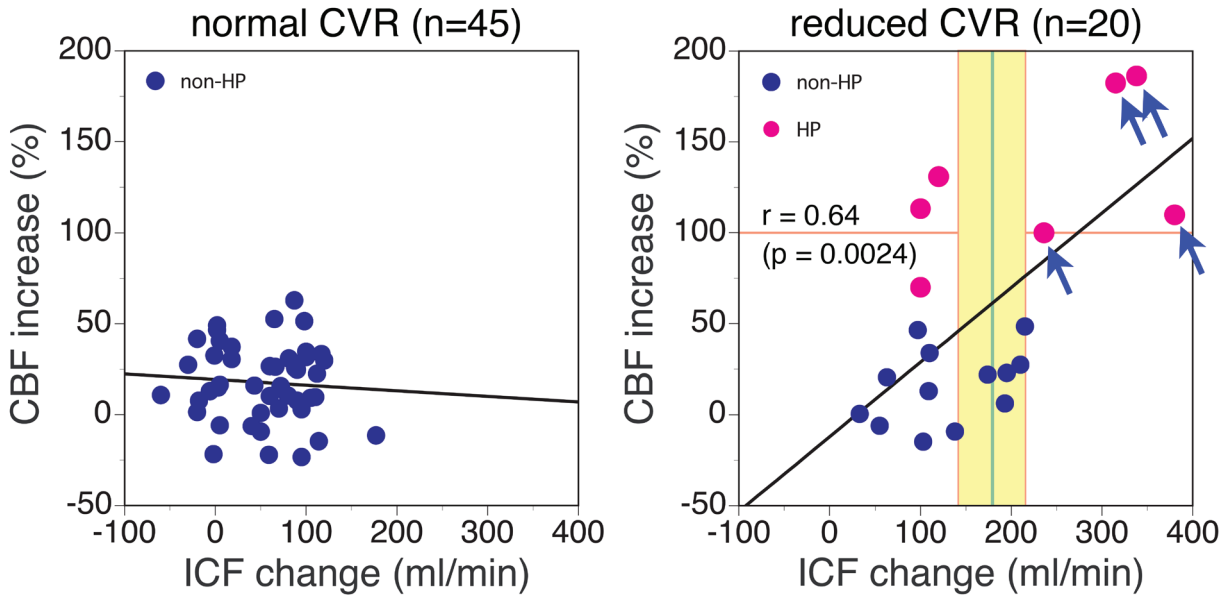

Fig. 2 ***Left*****: No significant linear correlation was observed between the internal carotid artery blood flow (ICF) increase after reconstruction and ipsilateral CBF increase on the first postoperative day as a percentage of the preoperative CBF in the normal CVR group.** ***Right*****: A significant linear correlation was observed between the ICF increase after CEA and ipsilateral CBF increase on the first postoperative day as a percentage of the preoperative CBF in the reduced CVR group (correlation coefficient r = 0.64, P = 0.0024). The** ***vertical green line*** **indicates a 179 mL/min increase in the ICA flow that seems to be the threshold for hyperperfusion. The** ***yellow area*** **is the 95% confidence interval for the threshold of hyperperfusion (142–216 mL/min). The** ***horizontal orange line*** **indicates a CBF increase of 100% as the definition of hyperperfusion. The** ***red circles*** **indicate patients with hyperperfusion. The** ***blue arrows*** **indicate patients with hyperperfusion syndrome. Cerebrovascular reactivity (CVR) is defined as the following: CVR (%) = (acetazolamide-challenge rCBF – resting rCBF) × 100/(resting rCBF). When the values of CVR were less than 10%, they were rated as reduced CVR. CBF: cerebral blood flow, CVR: cerebrovascular reactivity.**

a policy has been enacted of beginning strict blood pressure control during surgery in patients who demonstrate both reduced CVR in preoperative SPECT and an intraoperative increase in the ICA blood flow ≥ 140 mL/min. Using this method, CEA was performed for 320 patients without experiencing a single case of intracerebral hemorrhage. Based on the above investigations, assessing cerebral hemodynamics before and after CEA is considered useful for predicting and/or managing postoperative hyperperfusion and hyperperfusion syndrome.

II. Is cerebral hemodynamics assessment useful in determining the suitability of CEA for asymptomatic carotid artery stenosis?

In recent studies, cerebral hemodynamic impairment in asymptomatic carotid artery stenosis has been observed to be related to the occurrence of cerebral ischemia. In a report on 94 patients with asymptomatic carotid artery stenosis for whom cerebral hemodynamics was assessed by the breath-holding index (BHI) by transcranial Doppler (TCD) ultrasonography, Silvestrini et al. found that only lower BHI values (< 0.69) in the middle cerebral artery (MCA) ipsilateral to the carotid artery stenosis were significantly associated with the risk of an ischemic event (cerebral infarction and transient ischemic attack: hazard ratio, 0.09; 95%CI, 0.02–0.38; P = 0.001, by multivariate analysis).[11]

In a recent review that included the preceding study, the meta-analysis results showed that asymptomatic carotid stenosis patients with impaired cerebral hemodynamics had significantly more cerebral infarctions on the affected side than patients with normal hemodynamics (odds ratio [OR], 6.14; 95% CI, 1.27–29.5; P = 0.02).[12] However, all these reports were based on TCD. In a SPECT study, acetazolamide SPECT in symptomatic carotid artery stenosis demonstrated that patients with cerebral hemodynamic impairment had significantly more infarctions on the affected side and that CEA nearly eliminated this risk, although the study comprised only symptomatic 40 patients.[13] In addition, although not involving carotid stenosis and only involving symptomatic cases, a prospective ^{133}Xe SPECT study, which examined 77 symptomatic patients with ICA or MCA occlusion, demonstrated that the risks of total and ipsilateral stroke in patients with decreased

rCBF and rCVR (type 3 in Kuroda's classification) were significantly higher than in those without.[14] The relative risk conferred by decreased rCBF and rCVR was 8.0 (95% CI, 1.9–34.4) for ipsilateral stroke and 3.6 (95% CI, 1.4–9.3) for total stroke. Furthermore, a prospective PET study on 81 patients with symptomatic carotid occlusion reported that the age-adjusted relative risk conferred by stage II (increase in oxygen extraction fraction [OEF]) hemodynamic failure was 6.0 (95% CI, 1.7–21.6) for all strokes and 7.3 (95% CI, 1.6–33.4) for ipsilateral strokes.[15] Based on the above investigations, cerebral hemodynamic impairment in patients with asymptomatic carotid artery stenosis is highly likely to increase the risk of cerebral infarction. However, presently, there is no clear scientific evidence showing that improvements in cerebral hemodynamics achieved with CEA and CAS actually reduce the risk of infarction. This is an issue for future study.

Although not directly related to CEA, the Rotterdam Study, which examined a general population without carotid artery stenosis (n = 1,695), reported that subjects with reduced CVR (as measured by TCD under inhalation of a mixture of 5% CO_2 in 95% O_2 for 2 min) had a significantly higher all-cause mortality than did subjects with normal CVR.[16] However, no significant association was observed between the risk of stroke and CVR. The authors have hypothesized that reduced CVR reflects not only cerebrovascular injury but also more systematic dysfunction of the vascular system. Although the validity of this hypothesis is a subject for future investigation, it is fascinating to consider whether CVR improvement achieved with CEA or CAS affects life prognoses in patients with carotid artery stenosis.

III. Is cerebral hemodynamic impairment associated with cognitive function?

Several recent studies have indicated a relationship between cerebral hemodynamic impairment and cognitive impairment in carotid artery stenosis. In a 3-year prospective study of 210 patients with asymptomatic carotid artery stenosis (≥ 70%) and 109 healthy controls, Balestrini et al. reported that patients with asymptomatic carotid stenosis showed an increased probability of developing cognitive deterioration (a decrease of three or more points in the Mini-Mental State Examination score) compared with the group without stenosis (OR, 4.16; 95% CI, 1.89–9.11; $P < 0.001$).[17] Among patients with carotid stenosis, the presence of an impaired BHI ipsilateral to the stenosis measured by TCD (BHI < 0.69) was associated with an increased incidence of cognitive deterioration (OR, 14.66; 95% CI, 7.51–28.59; $P < 0.001$).

Additionally, although not involving stenosis, a study of symptomatic ICA occlusion patients reported a significant association between elevated OEF by PET, indicating stage II hemodynamic failure (asymmetrically increased OEF: OEF ratio > 1.13) and cognitive impairment.[18] Regarding the therapeutic effects of CEA for symptomatic carotid stenosis, Heyer et al. reported that a TCD baseline pulsatile index ≤ 0.80 was significantly associated with increased odds of cognitive improvement 1 day after CEA (OR, 7.32; 95% CI, 1.40–59.49; $P = 0.02$).[19] Furthermore, in a study of 140 carotid artery stenosis patients (44 asymptomatic patients), Yamashita et al. reported that low relative CBF in the cerebral hemisphere ipsilateral to CEA was significantly associated with postoperative cognitive improvement (95%CI: 0.623–0.868; $P = 0.0003$).[20] The sensitivity and specificity at the cutoff point (asymmetry index = 84.5: mean - 3 standard deviations of healthy volunteers) in predicting postoperative cognitive improvement were 78.6% and 85.7%, respectively.

By contrast, CEA itself has been reported to be associated with postoperative cognitive dysfunction. Approximately one-quarter of CEA patients experience early cognitive dysfunction 1 day after CEA.[21] Advanced age and diabetes predispose to early cognitive dysfunction after CEA.[21] A recent study reported that polymorphisms linked to the complement system were significantly associated with cognitive dysfunction after CEA.[22] An activating single-nucleotide polymorphism (SNP) on C3a and a deactivating SNP on the complement inhibitor gene CFH were independently associated with cognitive dysfunction 1 day after CEA. Another study using diffusion tensor imaging (DTI) demonstrated that cerebral hyperperfusion after CEA was significantly associated with postoperative cerebral white matter damage detected by DTI that correlated with postoperative cognitive impairment.[23]

Based on the results of the above studies, it is inferred that cerebral hemodynamic impairment is highly likely to be related to cognitive impairment in carotid artery stenosis. It is also inferred that this cognitive impairment is improved with CEA. However, CEA itself might be associated with postoperative cognitive dysfunction in combination with complement polymorphism and postoperative hyperperfusion. Future study is needed to resolve the conflicting findings.

Perfusion MRI

Regarding cerebral hemodynamics imaging methods besides PET and SPECT, remarkable technical developments have been made in recent years in perfusion

MRI. ASL has drawn particular attention as a cerebral hemodynamics assessment method because it allows for the noninvasive measurement of brain perfusion using magnetically labeled blood as an endogenous tracer.[24,25] As such, it allows repeated studies of both healthy subjects and different patient populations in whom the use of radiation and the injection of exogenous contrast agents may be restricted.

Cerebral hemodynamics assessments performed with ASL using the quantitative STAR labeling of arterial regions (QUASAR) sequence were reported to be highly consistent with those of SPECT.[26] Fig. 3 shows ASL images of the same patient in Fig. 1. These images demonstrate findings similar to those of SPECT in Fig. 1: reduced resting CBF on the affected side, reduced CVR on the affected side, and hyperperfusion after CEA. In addition, our preliminary data suggested that parameters such as arterial blood volume (aBV) and arterial transit time (ATT) may reflect cerebral hemodynamics. In Fig. 3, the increase of ATT was obvious in the right hemisphere. However, the change in aBV was obscure. It is particularly fascinating that ATT images are similar to reverse images of acetazolamide SPECT images. Further research developments are warranted.

Recent advances in regional perfusion imaging (RPI) visualize cerebral perfusion territories by selective ASL.[27] With RPI, the blood water protons in a single brain-feeding artery are magnetically labeled, and a delay allows the magnetically labeled blood to travel to the brain tissue before image acquisition.[27] Subsequent subtraction of this image from a control image in which no magnetic labeling is performed will demonstrate the perfusion territory of that single artery. Our preliminary data suggested that RPI could detect the change in arterial perfusion territories before and after surgery and that CEA equalizes ICA territories on both sides in patients with carotid stenosis (Fig. 4). Future studies are awaited to validate the usefulness of RPI.

Summary

Cerebral hemodynamics imaging assessments are useful in the prediction and assessment of post-CEA hyperperfusion. It is highly probable that such assessments are useful in determining the suitability of CEA. It is also likely that cerebral hemodynamics impairment is associated with cognitive function, which could perhaps be improved by CEA. However, there is a lack of sufficient scientific evidence to confirm these points, thus making further study necessary. Additionally, the ASL approach of perfusion

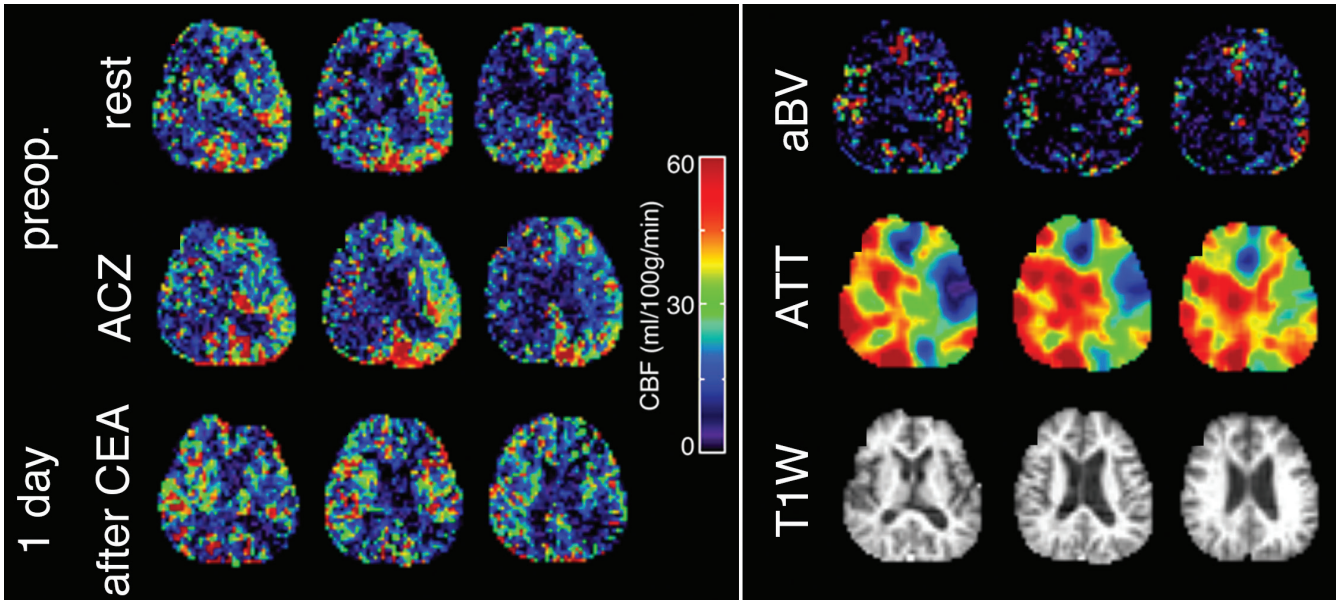

Fig. 3 ***Left*****: Typical cerebral blood flow maps obtained by arterial spin labeling (ASL) in patients with severe right carotid stenosis (the same patient as in Fig. 1). Preoperative resting images (*top row*), preoperative images with acetazolamide (ACZ) challenge (*middle row*), and postoperative images (*bottom row*) are shown. Preoperative hypoperfusion, poor vasoreactivity, and postoperative hyperperfusion in the right internal carotid artery region can be observed in the ASL.** ***Right*****: The arterial blood volume (aBV) map and arterial transit time (ATT) map of the same patient. The ATT map is similar to a reverse image of the acetazolamide single-photon emission computed tomography images. However, the change in aBV is obscure. T_1W represents T_1-weighted anatomical images.**

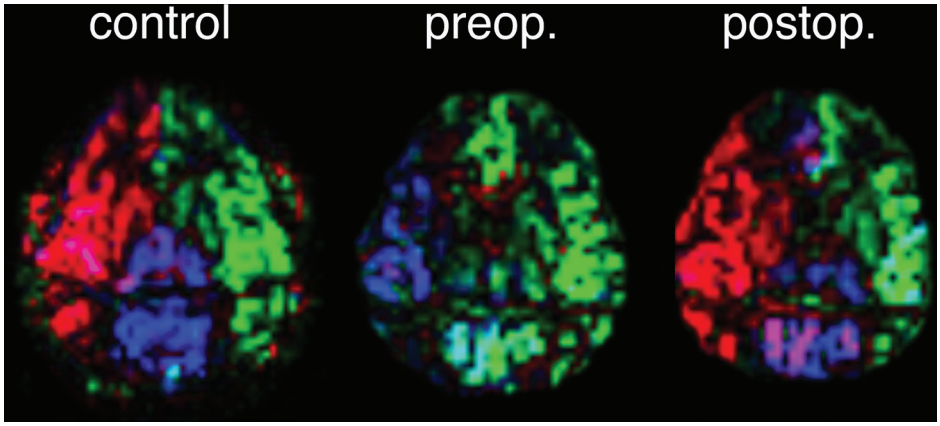

Fig. 4 ***Left*: A typical map of the intracranial artery territories obtained by regional perfusion imaging (RPI) in a normal volunteer. *Middle*: The preoperative map of intracranial artery territories obtained by RPI in a patient with severe stenosis of the right carotid artery before carotid endarterectomy (CEA). Almost no right internal carotid artery (ICA) perfusion is observed. The territory of the right middle cerebral artery is perfused by blood flow from the posterior circulation (*blue*). The territory of the right anterior cerebral artery is perfused by cross flow from the left ICA (*green*). *Right*: The postoperative map of the intracranial artery territories obtained by RPI in the same patients after CEA. The asymmetry of the ICA perfusion territories was resolved after surgery. The territory of the right ICA is labeled in *red*, the territory of the left ICA is labeled in *green*, and the territory of the posterior circulation is labeled in *blue*.**

MRI is a promising method for which further developments are expected.

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Conflicts of Interest Disclosure

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