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Published in:
World neurosurgery

DOI:
10.1016/j.wneu.2019.01.140

Publication date:
2019

Cerebrovascular Reactivity Measured with ASL Perfusion MRI, Ivy Sign, and Regional Tissue Vascularization in Moyamoya

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■ BACKGROUND: **Arterial spin labeling (ASL) perfusion magnetic resonance imaging (MRI) may be used to determine brain regions at risk for ischemia in patients with moyamoya vasculopathy and to identify patients who may benefit from surgical revascularization. We aimed to investigate whether 1) the severity of moyamoya is related to the presence of leptomeningeal collaterals and cerebrovascular reactivity (CVR), 2) the presence of collaterals and ivy sign reflects disturbed CVR, and 3) arterial transit artefacts (ATAs) and ivy sign reflect the presence of collaterals.**

■ METHODS: **We determined severity of moyamoya on digital subtraction angiography (DSA) according to the modified Suzuki classification in 20 brain regions and scored regional tissue revascularization using a 4-point scale. Regional CVR and ATAs were assessed on ASL perfusion MRI, ivy sign on fluid attenuation inversion recovery MRI.**

■ RESULTS: **In 11 patients (median age 36 years; 91% female), we studied 203 regions. ATAs were associated with the presence of collaterals on DSA ($P < 0.01$). Of all regions with clearly visible collateral vessels on DSA, however, only 24% had ATAs. Ivy sign was not related to the presence or absence of collaterals nor to CVR. In 10% of regions with good vascularization on DSA, CVR was poor or showed steal.**

■ CONCLUSIONS: **ATAs were associated with the presence of collaterals on DSA. Although DSA vascularization scores correlated with CVR, 10% of regions with good vascularization on DSA had absent CVR or steal on ASL-MRI. DSA and ivy sign did not provide adequate information on the hemodynamic status of brain tissue in patients with moyamoya vasculopathy.**

INTRODUCTION

Moyamoya vasculopathy (MMV) leads to progressive bilateral narrowing of the supraclinoid internal carotid artery and its proximal branches, and to the formation of a vascular network of vessels at the base of the brain.[1] The majority of patients are children and young adults, predominantly presenting with symptoms of cerebral ischemia or cognitive disorders.[2] There is often a disparity between the angiographic severity of arteriopathy and the severity of clinical symptoms. This could reflect the complex interplay of many factors that influence the hemodynamic state of the brain.[3,4] Vasodilatation of arterioles and collateral flow pathways play important compensatory roles in maintaining regional cerebral blood flow (CBF) and tissue viability.[5] Measurements of CBF change in response to a vasodilatory stimulus (cerebrovascular reactivity [CVR]) have been used to identify patients with MMV

Key words
- Brain ischemia
- Collateral circulation
- Moyamoya
- Perfusion imaging

Abbreviations and Acronyms
ACZ: Acetazolamide
ASL: Arterial spin labeling
ATA: Arterial transit artefacts
CBF: Cerebral blood flow
CVR: Cerebrovascular reactivity
DSA: Digital subtraction angiography
FLAIR: Fluid attenuation inversion recovery
MMD: Moyamoya disease
MMS: Moyamoya syndrome
MMV: Moyamoya vasculopathy
MRI: Magnetic resonance imaging
ROI: Region of interest

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Citation: World Neurosurg. (2019) 125:e639-e650.
https://doi.org/10.1016/j.wneu.2019.01.140

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

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who may benefit from surgical revascularization,[6,7] and to predict postoperative clinical outcome.[8] Arterial spin labeling (ASL) perfusion magnetic resonance imaging (MRI) can be used to measure CVR without requiring contrast agents,[9-12] and seems suitable as a noninvasive method to detect disturbed cerebral hemodynamics in patients with MMV.

Noninvasive methods to demonstrate the presence of leptomeningeal collaterals could also help to determine the vascularization of hypoperfused regions. So-called arterial transit artefacts (ATAs) on ASL CBF maps have been suggested to reflect the presence and intensity of leptomeningeal collaterals in MMV.[10,13,14] Furthermore, the "ivy sign," which refers to a hyperintense leptomeningeal signal on T2-weighted fluid attenuation inversion recovery (FLAIR) imaging,[15] may reflect the presence of leptomeningeal collaterals as seen on digital subtraction angiography (DSA), and has been correlated with a disturbed CBF and CVR.[16] The ivy sign has also been associated with the severity of clinical symptoms.[17] Therefore, it may be suggested that an ivy sign may indicate a hemisphere at risk for ischemia as represented by impaired hemodynamics in MMV.[18]

The aim of this study was to investigate in patients with MMV 1) the relation between the severity of MMV and the presence of collaterals and CVR, 2) whether ATAs and ivy sign are associated with the presence of leptomeningeal collaterals on DSA, and 3) whether collateral vascularization on DSA and the presence of an ivy sign reflect a disturbed CVR.

METHODS

This study was approved by the Institutional Medical Ethics Committee. Written informed consent for participation was obtained from all patients or their parents. The procedures followed were in accordance with institutional guidelines.

Patient Characteristics

We included patients diagnosed with moyamoya disease (MMD) or moyamoya syndrome (MMS, with known associated disease)[1] in the UMCU between 2009 and 2012 who underwent ASL-MRI. Symptoms included transient ischemic attack(s) or ischemic stroke. Patients underwent DSA and MRI for clinical workup. We excluded patients 1) with intracranial hemorrhage, 2) who previously underwent cerebral revascularization, and 3) who needed sedation for MRI. We obtained information on sex, medical history, age at first symptoms, clinical symptoms at the time of ASL perfusion MRI, and duration of follow-up.

DSA

Cerebral angiography was performed using standard fluoroscopic DSA techniques on a bi-plane Allura Xper FD20 system (Philips, Best, the Netherlands). The internal and external carotid arteries and both vertebral arteries were selectively catheterized in all patients. Anterior-posterior and lateral images were acquired after manual injection of contrast.

DSAs were reviewed independently by 2 investigators (CJMK, E-JV) who were blinded for the ASL perfusion results. Discrepancies were resolved in a consensus meeting (MMMB, E-JV, CJMK). Hemispheric severity of the MMV was categorized on DSA according to the modified Suzuki classification for each hemisphere individually (**Supplementary Table 1**).[19] Regional tissue vascularization, reflected by the presence or absence of anterograde flow through the branches of the circle of Willis and the presence and intensity of collateral blood vessels, was scored in 10 regions of interest (ROIs) of each hemisphere (**Figure 1**) using a 4-point vascularization scale according to a previously published method: 0, indicating *absence of capillary blush, no visible leptomeningeal collaterals*; 1, *filling through mild to moderate leptomeningeal collaterals*; 2, *complete irrigation of the region via leptomeningeal collateral flow*; 3, *normal antegrade flow without visible collaterals*.[20] We dichotomized DSA vascularization scores 0 and 1 as *abnormal vascularization* and scores 2 and 3 as *good vascularization* to determine the relation between vascularization and CVR. To relate ATAs and ivy sign with the presence of collaterals, we dichotomized DSA scores 0 and 3 as *collaterals absent*, and 1 and 2 as *collaterals present*. To statistically relate the presence or absence of ATAs and of the ivy sign with the presence or absence of collaterals on DSA, we dichotomized DSA scores 0 and 3 as collaterals absent, and 1 and 2 as collaterals present.

MRI Protocol

MRI was performed on a 3 Tesla MR scanner (Achieva; Philips Medical Systems, Best, the Netherlands), equipped with a 16-channel coil and locally developed software to enable ASL perfusion imaging for CBF assessment. ASL perfusion images were acquired using a pseudo-continuous labeling technique according to a previously published protocol (see **Supplementary Methods** for imaging and perfusion protocol).[21] All imaging markers were scored in the identical 10 ROIs of each hemisphere.

For visual assessment of regional CVR, we obtained CBF maps (in mL 100 g^{-1} min^{-1}) before and after administration of acetazolamide (ACZ). CVR was defined as an increase in CBF after administration of ACZ. Two investigators (MMMB, RPHB), blinded for the DSA results, visually scored the CVR on a 2-point scale: 0, indicating *CVR as absent or steal* (defined as a decrease of CBF after ACZ, **Figure 2A**); 1, *CVR present*. The presence or absence of ATAs defined as small foci of increased signal intensity on the CBF map before ACZ administration was noted for each region.[22] The presence of infarction was examined on the FLAIR sequence because diffusion and restriction images can be used to assess acute ischemic lesions but are less well suited to delineate established infarcts. In our study, we noted and delineated existing brain infarcts beyond the acute stage.

Ivy sign was defined as a linear high signal intensity along the cortical sulci on FLAIR images. Three investigators (AK, EJV, KPJB) together scored the ivy sign on a 3-point scale: 0, indicating *no ivy sign*; 1, linear ivy sign (more than 1 dot) in less than half of the region (*moderate ivy sign*); 2, linear ivy sign in more than half of the region (*clear ivy sign*; **Figure 2B**).[15]

Data Analysis

To measure the agreement between the 2 investigators who independently scored tissue vascularization on DSAs, we calculated a kappa score. Dichotomized DSA vascularization scores (where abnormal was defined as score 0 or 1) were compared between hemispheres with modified Suzuki stages I to IV, using modified Suzuki stage I as a reference, by χ^2 tests. In the same way, we assessed the relation between dichotomized CVR scores (abnormal score 0)

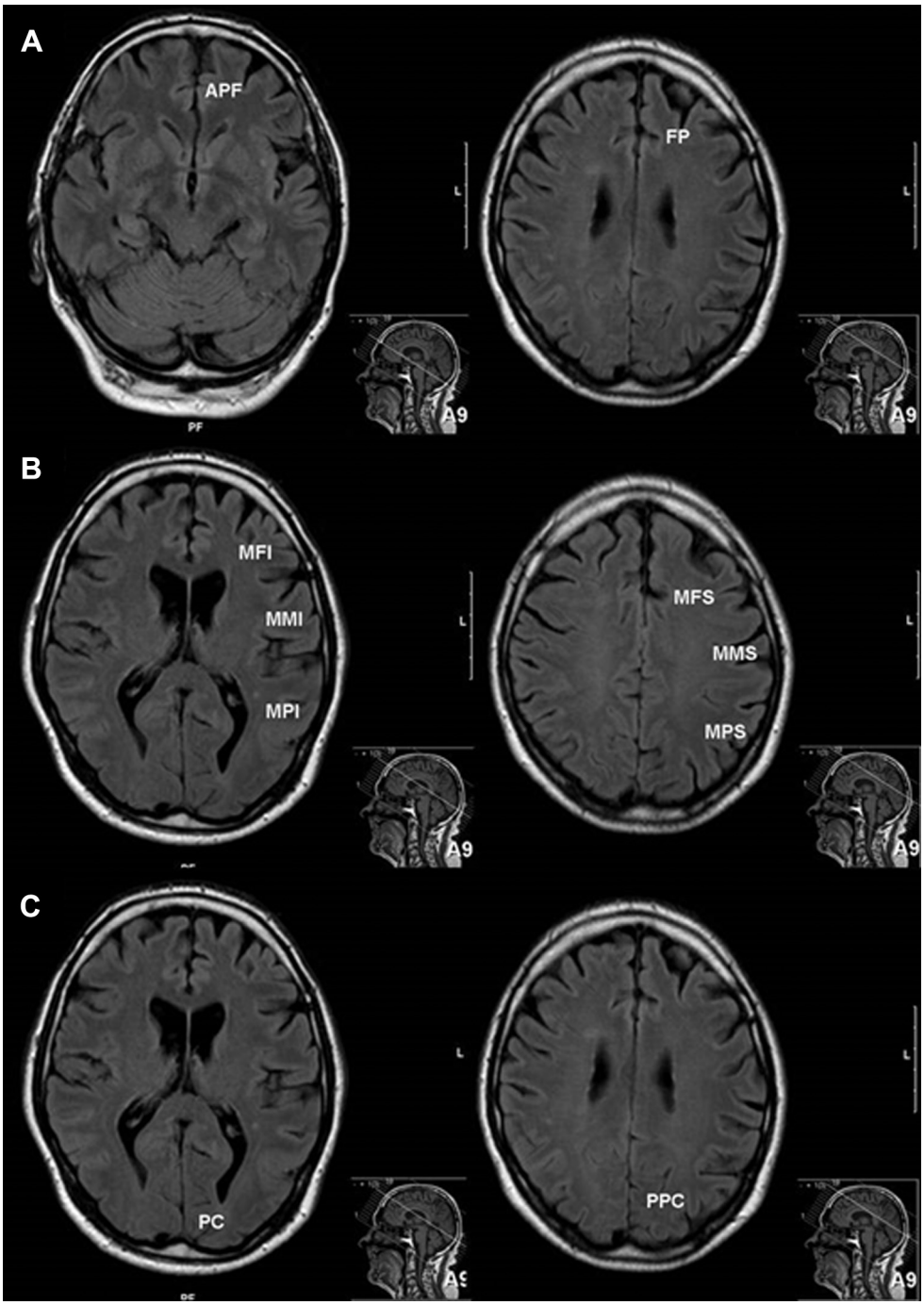

Figure 1. T2-weighted magnetic resonance image illustrating the location of the 10 regions of interest in each hemisphere in which tissue vascularization on digital subtraction angiography, cerebral vascular reactivity, the presence of arterial transit artefacts, and the ivy sign were scored. (**A**) The anterior cerebral territories; (**B**) the middle cerebral territories; (**C**) the posterior cerebral territories.

with modified Suzuki stages, and the association of dichotomized ivy scores (ivy sign present: scores 1 and 2) with modified Suzuki stages. We determined the relation between ATA and ivy sign and the presence of leptomeningeal collaterals on DSA, and between vascularization and ivy sign or the presence or absence of CVR. We used χ^2 tests to identify associations between all these variables.

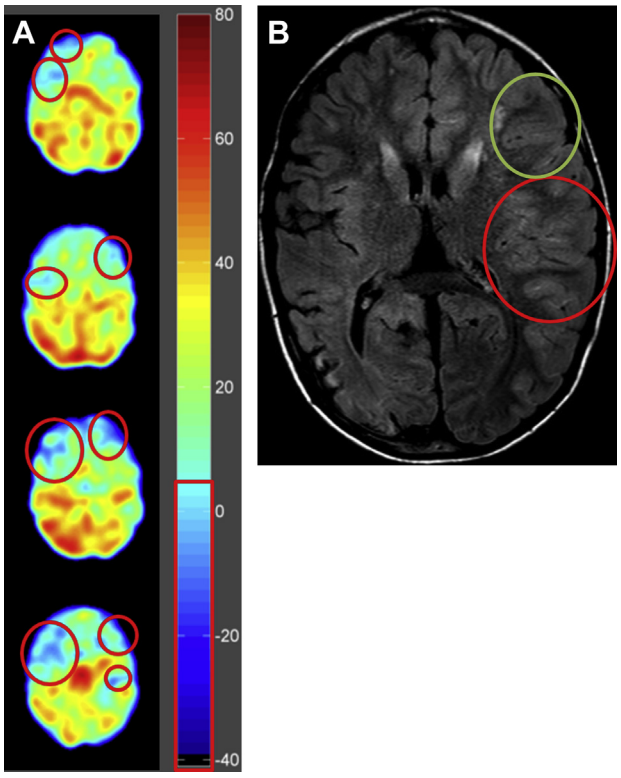

Figure 2. (**A**) Example of cerebrovascular (CVR) score 0 (absent CVR/steal; dark blue color [indicated by the *red circles*]; patient 5). (**B**) Example of score 1 (moderate; *green circle*) and score 2 (clear; *red circle*) ivy sign (patient 9) on fluid attenuation inversion recovery magnetic resonance imaging.

RESULTS

Patient Characteristics

We performed ASL perfusion MRI in 13 patients and excluded 2 patients with poor quality of the perfusion scans, showing a large region with high signal intensity at the base of the brain and large areas of absent signal in the cortex. Of the remaining 11 patients (1 male), 3 were children (median age 7 years, range 5–14 years) and 8 young adults (median age 36 years, range 18–43 years, Table 1). Eight patients had an ischemic stroke, and 3 patients had transient ischemic attacks only. Three patients were diagnosed with MMS (sickle cell disease, ependymoma resection, neurofibromatosis type I). There were clear ischemic lesions (white matter lesions or infarcts) in all but 1 hemisphere.

The right hemisphere of patient 2 with complete ischemic stroke was excluded. One of the left posterior areas in patient 7 was excluded because of a cortical infarction. The 2 left frontal regions were excluded in patient 8 (after resection of ependymoma). In patient 10, collateral flow on DSA could not be assessed in the bilateral posterior regions because of the absence of images. For further analysis, we included 203 regions.

Severity of MMV and DSA Vascularization Scores

The modified Suzuki classification was scored as stage 1 in 4 hemispheres, stage 2 in 6, stage 3 in 9, and stage 4 in 2 hemispheres. There was substantial agreement between the 2 investigators (kappa 0.74) in the scoring of tissue vascularization. There were 18 regions (9%) with mild-to-moderate collaterals (score 1), 103 regions (51%) in which there was complete irrigation via collaterals (score 2), 82 regions (40%) with normal antegrade flow (score 3), and no regions in which a visible capillary or collateral blush was absent (score 0). Good tissue vascularization (scores 2 and 3) was found in 185 regions (91%). The relative number of regions with abnormal DSA vascularization scores in hemispheres with modified Suzuki stages 2 (11%, $P = 0.03$) and 3 (14%, $P = 0.01$) was significantly higher than the number of abnormal regions in hemispheres with modified Suzuki stage 1 (0%) (Figure 3A).

CVR, ATAs, and Ivy Sign

CVR maps showed reactivity after administration of ACZ in 87% (176) of regions, and absent CVR or steal in 13% (27 regions). ATAs were present in 17% (34 regions), visible in all but 1 patient. Ivy sign was seen in 45% (92 regions), of which 92% (85 regions) were classified as moderate and 8% (7 regions) as severe.

Association of DSA Vascularization Scores with ATAs and Ivy Sign

The presence of ATAs was associated with collateral vascularization ($P < 0.01$). From the regions in which ATAs were detected, 85% (29/34) showed collaterals on DSA. However, of all regions with clearly visible collateral vessels on DSA (scores 1 and 2), only 24% (29/121) had ATAs (Table 2).

If an ivy sign was present (score 1 or 2), 59% of regions (54/92) showed collaterals on DSA. Only 45% of regions (54/121) with DSA collaterals showed an ivy sign. Ivy sign and DSA vascularization scores were not associated ($P = 0.94$).

In 53% of regions (18/34) with ATAs, an ivy sign was found. Of regions with an absent ivy sign, 86% showed no ATAs. Ivy sign and ATAs were not significantly associated ($P = 0.33$, Supplementary Table 2).

Association of DSA Vascularization Scores, Ivy Sign, ATAs, and CVR

DSA vascularization scores were related to the presence or absence of CVR ($P < 0.01$); of regions with good tissue vascularization (scores 2 and 3), only 10% of regions (19/185) had absent CVR or steal (Table 3), compared with 44% of regions with suboptimal vascularization (score 1). All 203 areas had either some degree of collaterals or normal antegrade vascularization on DSA. Of these, 13% (27/203) with proven absent CVR the diminished tissue perfusion at risk for ischemia would not have been appreciated using DSA alone.

We found no association between an ivy sign and CVR ($P = 0.55$); when an ivy sign was present (score 1 or 2), 88% of regions (81/92) still had preserved CVR, and if there was no ivy sign (score 0), 14% of regions (16/111) had absent CVR or steal. In only 12% of regions (11/92) with absent CVR or steal, we could identify an ivy sign.

Table 1. Clinical and Radiological Characteristics

Patient Sex (Age)	History	Site	Clinical Symptoms*	MRI Findings per Hemisphere	mSs	Abnormal Vascularization† (%)	Abnormal CVR‡ (%)	Cortical ATAs§ (%)	Abnormal Ivy Sign‖ (%)	Time ASL-DSA (weeks)	Follow-Up
1 F (14)	SCD, R MCA AIS, 3 and 1 year before, headache	R	—	Cortical atrophy, frontal SC MCA infarct, multiple WML	3	10	20	20	40	7	Stable for 2 years
		L	L pyramidal tract signs	Occipital SC infarct, multiple WML	1	0	0	0	50		
2 F (38)	Complete R hemispheric AIS 1 year before, hemicraniotomy	R	Signs of complete hemispheric AIS	Infarct complete hemisphere, signs of craniotomy	—	—	—	—	—	<1	L STA-MCA bypass after 4 months
		L	MCA TIAs	IWS infarcts, small cortical ACA + MCA infarcts	3	20	20	0	10		
3 F (39)	R MCA TIAs, R caudate nucleus infarct 3 years before, cognitive problems	R	—	Atrophy, multiple WML, BG + SC infarcts	2	10	60	10	40	1	L STA-MCA bypass after 3 months, L MCA AIS 5 months after bypass
		L	MCA TIAs	Atrophy, frontal CWS infarcts, multiple WML	2	20	60	0	40		
4 M (7)	None	R	Hemispheric TIAs for 5 months	Multiple WML	2	20	50	40	50	4	L STA-MCA bypass + indirect bypass after 6 months
		L	Hemispheric TIAs for 5 months	Multiple WML	3	20	40	60	40		
5 F (41)	R MCA AIS, 10, 9, and 7 years before, headache, cognitive problems	R	Pyramidal tract signs	Atrophy, frontal cortical MCA infarct, multiple WML	3	0	100	20	80	7	Stable during 2 years
		L	Pyramidal tract signs	Atrophy, multiple WML	3	0	100	20	50		
6 F (43)	Headache	R	MCA TIAs since 1 year	Frontal CWS + IWS infarcts	1	0	70	10	60	10	Stable during 1 year
		L	MCA TIAs since 1 year	Frontal CWS + IWS infarcts	1	0	10	20	30		

ACA, anterior cerebral artery; AIS, arterial ischemic stroke; ASL, arterial spin labeling; ATA, arterial transit artefacts; BG, basal ganglia; CVR, cerebrovascular reactivity; CWS, cortical watershed; DSA, digital subtraction angiography; IWS, internal watershed; L, left; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mSs, modified Suzuki stages; NF, neurofibromatosis; PCA, posterior cerebral artery; R, right; SC, subcortical; SCD, sickle cell disease; STA, superficial temporal artery; TIA, transient ischemic attack; WHO, World Health Organization; WML, white matter lesion.

*Clinical symptoms at the time of ASL MRI.

†The proportion of regions (%) per hemisphere with abnormal vascularization (score 0 or 1).

‡The proportion of regions (%) per hemisphere with moderate or absent CVR (score 0 or 1).

§The proportion of regions with ATAs per hemisphere.

‖The proportion of regions (%) per hemisphere with an abnormal ivy sign (score 1 or 2).

Continues

Table 1. Continued

Patient Sex (Age)	History	Site	Clinical Symptoms*	MRI Findings per Hemisphere	mSs	Abnormal Vascularization† (%)	Abnormal CVR‡ (%)	Cortical ATAs§ (%)	Abnormal Ivy Sign‖ (%)	Time ASL-DSA (weeks)	Follow-Up
7 F (35)	L MCA-PCA AIS 1 year before, R hemianopia	R	—	IWS infarcts	3	10	90	30	80	<1	L STA-MCA bypass after 2 months
		L	MCA TIAs since 1 year	Occipital cortical + IWS infarcts	3	22	100	0	56		
8 F (18)	Resection L frontal ependymoma (WHO3) 3 years before, radiotherapy	R	—	IWS infarcts	2	0	70	10	10	4	Indirect bypass after 2 months, no tumor recurrence
		L	MCA TIAs since weeks	IWS infarcts, frontal resection cavity with surrounding gliosis	3	0	75	13	0		
9 F (5)	R ACA infarct, 1 year before	R	MCA TIAs since 1 year	Atrophy, frontal CWS + IWS infarcts, multiple WML	3	40	100	20	60	<1	R STA-MCA bypass after 7 months, L STA-MCA bypass after 25 months
		L	—	Multiple WML	1	0	0	10	100		
10 F (19)	NF1, cerebral hamartomas, radiotherapy for optic glioma 15 years before, cognitive problems	R	Pyramidal tract signs	—	2	0	13	13	38	28	Stable during 4 years
		L	—	Atrophy, cortical/SC ACA + MCA infarcts	2	13	75	0	13		
11 F (27)	Headache, L MCA AIS 6 years before	R	Sensory disturbances	IWS infarcts	4	0	30	20	0	22	Stable during 1 year
		L	—	Cortical ACA infarct, IWS infarcts	4	0	20	30	10		

ACA, anterior cerebral artery; AIS, arterial ischemic stroke; ASL, arterial spin labeling; ATA, arterial transit artefacts; BG, basal ganglia; CVR, cerebrovascular reactivity; CWS, cortical watershed; DSA, digital subtraction angiography; IWS, internal watershed; L, left; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mSs, modified Suzuki stages; NF, neurofibromatosis; PCA, posterior cerebral artery; R, right; SC, subcortical; SCD, sickle cell disease; STA, superficial temporal artery; TIA, transient ischemic attack; WHO, World Health Organization; WML, white matter lesion.

*Clinical symptoms at the time of ASL MRI.

†The proportion of regions (%) per hemisphere with abnormal vascularization (score 0 or 1).

‡The proportion of regions (%) per hemisphere with moderate or absent CVR (score 0 or 1).

§The proportion of regions with ATAs per hemisphere.

‖The proportion of regions (%) per hemisphere with an abnormal ivy sign (score 1 or 2).

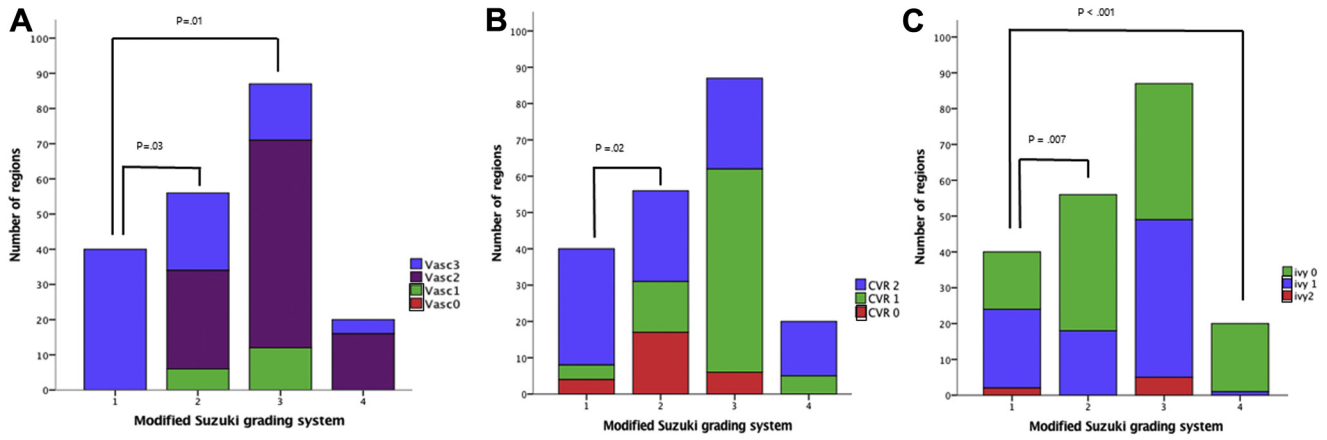

Figure 3. The modified Suzuki grading system per hemisphere in relation to the digital subtraction angiography vascularization scores (**A**, abnormal scores 0 and 1), cerebrovascular (CVR) scores (**B**, absent score 0), and ivy sign scores (**C**, present scores 1 and 2).

There was no association between the presence of ATAs and CVR ($P = 0.79$); when ATAs were present, 85% of regions (29/34) still had preserved CVR, and if there were no ATAs present, 13% of regions (22/169) had absent CVR or steal.

Regions with good and poor CVR were seen in each of the 4 hemispheric modified Suzuki stages. Nevertheless, the relative number of regions with absent CVR or steal in hemispheres with modified Suzuki stage 2 was significantly higher than the number of regions in hemispheres with modified Suzuki stage 1 ($P = 0.02$), which was not the case in hemispheres with modified Suzuki stage 3 ($P = 0.55$) or stage 4 ($P = 0.14$, Figure 3B). The relative number of regions with an ivy sign in hemispheres with modified Suzuki stages 2 and 4 was significantly higher than the number of regions in hemispheres with modified Suzuki stage 1 ($P = 0.01$; $P < 0.01$), but not in hemispheres with modified Suzuki stage 3 ($P = 0.70$, Figure 3C).

DISCUSSION

In patients with MMV, ATAs may reflect the presence of leptomeningeal collaterals on DSA, although ATAs were found in only a quarter of the regions with clear DSA collaterals. Ivy sign was not related to the presence or absence of collaterals on DSA, nor did it reflect absent CVR. In 13% of regions with normal antegrade vascularization or some degree of collaterals, ASL-MRI revealed absent CVR or steal. The number of regions with abnormal vascularization in hemispheres with modified Suzuki stages 2 and 3 was significantly higher than the number of regions in hemispheres with stage 1.

There is large variability in the clinical presentation of MMV,[1] which might reflect the complex interplay of many factors that influence the hemodynamic status of the brain.[3,4] Furthermore, the differences in disease characteristics between patients with

Table 2. Arterial Transit Artefacts (ATA) and Ivy Sign in Comparison with Digital Subtraction Angiography (DSA) Vascularization Score

	DSA Vascularization Score				
		Collaterals Present			
	0: No Visible Capillary or Collateral Blush	1: Mild-to-Moderate Collaterals	2: Complete Irrigation of the Region via Collateral Flow	3: Normal Antegrade Flow without Collaterals	Total
ATA					
Absent −	0	13	79	77	169
Present +	0	5	24	5	34
Ivy sign					
0: absent −	0	10	57	44	111
1: moderate +	0	8	42	35	85
2: clear +	0	0	4	3	7

Table 3. Digital Subtraction Angiography (DSA) Vascularization Score, Arterial Transit Artefacts (ATAs), and Ivy Sign in Comparison with Present and Absent Cerebrovascular Reactivity (CVR)/Steal

	CVR		
	Present	Absent	Total
DSA vascularization score			
Good vascularization			
3: normal antegrade flow without collaterals	74	8	82
2: complete irrigation of the region via collateral flow	92	11	103
Suboptimal vascularization			
1: mild-to-moderate collaterals	10	8	18
0: no visible capillary or collateral blush	0	0	0
Ivy sign			
0: absent −	95	16	111
1: moderate +	74	11	85
2: clear +	7	0	7
ATA			
0: absent −	147	22	169
1: cortical +	29	5	34

MMD and MMS are yet to be established.[23] Although there was no overall significant correlation between the regional absence or presence of CVR and hemispheric Suzuki grading, the relative number of regions with absent CVR or steal in hemispheres with modified Suzuki stage 2 was significantly higher than that in hemispheres with stage 1. This was not the case for the highest hemispheric Suzuki scores 3 and 4. An explanation could be that the Suzuki scoring is largely based on the development (or absence) of basal moyamoya collaterals, which not necessarily reflects the degree of vascularization in downstream tissue, illustrating the importance of being informed on the leptomeningeal collateralization status in addition to regional hemodynamics. Other studies that investigated the relationship between DSA findings and hemodynamic parameters in patients with MMV demonstrated that patients with extensive basal collaterals had significantly lower CBF than normal controls.[19] Also, there was a tendency for hemispheric CBF to decrease with advancing stages of MMD.[24] CVR however may be a more informative tool to measure hemodynamic compromise than CBF alone.[25,26] A previous study has shown a correlation between CVR and the presence of collateral vessels per vascular territory, and with the degree of MMV as graded by the modified Suzuki grade (although not significant).[27] Our results show that DSA vascularization scores relate to the presence of CVR, but do not accurately identify individual brain regions with compromised CVR, as measured in 203 regions. Regions with the same DSA vascularization status may have completely different CVR. Perhaps, some of the collaterals visible on DSA are unable to dilate to ACZ because they had already reached maximal dilatation, and therefore, the presence of these collaterals may be a sign of hemodynamic stress with severely impaired CVR instead of a dilatation caused by ACZ. Our findings support the hypothesis that the basal moyamoya collaterals probably do not reflect the degree of vascularization in downstream tissue and illustrate the importance of being informed on the leptomeningeal collateralization status in addition to regional hemodynamics.

This is the first study that measured ivy sign in more than 4 regions of the brain, related CVR as measured on ASL-MRI with an ivy sign, and associated ivy sign with leptomeningeal collaterals as seen on DSA and with ATAs. Although it has been suggested by previous authors that the presence of an ivy sign could be considered together with the other clinical and diagnostic parameters, like hemodynamic compromise, when considering revascularization,[17,18] we could not associate ivy sign with absent CVR or steal. In regions with an ivy sign present, 88% of regions still had good CVR, and in regions where CVR was absent or where we found steal, only 12% had ivy sign. Furthermore, we could not relate ivy sign to the presence of leptomeningeal collaterals, ivy sign was not detected in all the regions with collaterals on DSA, and collaterals were not detected in all the regions with an ivy sign. Several theories explaining the ivy sign have been be suggested.[18] It could represent arteriolar dilatation, caused by decreased perfusion pressure distal to the stenosis/occlusion.[15] This would agree with the cortical "conjunctivitis-like" appearance as seen peroperatively during revascularization, which would be in accordance with the previous finding that the ivy sign is related to impaired hemodynamic status,[15,17,18] a finding we could not replicate. Furthermore, an ivy sign could represent a retrograde slow flow of pial vasculature through the

leptomeningeal collaterals,[17] although this was not supported by increased oxygen extraction fraction on positron emission tomography.[15] In addition, a postoperative de novo ivy sign has been observed in hyperperfused hemispheres, explained by the authors as a (transient) focal increase of CBF in pial vessels,[28] which contradicts earlier studies.[15,18] One theory explaining our results could be that there are 2 phenomena that neutralize each other: 1) diminished perfusion causes maximal vasodilatation (thus absent CVR) of the leptomeningeal vessels causing an ivy sign and in these areas one could expect good vascularization scores on DSA, whereas, on the other hand, 2) in areas with diminished perfusion, there are an insufficient number of leptomeningeal vessels and thus an absent ivy sign. Another theory could be that the ivy sign represents blood in venous, rather than arterial vessels, becoming more apparent due to the slow flow of the leptomeningeal arterial vessels. Until the pathophysiology of the ivy sign is established, it remains unclear whether the ivy sign can be used as a parameter to identify regions with compromised perfusion in the preoperative diagnostic workup, or to evaluate the effect of cerebral revascularization.

A strength of our study is that we evaluated the relation between regional perfusion status based on DSA and CVR with a noninvasive technique that may provide additional information on tissue at risk for ischemia. Studies showed that ASL perfusion MRI can be applied to measure hemodynamics in MMV; however, there are limitations.[10,29] In ASL perfusion MRI, an image is acquired after a postlabel delay time, during which the tagged blood flows to the ROI. When blood travels through a collateral network of vessels, the delay between tagging and the time it reached the ROI (transit delay) increases. ASL perfusion MRI fails in regions with very long transit delay,[29,30] which was probably the case in 2 of our patients. Increasing the postlabel delay time is an option, but may be offset by loss of signal due to the relatively short tracer half-life determined by the T1 of blood.[10,29] Labeled arterial blood still traveling through the arteries when the ASL image is acquired causes ATAs.[10,25] A previous study concluded that the identification of ATAs on CBF maps can predict the presence and intensity of collateral flow in patients with MMV.[10] Our study confirms that the detection of ATAs is associated with the presence of collaterals. ATAs contain important information about late arriving flow, but they also make quantification of regional CBF less reliable because they can average out regions with hypoperfusion.[10] We therefore refrained from determining regional absolute CBF values in our patients. The CVR provides a relative measure of CBF changes that is independent of quantitative ASL perfusion CBF values in patients with vascular disease that have ATAs. This study has other limitations. First, the number of patients studied is relatively small. Furthermore, because we included only 3 patients with MMS of whom 6 brain areas had to be excluded for various reasons, we could not investigate differences in cerebral hemodynamics, ivy sign, and tissue vascularization between patients with MMD and MMS. Nevertheless, we think that the analysis of 203 brain regions in these 8 patients with different diagnostic modalities adds value in understanding the complexity of cerebral hemodynamics in patients with MMV.

CONCLUSIONS

The severity of moyamoya seems to be related to the number of regions with abnormal vascularization. Furthermore, DSA alone does not provide sufficient information on the hemodynamic status of brain tissue in MMV because some regions with good vascularization on DSA may still reveal absent or poor CVR. Regions with good and absent CVR were seen in each of the 4 hemispheric modified Suzuki stages. Although the presence of collaterals seems to be correlated to the presence or absence of CVR, 13% of regions with normal vascularization or some degree of collaterals had absent CVR or steal. The presence of an ivy sign is not related to the presence of collaterals on DSA, nor does it predict disturbed CVR. ATAs however may predict the presence of collaterals on DSA. This study shows that hemodynamic studies seem to be a valuable tool in the preoperative workup to determine a hemisphere at risk for ischemia.

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Conflict of interest statement: This work was supported by the Dutch Brain Foundation ([2012(1)-179]; the Christine Bader Fund Irene Children's Hospital), the Tutein Nolthenius Oldenhof Fund, the Johanna Children Fund, and Friends of the Wilhelmina Children's Hospital. C. J. M. Klijn is supported by a Clinical Established Investigator grant from the Dutch Heart Foundation (grant number 2012T077) and an Aspasia grant from ZonMw (grant number 015008048). R. P. H. Bokkers is supported by a Physician in Training grant from the Dutch Heart Foundation (grant number 2013T047).

Received 25 October 2018; accepted 14 January 2019

Citation: World Neurosurg. (2019) 125:e639-e650.
https://doi.org/10.1016/j.wneu.2019.01.140

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

SUPPLEMENTAL METHODS

Imaging Protocol

The imaging protocol was standardized and included diffusion-weighted imaging, T2-weighted fluid attenuation inversion recovery imaging, transverse dual turbo spin-echo, fast field echo, and an arterial spin labeling (ASL) perfusion-weighted imaging sequence before and 15 minutes after intravenous administration of am acetazolamide bolus (20 mg/kg; 1 g maximum). A T1-weighted spin-echo sequence was obtained in the sagittal plane for positioning of the imaging section.

Perfusion images were acquired using a pseudo-continuous arterial spin labeling sequence according to a previously published protocol.[1] Labeling was performed by employing a train of radiofrequency pulses at an interval of 1 millisecond (ms) for the duration of 1650 ms. Control images were acquired by adding 180° to the phase of all even radiofrequency pulses. Seventeen slices with an in-plane resolution of 3 × 3 mm^2 aligned parallel to the orbitomeatal angle were acquired in an ascending fashion with single shot echo planar imaging in combination with background suppression and parallel imaging (SENSE factor 2.5), 1525 ms after the labeling stopped. The other ASL magnetic resonance imaging parameters were repetition time 4000 ms; echo time 14 ms; pairs of control/label 38; field of view 240 × 240 × 119 mm; matrix 80 × 79; scan time 4½ minutes. All patients received intravenous acetazolamide before and after ASL perfusion magnetic resonance imaging, and capillary blood gas and clinical observation for several hours after imaging, according to a clinical protocol. Data were analyzed with Matlab (version 7.5; MathWorks, Natick, Massachusetts, USA), and SPM5 (Wellcome Trust Centre for Neuroimaging, Oxford, England). Cerebrovascular reactivity was defined as the percentage of increase in cerebral blood flow after administration of acetazolamide.

Supplemental Table 1. Modified Suzuki Classification[2]

Modified Suzuki angiographic stages	
I	Mild-to-moderate stenosis around carotid bifurcation with absent or slightly developed moyamoya vessels
II	Severe stenosis or occlusion around carotid bifurcation with well-developed moyamoya vessels. At least several of ACA or MCA branches remain opacified in an antegrade fashion
III	Occlusion of both proximal ACA and MCA with well-developed moyamoya vessels. Only a few of either ACA or MCA branches are faintly opacified in an antegrade fashion
IV	Complete occlusion of both proximal ACA and MCA with absent or small number of moyamoya vessels

ACA, anterior cerebral artery; MCA, middle cerebral artery.

Supplemental Table 2. Arterial Transit Artefacts (ATAs) in Relation to Ivy Sign in 203 Brain Regions

	Ivy Sign			
	No Sign	Moderate Sign	Clear Sign	Total
ATAs				
No ATAs	95	69	5	169
Cortical ATAs	16	16	2	34
Total	111	85	7	203

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