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Impaired cerebrovascular reactivity is associated with recurrent stroke in patients with severe intracranial arterial stenosis: A C02 BOLD fMRI study

AUTHORS

Jérémie Papassin^{a-c}, Olivier Heck^d, Eric Condamine^e, Johan Pietras^e, Olivier Detante^{a,c}, Alexandre Krainik^{c-e}

- a. Stroke Unit, Grenoble Alps University Hospital, 38043 Grenoble, France
- b. Stroke Unit, Metropole Savoie Hospital, 73000 Chambéry, France
- c. Univ. Grenoble Alps, Grenoble Institute of Neurosciences, 38042 Grenoble, France
- d. Department of Neuroradiology, Grenoble Alps University Hospital, 38043 Grenoble, France
- e. Univ. Grenoble Alps, Inserm, CNRS, Grenoble Alps University Hospital, IRMaGe, 38043 Grenoble, France

* Corresponding author:

Telephon number: +33 4 76 76 54 85

Fax number: +33 4 76 76 52 86

Email: akrainik@chu-grenoble.fr

Address: Pr A. KRAINIK, department of neuroradiology, University Hospital of Grenoble CS 10217, 38043 Grenoble cedex 9, France

INTRODUCTION

Severe intracranial arterial stenosis (SIAS) account for approximately 10% of cerebrovascular ischemic strokes[1]. SIAS are associated with high rates (18%/year) of recurrent ischemic stroke in the territory of the stenotic artery[2,3]. Large randomized trials demonstrated better outcomes with intensive medical management compared to recanalization procedures using intracranial stenting[4,5] or surgical extracranial-intracranial bypass[6]. Old infarct, new stroke presentation, border-zone infarct, impaired collateral flow, and absence of statin use at enrollment were independently associated with high recurrence rates of stroke in the “medical” group of SAMMPRIS trial[7,8]. Additionally, impaired cerebrovascular reserve was also suggested as a risk factor of stroke recurrence[9].

Indeed, when perfusion pressure drops downstream SIAS, autoregulation may maintain cerebral blood flow (CBF) constant by vasodilation increasing cerebral blood volume (CBV). This additional dilation, known as cerebrovascular reserve, might be insufficient to compensate further perfusion pressure decrease[10]. The estimation of cerebrovascular reactivity (CVR) using perfusion measures before and after vasodilatory stimulus has been proposed to identify patients with exhausted cerebrovascular reserve[10–12].

While positron emission tomography remains the “gold standard” technique[13] to assess CVR, alternative methods have been advocated, such as transcranial Doppler ultrasonography (TCD)[14], Xenon-enhanced computed tomography[15], single-photon emission computed tomography (SPECT)[16], and more recently functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast or arterial spin labelling (ASL)[12]. Most common vasodilatory stimuli are acetazolamide and CO₂[9,17]. Intravenous acetazolamide administration is exposed to side effects, contraindications, and large inter-subject variability[18]. Among these techniques, CVR BOLD fMRI is an accessible, non-invasive, and reproducible whole brain imaging method[19,20]. Thus, well tolerated CO₂

inhalation with immediate and transient vasodilation is now advocated to be the most suitable stimulus[18–21].

This study conducted on SIAS patients, evaluated the relationships between CVR fMRI and recurrence of ischemic stroke. We hypothesized that the occurrence of recurrent events downstream a unilateral SIAS would be related to a significant CVR asymmetry.

METHODS

Study participants

The study protocol was approved by our ethics committee on human research (B120620-10). We conducted an observational study on adult patients referred to the Grenoble Alps University Hospital for transient ischemic attack (TIA) or non-disabling ischemic stroke that was attributed to a unilateral severe (70–99%) intracranial arterial stenosis (SIAS) of the internal carotid (ICA) or the first segment of the middle cerebral artery (MCA). Optimal medical treatment was implemented for each patient, with management of blood pressure and diabetes, antiplatelet agents, and lipid-lowering statins.

We excluded patients with “tandem” extracranial carotid stenosis or occlusion, intraluminal thrombus proximal to the target lesion, non-atherosclerotic causes of intracranial stenosis, presence of a cardiac source of embolus, history of stent placement, cervical endarterectomy or extra-intracranial bypass surgery, contraindication to MRI or to Gadolinium-Dota injection. We also excluded patients with incomplete MRI protocol due to excessive head motion (translation or rotation $>2\text{mm}$ or $>2^\circ$ in any direction, respectively) or inappropriate hypercapnic stimulus.

Individual data collection and follow-up

Qualifying ischemic stroke related data were obtained from individual medical records and included: vascular risk factors, medical history, National Institutes of Health Stroke Scale (NIHSS) at hospital admission, modified Rankin Scale (mRS) at discharge, glycosylated hemoglobin and lipid testing. Severity of stenosis was assessed by brain CT angiography[22]. Clinical follow-up period ranged from qualifying event until death, loss of follow-up or study

end. All patients were seen yearly or more frequently if needed. Recurrent stroke or TIA, adverse events and assessment of the patient's functional abilities and mobility using the mRS were conducted by a neurologist. Any stroke or TIA in the territory of the qualifying artery was considered to be a recurrent ischemic stroke. Ischemic events out of the territory of the qualifying artery or death were also analyzed.

MRI Protocol

All participants were scanned using a 3T ACHIEVA TX MR scanner (Philips Healthcare®) in our institution from January 2012 to November 2018, using a whole-body RF transmit and 8 channels head receiver coil. All participants had anatomical, basal perfusion, and BOLD CVR studies.

Anatomical studies

Whole brain anatomical studies, acquired in an axial plane parallel to the anterior commissure-posterior commissure consisted of: 3D gradient-recalled-echo (GRE) T₁ weighted-images (WI) (160 slices; voxel size=1x1x1mm³; TR/TE/ α : 9.9/4.6ms/8°); axial T₂ Fluid Attenuated Inversion Recovery (FLAIR) images (30 slices; voxel size=0.9x1.2x4mm³; TR/TE/TI: 11000/125/2800ms).

Basal perfusion study

Perfusion imaging study was performed using dynamic T₂*-WI GRE echo-planar imaging (EPI) (25 slices; voxel size=2x1.6x4mm³; TR/TE/ α : 1660/40ms/75°; 80 dynamics), tracking a bolus of 0.1mmol/kg of Gadolinium (Guerbet®), injected at a rate of 5mL/s flushed by a bolus of physiological saline (60mL) using a MR compatible injector (MEDRAD®).

CVR study

CVR imaging consisted of BOLD sensitive T₂*-WI GRE EPI acquisition (32 axial slices; voxel size=4x4x4mm³; TR/TE/α: 3000/35ms/90°; 240 dynamics) with a whole brain coverage.

Each participant was exposed alternatively to medical air and to a hypercapnic normoxic gas mixture (8% CO₂, 21% O₂, and 71% N₂) through a non-rebreathing face mask, according to the following block-designed paradigm [air(1')–hypercapnia(2')–air(1')]×3, for a total duration of 12 minutes[11,23–29].

Physiological parameters, including end-tidal CO₂ pressure (EtCO₂), arterial oxygen saturation, breath frequency and heart rate were monitored using a MR compatible device (Maglife, Schiller medical). This protocol is well tolerated by patients and increases EtCO₂ of about 10 mmHg, as recorded *via* nasal cannula.

Images processing and analyses

Data analysis was performed with Amigo software, an in-house post-processing suite written in Python 3.6 using Matlab (MathWorks) and SPM12.

Anatomical data

White and gray matters (GM) were segmented through the 3D GRE T₁-WI using the standard space tissue probability maps from SPM12. GM maps were spatially normalized to the Montreal Neurologic Institute (MNI) T₁-WI template and resampled at 2x2x2mm resolution. GM maps were further smoothed with a 6-mm Gaussian Kernel for Regions of Interest (ROI) analyses. Modified Fazekas' microangiopathy scale (0-3) was used to estimate the severity of

white matter hyperintensities on FLAIR-WI[30]. Cerebral infarct topography was also analyzed and we identified isolated deep infarct from border-zone infarcts.

Basal perfusion data

Basal perfusion images preprocessing consisted of coregistration, motion correction by realignment of all time-series images onto the first volume using a least squares approach and a 6 parameters rigid spatial transformation, normalization, resampling onto anatomical images, and spatial smoothing with a 6-mm Gaussian Kernel. The arterial input function (AIF) was estimated by averaging 5 voxels from all slices of the perfusion scan during the dynamics. These 5 voxels were automatically detected by optimizing a function with a signal evolution characterized by the higher peak height, a faster dropout, concomitant to a smaller full-width-half-maximum and bolus arrival time (brain-feeding artery detection). Mean transit time (MTT) and time-to-maximum (Tmax) maps were calculated pixel-wise with a deconvolution approach. This approach was based on a singular value decomposition[31] using a tracer arrival timing insensitive method and an automatic regularization of oscillations (oSVD)[32]. CBV was estimated from the area under the curve of the voxel concentration. To obtain quantitative maps, the mean brain CBV was normalized to 5%. CBF was calculated as the ratio CBV/MTT according to the central volume theorem.

CVR data

BOLD CVR images preprocessing consisted of coregistration, motion correction motion correction by realignment of all time-series images onto the first volume using a least squares approach and a 6 parameters rigid spatial transformation, normalization, resampling onto anatomical images, and spatial smoothing with a 6-mm Gaussian Kernel. Statistical analysis was conducted using a general linear model and the individual EtCO₂ in mmHg corrected for

a 4.8s delay as a physiological regressor[11]. CVR maps were expressed as the percentage change of BOLD signal per mmHg change of EtCO₂ (%BOLD/EtCO₂ mmHg).

ROI analyses

Vascular territories ROIs were obtained by using a standard set of ROIs[33] masked by smoothed GM maps, giving individual ROIs in the territories of the middle (MCA), anterior (ACA), and posterior (PCA) cerebral arteries. We conducted ROI analyses on each basal perfusion parameter and CVR maps. For each parameter, we calculated mean values and a laterality index ($LI = (\text{Mean}_{\text{Left}} - \text{Mean}_{\text{Right}}) / (\text{Mean}_{\text{Left}} + \text{Mean}_{\text{Right}})$). Positive LI represent right-side impairment while negative LI left-side impairment. In our analyses we used the absolute values of LI ($|LI|$).

Patients' groups

We defined 2 groups based on $|LI|CVR_{\text{MCA}}$: NORMAL CVR_{MCA} for $|LI|CVR_{\text{MCA}} < 0.08$; IMPAIRED CVR_{MCA} for $|LI|CVR_{\text{MCA}} \geq 0.08$, as previously defined among 100 healthy volunteers[27]. We also identified 2 groups: patients with a single ischemic qualifying stroke (SINGLE group), and patients who experienced at least a recurrent ipsilateral ischemic event (RECURRENT group).

Statistical analyses

Analyses were performed using the SPSSv20. Because of small samples sizes, we used non-parametric Mann-Whitney tests for numerical variables, and Pearson's Chi-square with continuity correction for nominal variables. The relationship between the occurrence of

ipsilateral ischemic event over time and CVR was determined using Kaplan–Meier analysis with log-rank comparison. All tests were two-tailed and a $p < 0.05$ was considered statistically significant.

RESULTS

Twenty-two patients satisfied inclusion criteria. No adverse reaction to the Gadolinium-dota administration and to hypercapnic stimulus was noted. Two patients were excluded because of incomplete protocol realization resulting from discomfort due to the face mask within the head coil (n=1) and inappropriate hypercapnic stimulus (n=1). Thus, we kept 20 patients for analyses: 13 men and 7 women with a mean age of 61.1 ± 11.9 years-old. SIAS were located on ICA (n=5) and MCA (n=15). Qualifying events were ischemic stroke (n=15) and TIA (n=5). The mean follow-up duration was 3.3 ± 1.6 years.

Hypercapnic challenge induced very similar EtCO₂ increases across groups with: 1°) $+8.2 \pm 1.7$ and $+8.2 \pm 1.3$ mmHg in NORMAL and IMPAIRED CVR_{MCA} groups, respectively; 2°) $+7.9 \pm 1.6$ and $+8.7 \pm 1.4$ mmHg in SINGLE and RECURRENT groups, respectively.

Comparisons between IMPAIRED and NORMAL CVR_{MCA} groups

Ten patients had NORMAL CVR_{MCA}, and 10 had IMPAIRED CVR_{MCA}. There were no differences among clinical, biological baseline characteristics (Table 1). The use of dual antiplatelet agents, antihypertensive treatment and statins was similar in both groups. The recurrence of ipsilateral ischemic event in IMPAIRED CVR_{MCA} was more frequent than in NORMAL CVR_{MCA} group (n=7/10 vs n=1/10, p=0.02) with different survival curves (log rank, p=0.007) (Figure 1). There were no differences among |LI| CVR in other arterial territories nor in other basal perfusion parameters (Table 2).

Comparisons between SINGLE and RECURRENT groups

We identified 12 SINGLE event patients and 8 RECURRENT events patients. Half of recurrent ischemic events occurred within 3 months after the qualifying event, all ipsilateral recurrence occurred in the first year (Table 3). An ischemic stroke out of the qualifying SIAS territory occurred in 2 RECURRENT patients and 1 SINGLE patient. Most recurrent ischemic events occurred before the CVR evaluation, but delays between qualifying event and MRI examination were similar between SINGLE and RECURRENT groups. No intracranial hemorrhage was noted. One death caused by acute pulmonary edema was reported at 3.5 years follow-up in SINGLE group. The RECURRENT patients were older than SINGLE group patients (68.4 ± 9.0 vs 56.3 ± 11.4 yo, $p=0.04$). There were no differences among other clinical and biological data. The Fazekas scores and proportion of border-zone infarct were similar (Table 4). The use of dual antiplatelet agents, antihypertensive treatment and statins was similar in both groups. RECURRENT patients had higher |LI| CVR_{MCA} (0.14 ± 0.05 vs 0.06 ± 0.04 , $p=0.002$) revealing a significant asymmetry in CVR_{MCA} with a decreased CVR downstream the SIAS (Figure 2). There were no differences among |LI| CVR in other arterial territories. Subtle intergroup differences in basal perfusion parameters did not reach significance (Table 5).

DISCUSSION

Patients with symptomatic SIAS remain at risk of recurrent ischemic stroke despite optimal medical therapy[2,3]. Additional treatments such as endovascular angioplasty and stenting are still not validated[4,5]. To further address additional therapy, the assessment of cerebrovascular reserve into the symptomatic brain territory may help better identify patients at higher patients of stroke recurrence. In our study, half of patients with symptomatic SIAS had an impaired CVR downstream stenosis and patients with impaired CVR have a higher rate of recurrent ipsilateral ischemic events.

Impaired CVR has been identified as a strong and independent predictor of stroke recurrence in steno-occlusive disease[34,35]. Most of these CVR studies used TCD with several advantages, such as high temporal resolution, arterial velocity quantification, non-invasiveness, but also limitations such as insonation window access, interoperator variability, absence of parenchymal imaging[36]. However, fMRI studies in steno-occlusive diseases were heterogeneous regarding intra and/or extracranial stenosis or occlusion, and with different etiologies such as atheromatous or moya-moya syndromes[12,19,20,37,38]. This is the first fMRI study to evaluate CVR in a homogeneous group of patients with symptomatic SIAS of a major artery, corresponding to therapeutic trials' inclusion criteria[4].

In line with previous studies, BOLD fMRI with hypercapnic challenge has been shown as a safe and reliable brain imaging technique to estimate cerebrovascular reserve[19,20]. However BOLD signal, which reveals changes in blood oxygenation, remains an unclear combination of variation in oxygenation consumption, CBF, CBV, and vasomotricity. Perfusion MRI techniques such as ASL were also proposed to monitor quantitative CBF changes to vasomotor stimuli[12,39]. In our experience, CVR fMRI using ASL remains limited by a poor signal-to-noise ratio, a lower temporal resolution (e.g. 8s between 2 pairs of

tag-control images), a critical sensitivity to labeling temporal parameters with aging, arterial transit time changes related to CO₂-induced vasodilation, and asymmetry *a fortiori* downstream SIAS, and sophisticated postprocessing that requires parametric assumptions and signal corrections for “absolute” CBF quantification[21,25,40].

Because of the variability of basal perfusion and CVR, we chose to estimate these parameters independently, to calculate LI in order to minimize interindividual amplitude effects and variability, and to test their relationships[11]. We agree that the LI approach may underestimate CVR impairment in case of bilateral vascular disease. However, CVR absolute quantification using BOLD contrast, even scaled by CO₂ concentration change, remains questionable because BOLD contrast remains sensitive to imaging parameters, and reflects a complex combination of changes in cerebral oxygenation and perfusion[21]. Here, all RECURRENT patients but one had a CVR $|LI| \geq 0.08$. Based on these results, IMPAIRED CVR_{MCA} with $|LI| \geq 0.08$ had a much higher rate of ischemic event, suggesting a reliable threshold to select patients at high risk in a future prospective study.

Most recurrent stroke downstream SIAS occurred during the first year after qualifying event, in line with large clinical trials[4]. This observation suggests time-dependent changes of the plaque under aggressive medical management, collateral supply development, and adaptive cerebrovascular reserve increase. However, temporal changes of cerebrovascular reserve remain to be documented in larger studies. A systematic CVR mapping and basal perfusion imaging follow-up would be interesting in order to test spatial agreement between CVR impairment and recurrent stroke. Some studies have shown a CVR improvement after successful procedures such as extra-intracranial surgical bypass[38,41] or angioplasty-stenting[26] in steno-occlusive patients.

Despite these encouraging results, there remain limitations in the study. The small sample size weakens the statistical power of the results. In spite of this, intergroup differences in stroke recurrence and in CVR asymmetry are notable. However, the small sample size could also explain unexpected results such as the older age of patients in RECURRENT group when compared to SINGLE, while no age difference was detected between NORMAL and IMPAIRED CVR_{MCA} patients. Indeed, older age was not previously reported in the “medical group” of SAMMPRIS trial[8].

To minimize patient exclusion due to inappropriate examination, in the study concerning 2 patients because of discomfort due to the face mask within the head coil (n=1) and inappropriate hypercapnic stimulus (n=1), a shorter protocol could be now advocated, given the results of other groups.

We also used MRI with BOLD contrast to map CVR. While BOLD contrast is a partially understood combination of blood oxygenation and perfusion changes, sensitive to field strength and acquisition parameters, it remains the most popular functional neuroimaging technique, including to provide non-quantitative CVR maps[36]. Data interpretation must take this limitation into account. However, the spatial localization of the abnormalities in the vascular territory downstream the SIAS and the higher-risk of stroke recurrence when present provide convincing arguments to rely on, and to further investigate SIAS patients using this technique for clinical practice.

Given our results, prevention of stroke recurrence within the first year remains the most critical therapeutic challenge after acute stroke management. CVR fMRI would be useful to select high-risk patients for additional invasive treatment. For future therapeutic trials on endovascular techniques, we hypothesize higher benefit would occur in case of CVR impairment downstream SIAS.

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Figure 1: Kaplan-Meier survival curves illustrating the relationship between CVR_{MCA} and the recurrence of ipsilateral ischemic stroke or death.

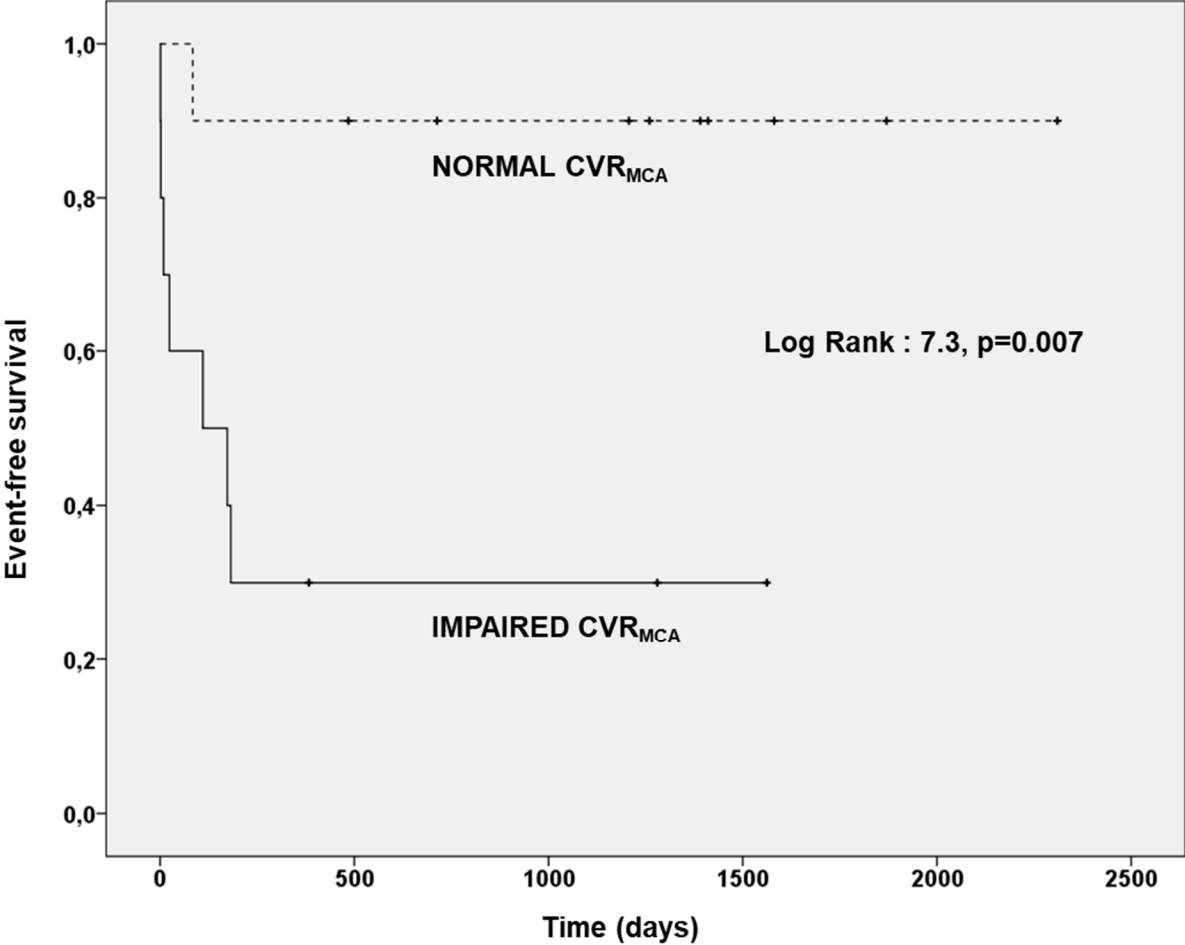
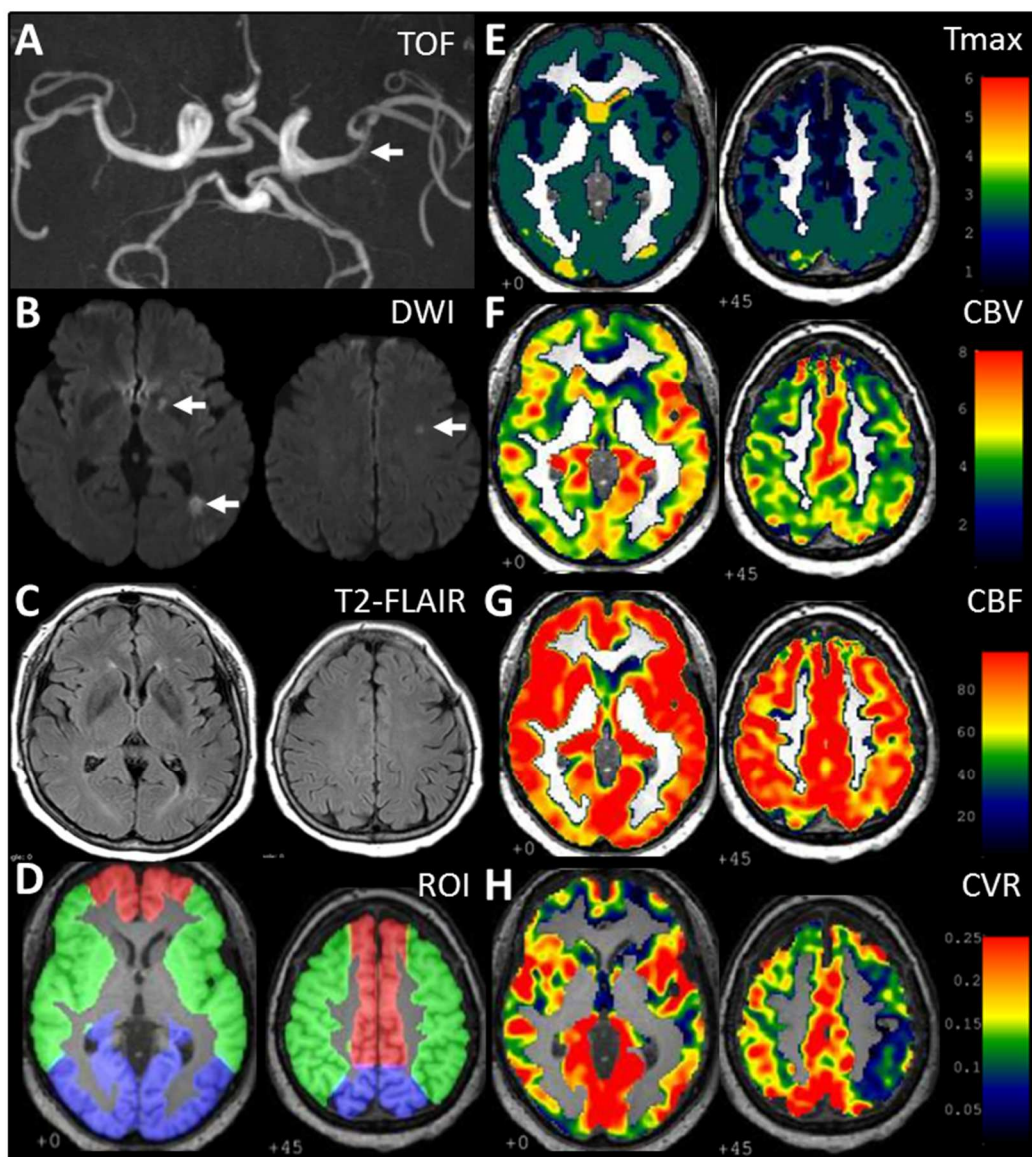


Figure 2: Illustrative case: a 62 years-old woman with a severe left middle cerebral artery (MCA) stenosis (A, arrow) revealed by deep and junctional stroke (B, arrows; C). Two recurrent transient ischemic attacks occurred during 2.3 years follow-up. Lateraly indices were calculated in vascular ROIs, with middle (green), anterior (red), posterior (blue) cerebral artery territories. Basal perfusion within MCA territories was symmetrical with $|LI| T_{max_{MCA}}=0.04$ (E), $|LI| CBV_{MCA}=0.01$ (F), $|LI| CBF_{MCA}=0.02$ (G), while CVR was decreased downstream the SIAS $|LI| CVR_{MCA}=0.12$ (H) (IMPAIRED CVR_{MCA}).



TABLES

Table 1: Baseline characteristics of NORMAL and IMPAIRED CVR_{MCA} groups.

	NORMAL CVR _{MCA} group (n=10)	IMPAIRED CVR _{MCA} group (n=10)	<i>p</i> value
Age in years	61.7±13.1	60.6±11.2	0.68
Men	6	7	1
History of hypertension	5	5	1
History of lipid disorder	6	5	1
Smoking	4	4	1
Diabetes	2	3	1
History of coronary artery disease	0	2	0.46
Low-density lipoprotein cholesterol (g/L)	1.2±0.4	1.0±0.4	0.12
High-density lipoprotein cholesterol (g/L)	0.5±0.1	0.5±0.3	0.74
Total cholesterol (g/L)	2.0±0.4	1.9±0.4	0.68
Triglycerid (g/L)	1.3±0.5	1.5±0.7	0.48
Glycosylated haemoglobin (%)	6.3±1.5	7.5±3.0	0.28
Overweigh or obesity (body-mass index > 25)	3	2	1
Qualifying event			
- Stroke	8	7	1
- TIA	2	3	
NIHSS at entrance (median [IQR])	1 [0.25-3]	2.5 [0.25-4]	0.35
mRS at discharge (median [IQR])	1.5 [0-2]	2 [0.25-2]	0.68
On antithrombotic therapy at qualifying event	2	2	1
Symptomatic qualifying artery			
- ICA	2	3	1
- MCA	8	7	
Fazekas score	1[1-2]	1[0.25-1.75]	0.53
Border-zone infarct	5	5	1

Follow-up duration in years	3.6±1.5	3.0±1.7	0.39
Last mRS status (median [IQR])	0.5 [0-1]	1 [0.25-2]	0.39

Clinical, biological, radiological data are similar between patients with and without CVR impairment downstream the intracranial stenosis. Data are mean ± standard deviation. TIA: transient ischemic attack; MCA: first segment of middle cerebral artery; ICA: internal carotid artery; NIHSS: National Institute of Health Stroke Score; mRS: modified Rankin Scale, [IQR]: interquartile range.

Table 2: Laterality indices (LI) of CVR and basal perfusion parameters calculated on vascular ROIs between NORMAL and IMPAIRED CVR_{MCA} groups.

		NORMAL CVR _{MCA} group (n=10)	IMPAIRED CVR _{MCA} group (n=10)	<i>p</i> value
LI CVR	MCA	0.04±0.02	0.14±0.03	<0.001
	ACA	0.04±0.04	0.05±0.05	0.68
	PCA	0.04±0.03	0.04±0.02	0.91
LI CBF	MCA	0.08±0.05	0.10±0.06	0.25
	ACA	0.07±0.05	0.04±0.02	0.22
	PCA	0.03±0.02	0.03±0.02	0.91
LI CBV	MCA	0.03±0.02	0.04±0.03	0.39
	ACA	0.04±0.03	0.03±0.03	0.74
	PCA	0.03±0.03	0.02±0.02	0.80
LI MTT	MCA	0.07±0.03	0.11±0.06	>0.05
	ACA	0.06±0.03	0.04±0.03	0.09
	PCA	0.03±0.02	0.03±0.02	0.91
LI Tmax	MCA	0.09±0.05	0.12±0.11	0.74
	ACA	0.07±0.07	0.03±0.02	0.53
	PCA	0.05±0.04	0.04±0.03	0.09

Except |LI| CVR_{MCA} used for patients' classification, no other hemodynamic parameters differs significantly between these two groups. Data are mean ± standard deviation. |LI|: absolute value of laterality index; CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean time transit; Tmax: time-to-maximum; ACA: anterior cerebral artery territories; PCA: posterior cerebral artery territories.

Table 3: Clinical and radiological details in RECURRENT patients.

Patient n°	Age in years	Sex	Qualifying event	Location of SIAS	LI CVR _{MCA}	Ipsilateral recurrent events (delay in days)	Follow-up duration in years
1	80	F	AIS	M1	0.05	TIA(84)	2.7
2	62	F	AIS	M1	0.12	TIA(182) TIA (232)	2.3
3	63	M	AIS	M1	0.12	AIS(24)	2.5
4	72	M	TIA	ICA	0.13	TIA(110) TIA (361)	2.2
5	64	M	AIS	ICA	0.14	AIS(173)	5.9
6	61	M	TIA	M1	0.15	AIS(1)	1.4
7	84	F	TIA	M1	0.19	TIA(2)	5.4
8	62	M	AIS	M1	0.20	AIS(9)	1.6

SIAS: severe intracranial arterial stenosis; |LI| CVR_{MCA}: absolute value of laterality index of cerebrovascular reactivity in middle cerebral artery territories, AIS: acute ischemic stroke; TIA: transient ischemic attack; M1: first segment of middle cerebral artery; ICA: internal carotid artery.

Table 4: Clinical, biological and radiological baseline characteristics of SINGLE and RECURRENT groups.

	SINGLE group (n=12)	RECURRENT group (n=8)	<i>p</i> value
Age in years	56.3±11.4	68.4±9.0	0.04
Men	8	5	1
History of hypertension	5	5	0.65
History of lipid disorder	8	3	0.41
Smoking	5	3	1
Diabetes	3	2	1
History of coronary artery disease	1	1	1
Low-density lipoprotein cholesterol (g/L)	1.2±0.4	1±0.4	0.31
High-density lipoprotein cholesterol (g/L)	0.4±0.1	0.6±0.3	0.14
Total cholesterol (g/L)	1.9±0.5	2.0±0.3	0.68
Triglycerid (g/L)	1.4±0.6	1.5±0.7	0.91
Glycosylated haemoglobin (%)	7.0±2.9	6.7±1.6	0.52
Overweigh or obesity (body-mass index > 25)	4	1	0.60
Qualifying event			
- Stroke	10	5	0.60
- TIA	2	3	
NIHSS at entrance (median [IQR])	3 [1-1.5]	1.5 [0-3.25]	0.73
mRS at discharge (median [IQR])	2 [0.8-2]	1.5 [0-2]	0.57
On antithrombotic therapy at qualifying event	3	1	0.91
Symptomatic qualifying artery			
- ICA	3	2	1
- MCA	9	6	
Fazekas score (median [IQR])	1[0.75-2]	1[1-2]	0.79
Border-zone infarct	6	4	1
Follow-up duration (years)	3.5±1.5	3.0±1.7	0.47

Last mRS status (median [IQR])	0.5 [0.5-1.25]	1 [0.75- 2]	0.47
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Data are mean \pm standard deviation. Abbreviations are defined in Table 1.

Table 5: Laterality indices (LI) of CVR and basal perfusion parameters calculated on vascular ROIs between SINGLE and RECURRENT groups.

		SINGLE group (n=12)	RECURRENT group (n=8)	<i>p</i> value
LI CVR	MCA	0.06±0.04	0.14±0.05	0.002
	ACA	0.04±0.04	0.05±0.05	0.57
	PCA	0.04±0.03	0.04±0.02	0.91
LI CBF	MCA	0.08±0.05	0.10±0.06	0.27
	ACA	0.06±0.05	0.04±0.02	0.47
	PCA	0.03±0.02	0.03±0.02	0.72
LI CBV	MCA	0.04±0.03	0.03±0.03	0.31
	ACA	0.04±0.03	0.03±0.03	0.18
	PCA	0.03±0.03	0.03±0.02	0.91
LI MTT	MCA	0.08±0.04	0.10±0.06	0.57
	ACA	0.06±0.03	0.05±0.04	0.43
	PCA	0.03±0.02	0.02±0.02	0.52
LI Tmax	MCA	0.09±0.07	0.13±0.10	0.52
	ACA	0.06±0.06	0.04±0.03	0.91
	PCA	0.04±0.04	0.05±0.03	0.73

The CVR is significantly impaired in patients who experienced ipsilateral recurrent event, without any changes in other hemodynamic parameters. Data are mean ± standard deviation. Abbreviations are defined in Table 2.

