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Original Article

Intracerebral steal phenomenon in symptomatic carotid artery disease

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ABSTRACT

Background and purpose. – Intracerebral steal is a paradoxical vasodilatory response that reduces cerebral blood flow (CBF) in hemodynamically compromised brain tissue when blood is rerouted to more healthy areas. The aim of our study was to investigate the presence and extent of steal in patients with steno-occlusive internal carotid artery (ICA) disease, and to assess its relation with collateral blood flow through the circle of Willis (CoW).
Materials and methods. – Thirty-eight patients with symptomatic steno-occlusive ICA disease underwent MRI examination with arterial spin labeling (ASL) perfusion imaging before and after a vasodilatory challenge. Intracerebral steal was defined as a decline in CBF after acetazolamide. Collateral flow via the CoW was assessed with time-of-flight and flow direction MR angiography (MRA) through the CoW was assessed with 2D phase-contrast MRA's.
Results. – Eight of 38 patients (21%) had steal in the hemisphere ipsilateral to the symptomatic ICA (mean tissue volume with steal, 6.9 ± 4.1 mL; mean CVR, −11 ± 30%). Cerebrovascular reactivity (CVR) was lower in the middle cerebral artery flow territory of the affected hemisphere in patients with steal compared those without ($P = 0.002$). Collateral blood flow was impaired in 4 of the 8 patients with steal. These patients had a larger area of steal ($P = 0.002$).
Conclusions. – Intracerebral steal occurs in patients with obstructive ICA disease and can be assesses at brain tissue level with ASL perfusion MRI. Its presence is related to more severely declined CVR in the surrounding brain tissue area and the volume is associated with impaired primary collateral blood flow through the CoW.

Introduction

Patients with steno-occlusive internal carotid artery (ICA) disease are at increased risk for ischemic stroke, with 1-year stroke risk rates varying from 5–18% [1–3]. Although revascularization therapy is beneficial, there is no clear way to identify those patients that may benefit the most. Observational studies have found decreased cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to be important risk factors for stroke [3,4]. The degree of hemodynamic impairment distal to an obstructive lesion is however highly variable and depends on a multitude of factors, among which the most important are the amount of stenosis and the capability of collateral vessels to provide additional blood flow [5–7].

Hemodynamic impairment can be assessed by measuring the autoregulatory capacity of the brains vasculature [8]. This compensatory mechanism allows for the brain to dynamically compensate to a drop in the cerebral perfusion pressure by dilatation of the cerebral resistance vessels, thus maintaining normal CBF. When this vasodilatory capacity, also called cerebral vascular reactivity (CVR) is however exhausted, the CBF will fall as a function of perfusion pressure.

CVR may be assessed either by measuring the increase in flow-velocity after a vasodilatory challenge in a major cerebral artery with transcranial Doppler (TCD) or directly at brain tissue level with techniques like single photon emission tomography, positron emission tomography and arterial spin labeling perfusion (ASL) MRI [5,9,10]. Observation studies imaging CVR at brain tissue level have indicated that a paradoxical decline in CBF may occur in areas with severe dysfunctional vessels, i.e. impaired CVR hemodynamics, potentially leading to transient ischemia [11–14]. Although this

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Table 1
Demographic and clinical characteristics of the study population.

	Patients	
	Stenosis	Occlusion
Number	20	18
Male (*n* [%])	13 (65%)	12 (67%)
Age (mean years ± SD)	68 ± 8.6	55 ± 15
Degree of ICA stenosis (*n*)		
0–49%	0	–
50–69%	2	–
70–99%	18	–
Occluded	–	18
Degree of contralateral ICA stenosis (*n*)		
0–49%	17	10
50–69%	3	8
70–99 %	0	0
Occluded	–	0
Presenting events (*n*)[a]		
Transient ischemic attack	10	11
Ischemic stroke	6	7
Retinal ischemia	4	1

[a] Some patients presented with more than one symptom.

phenomenon is poorly understood, it is thought to be caused by blood being rerouted from the afferent arteries and surrounding small pial collaterals, to more healthy brain tissue areas with an uncompromised hemodynamic reserve.

The aim of our study was to investigate the presence and extent of intracerebral steal in patients with steno-occlusive ICA disease by means of ASL perfusion MRI, and to assess the relation between intracerebral steal and the presence of collateral blood flow through the circle of Willis.

Materials and methods

Patients

Thirty-eight patients with recently symptomatic steno-occlusive ICA disease were prospectively included into the study. All patients were referred consecutively by a general practitioner or neurologist to our hospital, a tertiary referral center for stroke, for follow-up symptoms. All patients had had a TIA or non-disabling ischemic stroke ipsilateral to the affected ICA in the previous 3 months. Twenty patients had an ICA stenosis ≥ 50% and 18 had an ICA occlusion. Eight of the 18 patients with ICA occlusion had a contralateral ICA stenosis ≥ 50% (Table 1). Diagnosis and grading of the ICA stenosis or occlusion was performed with duplex ultrasonography [15], and confirmed with either computed tomography or magnetic resonance (MR) angiography as measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [1]. Patients with diabetes mellitus, severe renal or liver dysfunction, which are a contraindication for the use of acetazolamide, or disabling stroke (modified Rankin scale score of 3–5) were excluded from this study [2].

This study was approved by the institutional ethical review board. All procedures performed were in accordance with the ethical standards of the institution, and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Imaging protocol

Imaging was performed on a clinical 3 Tesla MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands) equipped with an eight-channel coil and locally developed software to enable ASL perfusion imaging. A standardized imaging protocol was used including diffusion-weighted imaging (DWI), T_2-weighted fluid attenuation inversion recovery (FLAIR) imaging and ASL perfusion-weighted imaging. Perfusion images were obtained before and 15 minutes after administration of a bolus of 14 mg/kg acetazolamide (Goldshield Pharmaceuticals, Croydon, UK), with a maximum dose of 1200 mg.

ASL perfusion-weighted images were acquired with a pseudo-continuous labeling technique according to a previously published protocol [16]. Labeling was performed by employing a train of 18 degrees, 0.5 ms, Hanning shaped RF pulses at an interval of 1 ms, for a duration of 1650 ms, with a balanced gradient scheme [17,18]. The control images were acquired by adding 180° to the phase of all even RF pulses. After a 1525 ms delay, 17 slices were acquired in ascending order with an in-plane resolution of $3 \times 3\,mm^2$ with single-shot gradient echo imaging in combination with background suppression and parallel imaging (SENSE factor 2.5) [19,20]. The other ASL parameters were: repetition time (TR), 4000 ms; echo time (TE), 14 ms; field of view (FOV), $240 \times 240 \times 119$ mm; matrix size, 80×79; slices, 17; averages, 38 control/label pairs; scan time, 5 minutes.

An inversion recovery sequence was acquired prior to the perfusion scans to measure the magnetization of arterial blood (M_0) which is needed to quantitatively calculate cerebral blood flow (CBF), and to segment brain tissue into gray and white matter [21]. The inversion recovery sequence was acquired with echo planar imaging with the same geometry and resolution as the ASL images. T_2-weighted FLAIRs images and a three-dimensional time-of-flight MR angiography with subsequent maximum intensity projection reconstruction were acquired with standard imaging sequences provided by the MRI vendor. The presence of collateral blood flow and its direction was determined according to a previously published imaging protocol with two consecutive two-dimensional phase-contrast (2DPC) MRI measurements, of which one was phase-encoded in the anterior-posterior direction and one in the right-left direction (TR/TE, 9.4/5.9 ms; flip angle, 7.5°; FOV, 250×187.5; averages, 8; slice thickness, 13 mm; velocity sensitivity, 40 cm/s; scan time, 20 seconds) [22].

Perfusion-weighted image analysis

Data were analyzed with Matlab (version 7.13, The MathWorks Inc., Natick, Massachusetts) and SPM8 (Wellcome Trust Centre for Neuroimaging, Oxford, United Kingdom). CBF images were calculated in mL/100 g/min from the ASL MR images according to a previously published model that corrects for T_1 decay, T_2^* decay and the different delay times of the imaging slices [23]. The T_2^* transversal relaxation rate and T_1 of arterial blood at 3T were assumed to be, respectively, 50 ms and 1680 ms [24,25]. The blood magnetization at thermal equilibrium (M_0) for all subjects was determined by selecting a region of interest in the cerebral spinal fluid and iteratively fitting the inversion recovery data by a non-linear least-square method. The water content of blood was assumed to be 0.76 mL per mL of arterial blood [21].

In patients with motion artifacts, in-plane motion was first corrected for by pairwise coregistration of the source images with SPM8 (Wellcome Trust Centre for Neuroimaging, Oxford, United Kingdom) using the normalized mutual information and rigid body transformation and pairs of images that showed strong motion artefacts were discarded prior to averaging. To correct for motion between pre- and post-acetazolamide image acquisition, the post-acetazolamide ASL images were also coregistered with SPM8 to the baseline ASL images using the normalized mutual information and a rigid body transformation.

To avoid partial voluming of white matter, a surrogate T_1-weighted image was calculated from the inversion recovery sequence by calculating the reciprocal of the quantitative T_1 [21]. This was segmented into gray and white matter probability maps

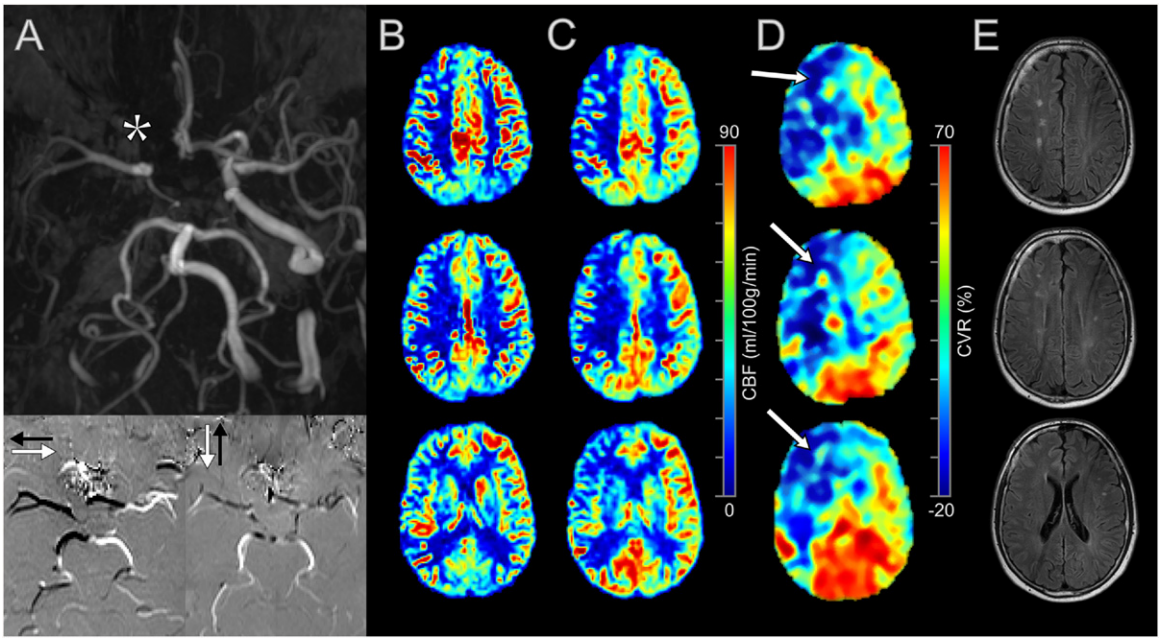

Fig. 1. Example of 50-year-old patient with a right-sided ICA occlusion. MR time-of-flight image and flow direction angiography (A) shows the occluded right internal carotid artery in combination with a missing pre-communicating segment (A, star) of the right anterior cerebral artery and patent pCom arterial spin labelling (ASL) MRI perfusion images before (B) and after (C) the acetazolamide vasodilatory challenge show three consecutive slices from caudal (bottom) to cranial (top) and an increase in CBF is observed in the left hemisphere. The right hemisphere shows no increase and even a slight decrease in CBF. The percentage reactivity map (D) shows the absence of reactivity in the right hemisphere, where darker blue areas (D, arrows) show a negative reactivity, corresponding with hemodynamic steal. FLAIR MRI images (E) show internal borderzone infarcts in the semiovale centre.

with SPM8 and a corrective threshold was furthermore applied to ensure maximal exclusion of all white matter. CBF was calculated in the resulting gray matter mask. CVR was defined as the percentage change (increase or decrease) in CBF after acetazolamide administration using the following equation, in which "*CBF pre ACZ*" and "*CBF post ACZ*" stands for CBF before and after the vasodilatory challenge with acetazolamide:

$$CVR = \frac{CBF_{post\,ACZ} - CBF_{pre\,ACZ}}{CBF_{pre\,ACZ}} \cdot 100\%$$

Evaluation of intracerebral steal

Presence of intracerebral vascular steal was evaluated by two expert readers (NH, RB) blinded to the patient's identity, clinical information and diagnosis. Occurrence of intracerebral vascular steal was defined as a visually significant area with a decrease in CBF after administration of acetazolamide, resulting in a negative CVR. The readers had access to the DWI and FLAIR images for exclusion of brain tissue areas with ischemic stroke. Discrepancies in the assessment of steal were resolved in a consensus meeting.

The volume of the area with intracerebral vascular steal was measured by segmenting the lesion on the CBV maps. This done on a slice-by-slice basis with user-selected seed points followed by user-driven editing. The volume of the lesion was calculated by multiplying the total lesion area by the slice thickness. After segmentation of the lesions, the volumes of interest were copied to the co-registered CBF images before and after acetazolamide, where the average CBF was measured within the volume. The CBF and CVR was also measured in the flow territory of both the ipsilateral and contralateral middle cerebral artery (MCA). This was done by manually outlining the boundaries based on conventional flow territory maps [26].

Assessment of collateral blood flow

The morphology of the circle of Willis and presence of collateral blood flow was determined by two readers (NH, RB). Anterior collateral flow was defined as blood flow across the anterior communicating artery (AComA) with retrograde flow in the pre-communicating part (A1 segment) of the anterior cerebral artery (ACA) ipsilateral to the ICA stenosis or occlusion. Posterior collateral blood flow was defined as posterior-to-anterior flow through the posterior communicating (PComA) artery ipsilateral to the ICA stenosis or occlusion, which may be reduced or prevented due to a small or absent PComA or precommunicating part (P1 segment) of the posterior cerebral artery (PCA).

Each circle of Willis was assessed using the time-of-flight MRA for the presence of the AComA, A1, PComA, and P1 segments. An absent segment preventing collateral blood flow, i.e. missing either A1 segment, the AComA, or the PComA or P1 ipsilateral to the ICA with stenosis or occlusion, was presumed to lead to impaired collateral blood flow via the circle of Willis. Presence of collateral blood flow was established by evaluating the blood flow direction through the CoW by means of the 2DPC images. It was determined that no collateral blood flow was present when the ACA and MCA were supplied by the ipsilateral ICA, and the PCA was supplied by the BA.

Statistical analyses

Descriptive statistical analyses were performed to summarize patient characteristics. Values are illustrated as box-and-whisker plots. CVRs in the MCA-territories ipsilateral and contralateral to the ICA stenosis or occlusion of patients with and without steal were compared with an independent *t*-test. Values are reported as mean ± standard deviation (SD). A *P*-value ≤ 0.05 was considered statistical significant.

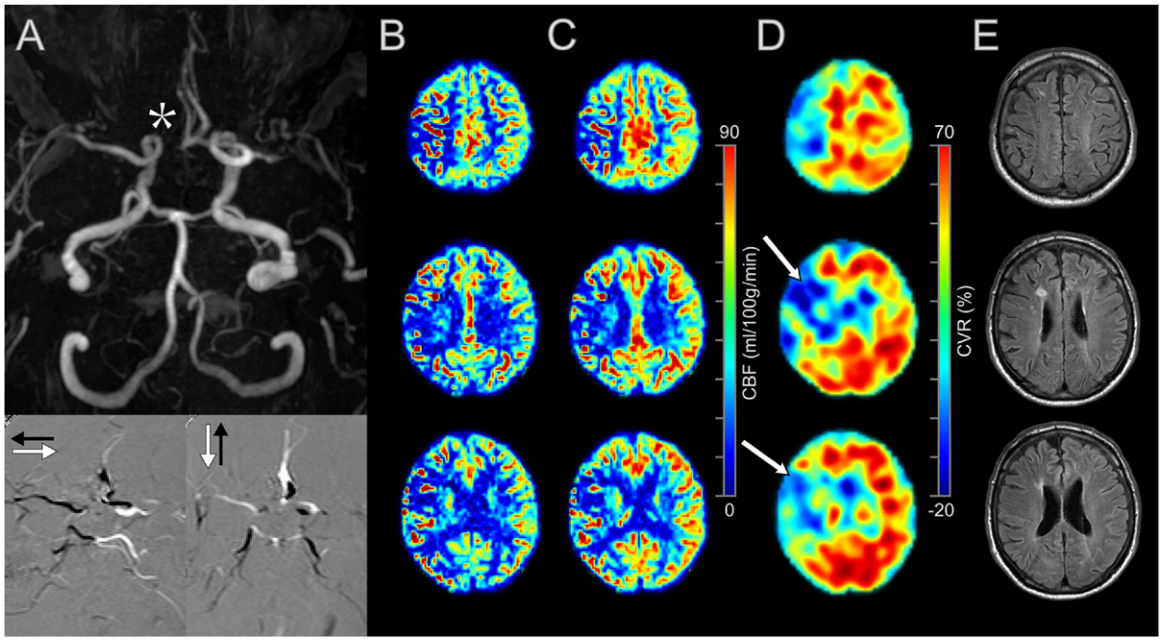

Fig. 2. Example of 67-year-old patient with a right-sided ICA stenosis. MR time-of-flight image and flow direction angiography (A) shows a missing pre-communicating segment (A, star) of the right anterior cerebral artery. Before (B) and after (C) the acetazolamide reactivity challenge an increase in CBF in the left hemisphere is observed in the ASL MRI perfusion images. The right hemisphere shows large areas with a CBF increase but a decrease in CBF is observed centrally in the right hemisphere. The percentage reactivity image (D) shows the absence of reactivity in the central area of the right hemisphere with hemodynamic steal in the dark blue area (D, arrows) corresponding with a decrease in CBF. FLAIR MRI images (E) show no infarct in this region although a small hyperintense lesion is seen next to the frontal horn of the right ventricle.

Results

The demographic and clinical characteristics of the subjects are outlined in Table 1. Intracerebral steal was present in 8 of the 38 patients (21%). Intracerebral steal occurred in 3 of the 20 patients (15%) with a significant ICAS stenosis and 5 of 18 patients (28%) with an ICA occlusion. The three patients with steal and an ICA stenosis, had a significant stenosis > 70%. All occurrences were in the hemisphere ipsilateral to the symptomatic ICA stenosis or occlusion. The mean volume of brain tissue with steal, 6.9 ± 4.1 mL and the mean CVR in tissue with steal was $-11 \pm 30\%$. Fig. 1 shows an example of intracerebral vascular steal in a patient with an ICA occlusion. In patients with a symptomatic ICA stenosis, intracerebral steal was observed in 3 of 20 patients (15%). Fig. 2 shows an example of intracerebral vascular steal in a patient with an ICA stenosis. No statistical difference was found in the number of patients with hemodynamic steal between patients with ICA stenosis and occlusion ($P = 0.44$, two-tailed Fishers' exact test). None of our patients had an adverse event during the examination.

For all patients with steal, the CVR was lower in the ipsilateral MCA flow territory when compared to the contralateral hemisphere ($15 \pm 7.1\%$ vs. $32 \pm 14\%$, $P = 0.002$; Fig. 3). There was a trend towards a lower CVR in the contralateral MCA flow territory in patients with steal compared to patients without steal ($30 \pm 8.5\%$ vs. $39 \pm 12\%$, $P = 0.06$). In the patients with an ICA occlusion, CVR was significantly lower in the ipsilateral MCA flow territory of patients with steal than in patients without steal ($9.7 \pm 2.0\%$ vs. $22 \pm 10\%$, $P = 0.001$). In the patients with an ICA stenosis, CVR was significantly lower in the ipsilateral MCA flow territory in patients with steal than in patients without steal ($23 \pm 3.8\%$ vs. $38 \pm 13\%$, $P = 0.05$).

Collateral blood flow via the circle of Willis

Anterior collateral flow towards the hemisphere ipsilateral to the ICA disease was present in 3 patients (15%) with ICA stenosis and in all patients with ICA occlusion. Ipsilateral posterior-to-anterior collateral flow was present in none of the patients with ICA stenosis and in 5 patients (28%) with ICA occlusion. None of the patients with anterior or posterior collateral flow through the Circle of Willis had intracerebral vascular steal.

Collateral flow via the circle of Willis was considered impaired in 8 of the 38 patients (21%). In one patient with an ICA occlusion the ipsilateral A1 segment was absent, preventing anterior collateral blood flow towards the affected MCA flow territory. Another two patients with an ICA occlusion and five patients with an ICA stenosis had either a hypoplastic PComA or missing P1 segment, preventing posterior collateral blood flow towards the affected MCA flow territory.

The CVR in the MCA flow territory ipsilateral to the ICA stenosis or occlusion did not differ between patients with or without impaired collateral blood flow ($26 \pm 13\%$ vs. $35 \pm 19\%$, $P = 0.18$). Collateral blood flow was impaired in 4 of the 8 patients with intracerebral vascular steal. The volume of the tissue with steal was larger in patients with impaired collateral blood flow than in patients without such impairment (12 ± 5.4 vs. 5.3 ± 1.8 mL brain tissue, $P = 0.002$); the severity of intracerebral vascular steal, i.e. CVR percentage, was not different ($-11 \pm 30\%$ vs. $-12 \pm 33\%$, $P = 0.94$).

Discussion

In the present study, we investigated the extent and severity of intracerebral steal at brain tissue level in patients with steno-occlusive carotid artery disease by combining ASL perfusion MRI with a vascular challenge. Intracerebral steal with a decrease in CBF after acetazolamide was found to be present in about one out of five patients (21%). The volume of intracerebral vascular steal was found to be larger in patients of whom collateral blood flow via the primary collaterals was impaired due to missing segments of the circle of Willis.

Observational studies have found CVR hemodynamic impairment is associated with a higher risk for ischemic stroke in patients with carotid artery disease [3,4]. Less is known about intracerebral steal. It has been incidentally reported to occur in several cere-

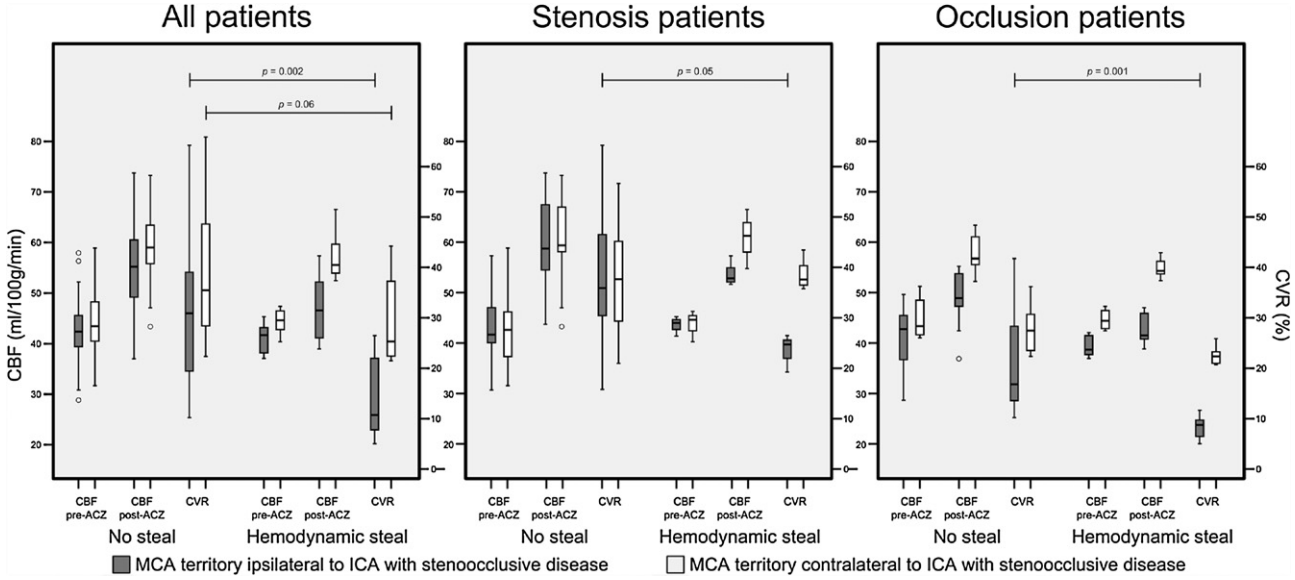

Fig. 3. Cerebral blood flow (left axis, mL/100 mg/min) before (CBF pre-ACZ) and after (CBF post-ACZ) administration of acetazolamide, and reactivity (right axis, percentage increase in CBF) as measured in the territory of the middle cerebral artery (MCA) ipsilateral (gray) and contralateral (white) to the internal carotid artery (ICA) with symptomatic steno-occlusive disease, for all patients (first panel) with and without the presence of hemodynamic steal, and separately per patient group with an ICA stenosis (second panel) or occlusion (third panel).

brovascular diseases that affect the cerebral hemodynamics, such as moyamoya, carotid artery disease and arteriovenous malformations. Case reports have furthermore reported it to be a mechanism for ischemic stroke in a patient undergoing carotid artery stenting with a contralateral ICA stenosis [27]. In the current study, we found intracerebral steal to be present in 15% of the patients with a ICA stenosis and 28% of the patients with an occlusion. This particular result is not sufficiently powered due to the small number of subjects in these groups and does not allow for further comparison. However, we hypothesize that these patients are at higher risk for future cerebral infarction due to severe hemodynamic (CVR) impairment.

Collateral blood flow plays an important role in sustaining adequate tissue perfusion in these patients with flow limiting carotid artery disease and its presence is associated with more favorable outcome [28]. Our results showed that collateralization through the circle of Willis did not have an impact upon the CVR, however that the area of steal was larger in patients without a patent circle of Willis. These findings may indicate that intracerebral vascular steal occurs predominately through leptomeningeal branches from neighboring brain regions, as we found an association between the volume of steal and the completeness of the CoW, presence of collaterals via the circle of Willis, or impairment thereof, and the volume of the tissue with intracerebral vascular steal, but not with the severity of intracerebral vascular steal. Furthermore, the small size of the areas of steal, often within a (collateral) perfusion territory, also suggests the role of leptomeningeal branches from neighboring brain regions. Future studies may use quantitative assessment of the flow volume via the circle of Willis or leptomeningeal vessels, for instance with 3D phase-contrast MRA flow measurements, before and after a vasodilatory challenge to further investigate this.

This is the first study in which ASL perfusion MRI is used to assess the presence of intracerebral steal at brain tissue level. Transcranial Doppler ultrasound is currently the most widely implemented tool in clinical practice for measuring CVR. As this technique measures the flow velocity within major cerebral artery, its use is however limited to measuring the hemodynamic status of large perfusion areas and is unable to assess perfusion and possible steal at brain tissue level. Other techniques are available, such as SPECT or $H_2{}^{15}O$ PET, however require highly specialized facilities and offer limited anatomical information due to low resolution [11–14]. Previously, Heijtel et al. have found that ASL CBF imaging has comparable accuracy and precision to the gold standard of $H_2{}^{15}O$ PET in both resting state and hypercapnia [29]. The main advantage of MRI is that it can more accurately detect ischemic lesions and offers a better discriminative performance in differentiating cerebrovascular events from other diseases that may cause stroke-like symptoms. Further studies are needed to more accurately understand the importance of this hemodynamic steal phenomenon and determine its effect upon the risk of stroke recurrence. By adding functional CVR measurements to the routine clinical imaging protocol, it may offer important information regarding the hemodynamic status and help identify patients that may benefit from treatment.

This study has limitations. First of all, this is an observational study in which we were not able to assess whether presence intracerebral steal in patients with steno-occlusive ICA disease is associated with an increased risk of recurrent stroke. A previous study with blood oxygen level-dependent MRI in patients with carotid artery occlusion showed that patients with a negative CVR had the greatest intracerebral vascular improvement from extracranial-intracranial bypass surgery [30]. However, a large multi-center study, using the PET based oxygen extraction fraction to select patients for bypass surgery, did not show a benefit of surgical treatment when compared to best medical treatment [31]. Further studies are needed to more accurately understand the importance of this hemodynamic steal phenomenon. In the current study, we found intracerebral steal to be present in 15% of the patients with an ICA stenosis and 28% of the patients with an occlusion. This particular result is not sufficiently powered due to the small number of subjects in these groups and does not allow for further comparison. However, we hypothesize that these patients are at higher risk for future cerebral infarction due to severe hemodynamic (CVR) impairment. Another limitation is that the ASL perfusion-weighted images were acquired after a fixed labeling delay. Timing artifacts may have occurred due to delayed arrival of the magnetically labeled blood spins. To minimize this effect, we employed a delay time of 1525 ms seconds, in which there is an effective delay time of more than 3 s for the first protons that were labeled directly after start of labeling.

Conclusions

Intracerebral steal occurs at brain tissue level in patients with carotid artery disease and can be assessed with ASL perfusion MRI. The presence of intracerebral vascular steal is related to more severely declined cerebrovascular reactivity in the surrounding brain tissue area and the volume is associated with impaired primary collateral blood flow through the CoW. Whether patients with intracerebral vascular steal are at higher risk for cerebral ischemic stroke deserves to be studied in future studies.

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Disclosure of interest

The authors declare that they have no competing interest.

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