Altered flow territories after carotid stenting and carotid endarterectomy

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Background: **The hemodynamic effects of carotid angioplasty with stent placement (CAS) on the collateral blood supply and on the regional cerebral blood flow (rCBF) have not been established. Recently, arterial spin-labeling (ASL) magnetic resonance imaging (MRI) has been introduced as the first method to quantify the actual territorial contribution of individual collateral arteries as well as to noninvasively measure rCBF. This study investigated alterations in flow territories and rCBF in patients with symptomatic internal carotid artery (ICA) stenosis and compared them with healthy control subjects. In addition, we investigated whether possible differences in flow territories and rCBF were present between patients undergoing CAS and patients undergoing carotid endarterectomy (CEA).**

Methods: **The study included 24 consecutive patients (15 men and 9 women; age 67 ± 9 years) with symptomatic ICA stenosis. CAS was performed in 12 patients, and 12 patients underwent CEA. Flow territory mapping and rCBF measurements were performed with ASL MRI before intervention and 1 month after. The control group consisted of 40 subjects (25 men and 15 women; age 67 ± 8 years).**

Results: **The flow territory of the ipsilateral ICA in patients with ICA stenosis was smaller, and the territories of the contralateral ICA and vertebrobasilar arteries were larger compared with control subjects ($P < .05$). After CAS, rCBF in the ipsilateral hemisphere increased from 60.2 ± 16.9 mL/(min · 100 g) to 68.9 ± 9.2 mL/(min · 100 g) ($P < .05$). Differences in flow territories and rCBF between patients and control subjects disappeared after CAS. Changes in flow territories and rCBF were similar in patients who underwent CAS or CEA.**

Conclusions: **CAS results in a normalization of the territorial distribution and rCBF, as assessed by ASL MRI. The degree of improvement is similar to that seen after CEA. (J Vasc Surg 2007;45:1155-61.)**

In patients with a severe symptomatic stenosis of the internal carotid artery (ICA), carotid endarterectomy (CEA) reduces the risk of recurrent stroke.[1,2] Removal of the atheromatous plaque as a source of thromboembolism decreases the risk of embolic stroke[3] and may prevent the progression of a stenosis to occlusion.[4] Moreover, improvement of cerebral perfusion after CEA may further decrease stroke risk by a better wash out of cerebral emboli from the borderzone areas.[5] Carotid angioplasty with stent placement (CAS) has emerged as a potential alternative to CEA for the treatment of high-grade ICA stenosis.

The recently published results of major trials directly comparing CAS with CEA have a tendency to show a lower rate of death and stroke with CEA.[6,7] We hypothesized that a potential difference in outcome may be explained by a difference in hemodynamic improvement after CEA and CAS. CEA has previously been shown to restore collateral blood flow distribution[8-11] and normalize regional cerebral blood flow (rCBF).[12,13] However, the hemodynamic effects of CAS on the collateral blood supply and rCBF have not been established.

Thus far, the actual contribution of individual collateral pathways has been difficult to assess and quantify. Magnetic resonance angiography (MRA) and transcranial Doppler imaging in patients with ICA stenosis depict collateral flow but not its actual contribution to brain perfusion.[11,14] Intra-arterial digital subtraction angiography (DSA) offers more information by also showing the distal arteries of a collateral pathway. This technique, however, requires an invasive, selective four-vessel approach to visualize all collateral pathways.[15] The current methods to measure rCBF in patients with ICA obstruction, such as positron emission tomography (PET) and single photon emission computed tomography, are invasive and require an injection of radioactive tracers or contrast agents.[12,16]

Arterial spin-labeling (ASL) magnetic resonance imaging (MRI) was recently introduced as the first method to quantify the actual territorial contribution of individual arteries as well as to noninvasively measure rCBF (mL/[min · 100 g] of tissue).[17] The aim of our study was to investigate alterations in flow territories and rCBF in patients with symptomatic ICA stenosis and to compare them with healthy control subjects. We also investigated whether possible differences in flow territories and rCBF were present between patients undergoing CEA and patients undergoing CAS.

METHODS

Patients and control subjects. Between November 2004 and July 2005, 24 consecutive patients (15 men and 9 women; age 67 ± 9 years) with ICA stenosis of ≥50%

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who had been symptomatic in the previous 12 weeks were included in the study. Sixteen patients had transient ischemic attacks and eight patients had minor ischemic stroke (Rankin grade $\geq$2).[18] Patients who had had a stroke causing major disability (modified Rankin score 3 to 5)[18] were excluded.

All patients were participants of the International Carotid Stenting Study, a randomized controlled trial to compare CEA and CAS and provided written informed consent. In our institution, additional MRI investigations were performed in all patients. The Ethics Committee of our institution approved the additional MRI investigations and the study protocol. Separate written informed consent for the MRI and to participate in our study was obtained from all patients.

All patients underwent contrast-enhanced MRA and duplex ultrasonography. Grading of stenosis in the ICA was performed with contrast-enhanced MRA according to North American Symptomatic Carotid Endarterectomy Trial criteria (NASCET).[19] Several diagnostic studies showed high sensitivities and specificities of contrast-enhanced MRA compared with intra-arterial DSA for the detection of ICA stenosis according to the NASCET criteria.[20,21]

CAS was performed in 12 patients (8 men and 4 women, age 68 ± 8 years), and 12 patients underwent CEA (7 men and 5 women, age 66 ± 11 years). In the CAS group, the degree of stenosis (mean ± standard deviation) was 80% ± 14% in the ipsilateral ICA and 36% ± 32% in the contralateral ICA. In the CEA group, the degree of stenosis was 83% ± 12% in the ipsilateral ICA and 30% ± 20% in the contralateral ICA. The degree of stenosis was 3% ± 9% in the ipsilateral ICA after CAS and 5% ± 9% after CEA. None of the patients had stenosis of >30% in the vertebrobasilar system on contrast-enhanced MRA. All operations and CAS procedures were uncomplicated.

Morphology assessment of the circle of Willis was performed on the individual source sections of the time-of-flight MRA (TR, 30 milliseconds [ms]; TE, 6.9; flip angle, 20°), using a workstation (Easy Vision, Philips Medical Systems, Best, the Netherlands). A nonvariant-type circle of Willis was present in 16 (67%), five (21%) had a fetal-type posterior cerebral artery, and three (13%) had a missing A1 segment.

The control group consisted of 40 subjects (25 men, and 15 women; age 67 ± 8 years) matched for age and sex, without abnormalities on MRI and MRA images of the brain and without ICA stenosis of $\geq$30% on duplex ultrasonography. A nonvariant type circle of Willis was present in 26 (65%), 10 (25%) had a fetal-type posterior cerebral artery, and four (10%) had a missing A1 segment.

Magnetic resonance imaging. The ASL MRI investigations were performed 1 day before and 1 month after (range, 27 to 35 days) carotid revascularization on a 1.5 T whole-body system (Gyroscan ACS-NT, Philips Medical Systems). The technique of using ASL MRI to map the flow territory of the arteries feeding the brain has been described in detail in previous articles.[17,22] Briefly, mapping of the flow territory was achieved with regional perfusion imaging (RPI), which is based on a pulsed-ASL sequence with selective labeling of the ipsilateral ICA, contralateral ICA, and vertebrobasilar arteries (VBAs). After a labeling delay of 1600 ms, five slices were acquired in the cranial-to-caudal direction with a delay time of 25 ms between slices. For image acquisition, a single-shot echo-planar imaging readout was used. Other MRI parameters of the RPI scans were TR, 3000 ms; TE, 5.6 ms; 62% partial Fourier acquisition; slice thickness, 8 mm; slice gap, 1 mm; field-of-view, 240 × 240 mm; matrix, 64 × 64; zero filling to 128 × 128 matrix; averages, 30; and RPI scan time, 3 minutes per territory. To quantify rCBF in milliliters per minute per 100 grams of tissue (mL/[min · 100 g]), a conventional multi-inversion-time nonselective ASL sequence was used.[23] The coefficient of variation of the ASL MRI measurements is 11 %.[24]

Data processing. Data were analyzed as described previously.[17] In brief, after visual evaluation of the RPI images, one of the authors (P. J. V. L.) manually segmented and registered the flow territories on a standard brain (SPM, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK).[25] Left-sided and right-sided symptomatic ICA stenosis were pooled: flow territory maps of subjects with right-sided symptomatic ICA stenosis were mirrored in the midline, and flow territory maps of subjects with left-sided symptomatic ICA stenosis remained unchanged. For rCBF quantification, regions of interest were selected in the grey matter of the flow territory of the middle cerebral arteries. Quantification was performed on the basis of established kinetic perfusion models with the following values for the physical constants: α (efficiency of the inversions pulse) = 1.0, $T_{1\text{-grey-matter}} = 1000$ ms, $T_{1\text{-white-matter}} = 700$ ms, $T_{1\text{-blood}} = 1400$ ms, and $\lambda = 0.9$ mL/g.[26,27]

Statistical analysis. Voxel-based χ^2 testing with Bonferroni correction for the number of brain voxels in the RPI slices was performed to analyze differences in extent of the flow territories. After correction, $P < .05$ was considered statistically significant. Differences in rCBF between baseline and 1 month after intervention were analyzed with a paired sampled *t* test. Differences in rCBF between patients and control subjects, between CAS and CEA, and between ipsilateral and contralateral hemisphere were analyzed with the Student *t* test. $P < .05$ was considered significant. For statistical analysis, SPSS 10.0.7 (SPSS Inc, Chicago, Ill) for Windows (Microsoft Corp, Redmond, Wash) was used. Baseline and rCBF data are expressed as mean ± standard deviation.

RESULTS

Flow territories. Fig 1 shows the representative flow territory images of a 56-year-old man with a symptomatic left-sided ICA stenosis of 90%, resulting from selective labeling of the stenotic ICA, contralateral ICA, and VBA before and after CAS.

Flow territory maps of patients with symptomatic ICA stenosis show that the stenotic ICA supplies a significantly

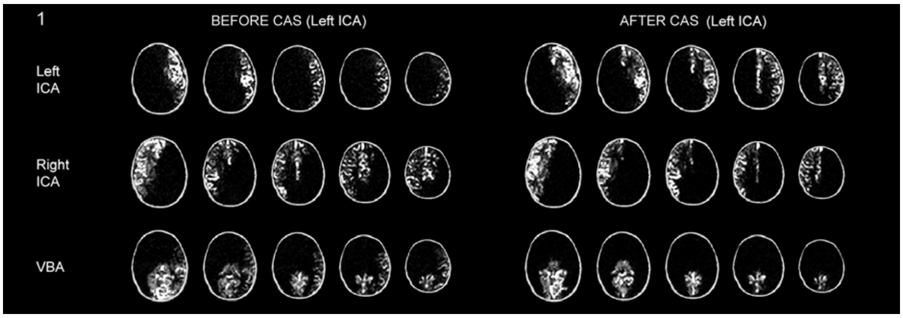

Fig 1. Flow territory images of a 56-year-old man before and after carotid angioplasty with stent placement *(CAS)* of the 90% stenosis in the left internal carotid artery *(ICA)*. When the stenosed left ICA is labeled selectively, the perfusion signal is observed only in the left middle cerebral artery territory. After CAS, the flow territory of the left ICA has extended into the ipsilateral anterior cerebral artery territory. When labeling the right ICA before intervention, the signal is detected in the right middle cerebral artery territory and in both the left and right anterior cerebral artery territories; but after CAS, the flow territory is restricted to the right anterior cerebral artery and middle cerebral artery territories. Before CAS, the territory of the vertebrobasilar arteries *(VBA)* extends into the middle cerebral artery flow territory ipsilateral to the ICA stenosis, but after intervention the flow territory is restricted to the posterior part of the imaging slices.

($P < .05$) smaller part of the anterior cerebral artery flow territory than in controls (Fig 2, *a*). The flow territory of the contralateral ICA in these patients is significantly ($P <$ .05) extended into the anterior cerebral artery flow territory on the side of the stenosis (Fig 2, *b*). The VBA in patients with ICA stenosis is significantly ($P < .05$) extended into the flow territory of the middle cerebral arteries on the side of the stenosis (Fig 2, *c*).

Flow territory maps of the ipsilateral ICA, contralateral ICA, and VBAs after CAS are shown in Fig 3, *a*. After CAS, no significant differences in flow territories between patients and control subjects were found. Changes in flow territories did not differ between patients who CAS and those who had CEA (Fig 3, *b*). No significant postoperative differences were seen between patients and control subjects.

Regional cerebral blood flow. Fig 4 shows for patients and control subjects the rCBF for the grey matter of the ipsilateral and the contralateral hemisphere. Before CAS, rCBF in the ipsilateral hemisphere (60.2 ± 16.9 mL/[min · 100 g]) was significantly lower than in the contralateral hemisphere (72.3 ± 13.9 mL/[min · 100 g; $P < .05$) and in control subjects (78.7 ± 18.4 mL/[min · 100 g]; $P < .05$). After CAS, rCBF in the ipsilateral hemisphere significantly increased (68.9 ± 9.2 mL/[min · 100 g]; $P < .05$). In patients undergoing CEA, rCBF in the ipsilateral hemisphere (60.9 ± 13.7 mL/[min · 100 g]) was significant lower than in the contralateral hemisphere (70.9 ± 11.5 mL/[min · 100 g]; $P < .05$) and control subjects ($P < .05$). Postoperatively, ipsilateral rCBF increased significantly (71.2 ± 13.9 mL/[min · 100 g]; $P <$ .05). No significant difference in rCBF was found between patients who had CAS and patients undergoing CEA. After carotid revascularization, no significant differences in rCBF between patients and control subjects were seen.

DISCUSSION

The present study had three findings that were most important:

1. The flow territory of the stenotic ICA in patients with recently symptomatic severe ICA stenosis was smaller and the territories of the contralateral ICA and VBAs were larger than those in control subjects.
2. CAS resulted in a normalization of the territorial distribution and rCBF.
3. The degree of improvement was similar to that seen after CEA.

In the light of the recently published CEA vs CAS trials, which have a tendency to show a lower stroke risk in the CEA group relative to the CAS group,[6,7] we hypothesized that a potential difference in outcome may be explained by a difference in the hemodynamic improvement after CEA and CAS in addition to thromboembolic risks related to CAS. Especially, during the stenting procedure and the early postintervention period, an adequate regional cerebral hemodynamics may have the ability to wash out emboli and prevent ischemia and infarction.[5,28] In this respect, Henderson et al[15] demonstrated in a subanalysis of the NASCET data that the collateral capacity of the cerebral circulation influences the stroke risk both in the control group and in the CEA group in the perioperative period. We demonstrate in the present study that the normalization of the regional cerebral hemodynamics in both the rCBF and the flow territories of the brain feeding arteries are similar for the CAS and the CEA groups. This is in agreement with previous studies demonstrating a normalization of blood flow in the ICAs and VBAs after CEA,[8-10] restoration of vessel diameters of the circle of Willis, and redistribution of collateral flow patterns in the circle of Willis.[11]

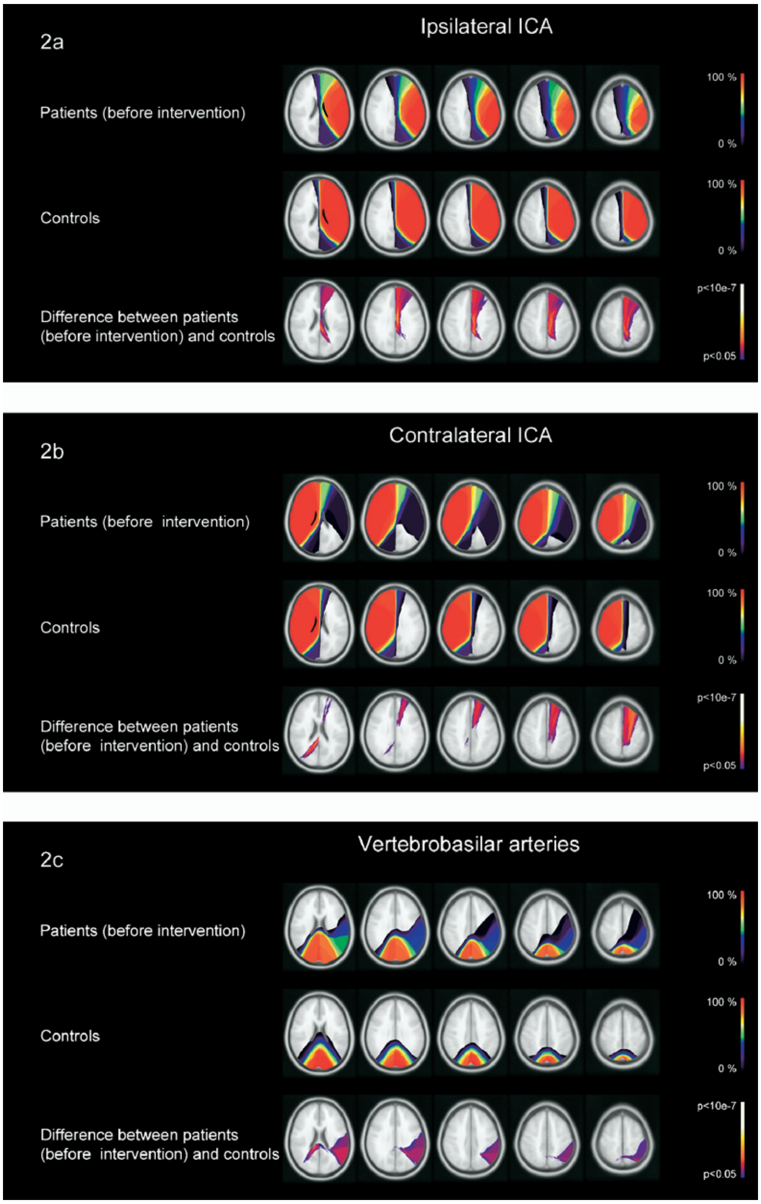

Fig 2. a, Flow territory maps of the ipsilateral internal carotid artery *(ICA)* for all patients *(top row)* and control subjects *(middle row)*. Colors indicate the percentage of subjects that demonstrated perfusion in that brain region. The *bottom row* shows differences in flow territories of the ipsilateral ICA between patients and controls. The *color bar* with logarithmic scale indicates significant *P* values. **b,** Flow territory maps of the contralateral ICA for all patients *(top row)* and control subjects *(middle row)*. The *bottom row* shows differences in flow territories of the contralateral ICA between patients and controls. **c,** Flow territory maps of the vertebrobasilar arteries for all patients *(top row)* and control subjects *(middle row)*. The *bottom row* shows differences in flow territories of the VBA between patients and controls.

Our finding of a significantly smaller flow territory of the stenotic ICA compared with control subjects is consistent with previous reports of a reduced contribution from the stenotic ICA to the total blood supply.[8,9] Because we studied patients with severe ICA stenosis without major neurologic deficit, collateral pathways are expected to exist in these patients to reroute the blood to compensate for the relatively small flow territory of the stenotic ICA.[29] The flow territory maps in our study demonstrate that in patients with severe ICA stenosis, the contralateral ICA is important for the supply of the anterior cerebral artery territory ipsilateral to the stenotic ICA, and the VBAs for the perfusion of the ipsilateral middle cerebral arteries territory.

In addition, it is known in subjects with an anatomic variant type of the circle of Willis that the configuration of the

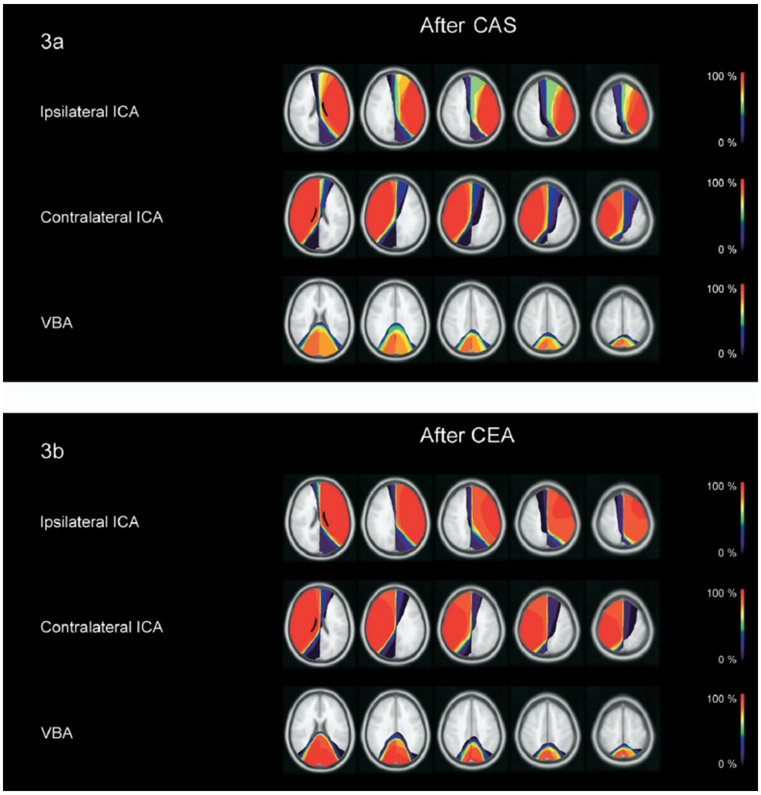

Fig 3. **a,** Flow territory maps of patients after carotid angioplasty with stenting *(CAS)* of the ipsilateral internal carotid artery *(ICA)*. **b,** Flow territory maps of patients after carotid endarterectomy *(CEA)* of the ipsilateral ICA. Colors indicate the percentage of subjects that demonstrated perfusion in that brain region.

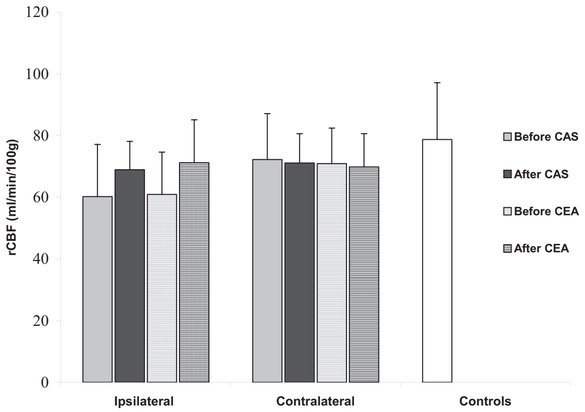

Fig 4. Mean regional cerebral blood flow *(rCBF)* for the grey matter of the ipsilateral and contralateral hemispheres in patients before and after carotid angioplasty with stenting *(CAS)* and carotid endarterectomy *(CEA)* and in control subjects. Data presented as means ± standard deviation.

circle of Willis strongly affects the extent of the cerebral flow territories.[17] For instance, in patients with unilateral ICA stenosis and an ipsilateral missing A1 variant, the contralateral ICA may supply the flow territories of both anterior cerebral arteries. Several studies have demonstrated that the variant type of the circle of Willis with a missing A1 segment has a prevalence up to 10%.[30-32] In the posterior part of the circle of Willis, the variant type with a fetal-type posterior cerebral artery has a prevalence up to 25%.[32,33] The prevalence of variant types in our study corresponds with these percentages.

In our study, rCBF in the hemisphere ipsilateral to the stenotic ICA improved after CAS in a manner similar to that of CEA. We observed a small but significant 15% increase in ipsilateral rCBF after CAS and 17% increase after CEA, which is similar to the extent of increases reported in previous studies after CEA or CAS.[12,13,34] However, others did not demonstrate any change in rCBF after carotid revascularization.[8,35] It is difficult to compare the results of these studies because the patients included differ considerably in severity of stenosis and collateral circulation.

The finding of a lower rCBF in the hemisphere ipsilateral to the stenosis compared with the contralateral hemisphere may have been caused by differences in transit delays within the region of interest.[36] Such a distribution in transit delay can occur when the posterior and anterior circulation simultaneously supply brain tissue. In such cases, transit delays differ even within a single voxel, also making single-voxel approaches erroneous. Extension of the selective ASL technique to a multiple-inversion-times sequence could circumvent these quantification problems. In our study, the rCBF values measured in the grey matter of the contralateral hemisphere and in control subjects are in agreement with previous ASL rCBF measurements at multiple inversion times.[37,38] Furthermore, measured rCBF values are in agreement with previous PET-based perfusion values.[39] We therefore think rCBF differences measured in the present study are real and not caused by technical errors.

Potentially, the contrast-enhanced MRA measurement of ICA stenosis may be slightly overestimated compared with intra-arterial DSA; however, this will be similar in the CAS and the CEA group.[20,21]

CONCLUSION

In patients with recently symptomatic severe ICA stenosis, CAS results in a normalization of the territorial distribution and rCBF in a manner similar to that of CEA. Although the true role of CAS in the management of ICA stenosis remains to be determined by large randomized trials, this study suggests that there is no difference in cerebral hemodynamic effect between both approaches. ASL MRI is a noninvasive method of monitoring the hemodynamic effects of CAS and CEA in patients with ICA stenosis. This method may be useful for noninvasive quantification of possible hemodynamic effects of a restenosis, which may not be similar in the CAS and CEA subgroups. In addition, ASL MRI may provide valuable information to measure rCBF in patients with cerebral hyperperfusion syndrome after CAS or CEA.

AUTHOR CONTRIBUTIONS

Conception and design: PJL, JH, JG
Analysis and interpretation : PJL, JH, WPM, FLM, HBW, MJO, JG
Data collection: PJL
Writing the article: PJL, JH, JG
Critical revision of the article: WPM, FLM, HBW, MJO
Final approval of the article: PJL, JH, WPM, FLM, HBW, MJO, JG
Statistical analysis: PJL, JH, MJO, JG
Obtained funding: Not applicable.
Overall responsibility: PJL, JG

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