Impaired cerebrovascular reactivity assessed by BOLD hypercapnic fMRI is associated with increased risk of stroke in patients with symptomatic intracranial atherosclerotic stenosis

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Altération de la vasoréactivité cérébrale en IRMf hypercapnique chez les patients présentant une sténose artérielle intracrânienne symptomatique d'origine athéromateuse à haut risque de récidive.

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A Agathe, MA fille**.**

TITLE:

Impaired cerebrovascular reactivity assessed by BOLD hypercapnic fMRI is associated with increased risk of stroke in patients with symptomatic intracranial atherosclerotic stenosis

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Key words: brain; stroke; intracranial arterial stenosis; DSC perfusion; BOLD fMRI; hypercapnia; cerebrovascular reserve

LIST OF ABBREVIATIONS

ACA: anterior cerebral artery

AIF: arterial input function

ASL: arterial spin labelling

BOLD: blood oxygenation level dependent

CBF: cerebral blood flow

CBV: cerebral blood volume

CVR: cerebrovascular reactivity

EPI: echo-planar imaging

fMRI: functional magnetic resonance imaging

FOV: field of view

GM: gray matter

GRE: gradient recalled echo

IAS: intracranial atherosclerotic stenosis

ICA: internal carotid artery

LDLc: low-density lipoprotein cholesterol

LI: laterality index

MCA: middle cerebral artery

MNI: Montreal Neurologic Institute

mRS: modified Rankin scale

MTT: Mean Transit Time

NIHSS: National Institutes of Health Stroke Scale

PCA: posterior cerebral artery

PET: positron emission tomography

$PetCO_2$: end-tidal CO_2 pressure

RECURRENT: recurrent ipsilateral ischemic event

ROI: regions of interest

SINGLE: single ischemic qualifying event

SPECT: single-photon emission computed tomography

TDS: transcranial Doppler sonography

TIA: transient ischemic attack

WI: weighted images

ABSTRACT:

***Introduction*:** Despite intensive medical management, intracranial atherosclerotic stenosis (IAS) remains at risk of recurrent ischemic events. Impaired cerebrovascular reserve is suggested to explain hemodynamic stroke. Cerebrovascular reactivity assessed by hypercapnic challenge using BOLD functional MRI (CVR BOLD fMRI) has been proposed to estimate cerebrovascular reserve and to identify patients at higher risk. To discuss patients' selection for additional therapy such as intracranial angioplasty and stenting, we studied the relationships between baseline characteristics of patients with unilateral symptomatic IAS, recurrence of ischemic events, and CVR BOLD fMRI.

***Subjects and methods*:** Nineteen patients with symptomatic unilateral IAS of middle cerebral artery (MCA) or internal carotid artery were selected. We calculated statistical relationships between individual clinical and biological baseline characteristics, recurrent ischemic events, basal perfusion estimated by dynamic susceptibility contrast MRI, and CVR BOLD fMRI measured in MCA territories (CVR_{MCA}), and reported using laterality indices (LI).

***Results*:** Eight patients (42%) had an abnormal LI CVR_{MCA} ($|LI|\ CVR_{MCA} \geq 0.08$). During a mean follow-up of 3.6 years, recurrent ischemic events occurred within the first year. They were more frequent in impaired CVR_{MCA} group (n=6/8) than in normal CVR_{MCA} group (n=1/11), with different survival curves (log rank, p=0.003). Baseline characteristics were similar in both groups.

***Conclusion*:** Impaired CVR assessed by BOLD hypercapnic fMRI is associated with increased risk of stroke in patients with symptomatic IAS. CVR mapping should be proposed to select high-risk patients in order to discuss additional treatment.

INTRODUCTION:

Intracranial atherosclerotic stenosis management

Intracranial atherosclerotic stenoses (IAS) account for approximately 10% of cerebrovascular ischemic strokes, and up to 50% in Asian populations[1–3]. IAS are associated with high rates of recurrent ischemic event and cerebrovascular mortality when compared with other stroke subtypes[4,5]. The recurrence rate of ischemic events in the territory of the stenotic artery remains high[6,7], with a major risk of subsequent disabling stroke[8], despite optimal medical treatment.

Large randomized trials demonstrated better outcomes with aggressive medical management compared to IAS recanalization using intracranial stenting[9,10] or surgical extracranial-intracranial bypass[11,12] to prevent recurrent stroke because of the high rate of procedural complications. Actually, a combination of antiplatelet therapies (aspirin 325mg per day plus clopidogrel 75mg per day for 90 days) is recommended with an intensive medical management of risk factors: high blood pressure, elevated low-density lipoprotein cholesterol (LDLc) levels, diabetes, smoking, overweight, and insufficient exercise[13]. When life style adaptation is insufficient, antihypertensive drug and statin should be used to obtain a systolic blood pressure below 140 mmHg and LDLc level below 0.7g/l, respectively.

Vitamin K antagonists were associated with higher rates of adverse events and without benefit over aspirin[4]. No clinical benefit was demonstrated for direct oral anticoagulant (direct IIa and Xa factor inhibitors) or other anti-platelet agents such as cilostazole or dipyridamole.

Despite optimal medical management, IAS remains associated with a recurrence rate of stroke events at 2 years of 15-25%[4,9]. The identification of risk factors of stroke recurrence among IAS patients under aggressive medical management would be helpful to consider alternative therapy[14,15]. Indeed, old infarct in the territory of the stenosis, new stroke presentation, and absence of statin use at enrollment were independently associated with high recurrence rates of stroke events in the medical group in the SAMMPRIS trial[16]. Additionally, impaired cerebrovascular reserve was suggested as a risk factor of stroke recurrence[17].

Cerebrovascular functions

The cerebral vasomotricity leads to active changes of vessels resistance, through dilation and contraction, in order to adjust cerebral blood flow (CBF) in response to variations of neural activity (neurovascular coupling), to cerebral perfusion pressure (autoregulation), and to circulating gases and metabolites (vasoreactivity).

The neurovascular coupling adapts the cerebral blood flow to local neuronal activity providing oxygen, glucose and adenosine triphosphate to neurons and glia, and removing heat and catabolites[18].

The cerebral autoregulation refers to the ability of vasculature to maintain CBF constant, despite changes of perfusion pressure, to prevent ischemia-related brain damage. Combination of myogenic, humoral and neurogenic feedback mechanisms are implicated in the regulation of adequate CBF maintaining constant distal perfusion pressure in brain capillaries during large arterial pressure variations[19,20].

The cerebrovascular reactivity (CVR) modulates CBF in response to changes of circulating stimulus. Circulating gases such CO_2 and O_2 elicit vascular dilation and contraction, respectively, to maintain brain oxygenation.

Magnitude of the cerebrovascular properties is modulated by physiological changes (e.g. age, sex, hypoxia, arterial pressure, basal perfusion…), brain diseases (e.g. Alzheimer's disease; stroke,…), and structural vascular damage such as atherosclerosis (chronic arterial hypertension, diabetes,…)[18,21].

CVR assessment

When perfusion pressure decreases downstream the IAS, autoregulation may maintain CBF by vasodilation and cerebral blood volume increase. This additional dilation, known as cerebrovascular reserve, might be insufficient to compensate further perfusion pressure decrease. When cerebrovascular reserve is exhausted, patients are at risk of low grade ischemia and recurrent hemodynamic events[22,23]. Thus, the estimation of the cerebrovascular reserve using perfusion measures before and after vasodilatory stimulus has been proposed to identify patients at risk of ischemia [17,24].

While Positron Emission Tomography (PET) remains the "gold standard" technique[25], non-invasive alternative methods have been advocated, such as transcranial Doppler sonography (TDS)[26], xenon-enhanced computed tomography[27], single-photon emission computed tomography (SPECT)[28], and more recently by functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast or arterial spin labelling (ASL)[24]. Most common vasodilatory stimuli are acetazolamide and CO_2[17,18].

Among these techniques, BOLD CVR fMRI is an accessible, non-invasive, and reproducible whole brain imaging method[29,30]. Among vasoactive stimuli, CO_2 challenge is safer when compared to hypotensive provocation. Intravenous acetazolamide administration is exposed to side effects, contraindications, and large inter-subject variability[31]. Thus, well tolerated CO_2 inhalation with immediate and transient vasodilation is now advocated to be the most suitable stimulus[29–31].

Objectives

Our objective was to investigate the relationships between clinical and biological characteristics of patients with unilateral symptomatic IAS, recurrence of ischemic events, basal perfusion parameters, and individual CVR mapping using BOLD hypercapnic fMRI. The study allowed to estimate: 1°) CVR and basal perfusion characteristics among patients with recurrent ischemic event, and 2°) occurrence of recurrent ischemic event in patients with CVR impairment.

SUBJECTS AND METHODS

Study participants

We conducted an observational study on adult patients referred at the University Hospital Grenoble Alps between February 2011 and August 2016 for transient ischemic attack (TIA) or non-disabling stroke that was attributed to 50–99% unilateral IAS of internal carotid (ICA) or first segment of the middle cerebral artery (MCA) assessed by catheter angiography or brain CT angiography[32]. Optimal medical treatment, consisting of dual antiplatelet therapy aspirin (75-300 mg per day) plus clopidogrel (75 mg per day), and management of risk factors (high blood pressure, hypercholesterolemia, diabetes, smoking, overweight) was implemented for each patient.

We excluded patients with tandem extracranial stenosis (70–99%) or occlusion, intraluminal thrombus proximal to or at the target lesion, any hemorrhagic infarct within 14 days before enrolment, 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 and Gadolinium-Dota intravenous administration. We also excluded patients with incomplete MRI protocol due to excessive head motion (translation or rotation >2mm or >2° in any direction, respectively) or inappropriate hypercapnic stimulus. The study protocol was approved by our institute's committee on human research (B120620-10).

Clinical data collection and follow-up

Qualifying ischemic event-related data was obtained from medical records and included stroke risk factors, medical history, National Institutes of Health Stroke Scale (NIHSS; 0 to 42,

higher score indicating greater severity) at hospital admission, modified Rankin Scale (mRS; 0: no symptom to 6: death) at discharge, serum creatinine, glycosylated haemoglobin and lipid testing. 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 (JP, IF, KG, SM, OD) during visits or by telephone interview. Any stroke or TIA in the territory of the qualifying artery was considered to be a recurrent ischemic event. 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®, the Netherlands) at University Hospital Grenoble Alps, using a whole-body RF transmit and 8 channels head receive coils. All participants had anatomical, basal perfusion, and BOLD CVR studies.

Anatomical study

Anatomical study consisted in a 3D gradient recalled echo (GRE) T1-weighted image (WI) (160 contiguous slices, slice thickness=1mm, TR/TE/α: 9.9/4.6ms/8°, 256x256 matrix, field of view (FOV) of 256x160 mm for 4.5 min acquisition time).

Basal perfusion study

Perfusion-WI was performed using dynamic T2*-WI GRE echo-planar imaging (EPI) (25 contiguous slices, thickness=4mm, TR/TE/α: 1660/40ms/75°, 112x112 matrix, FOV=224x184mm), tracking a bolus of 0.1mmol/kg of Gadolinium (Guerbet®, France), injected at a rate of 5mL/s with a MR compatible injector (MEDRAD®, USA). This injection

was flushed by a bolus of physiological saline (60mL). To obtain an accurate estimate of the baseline MR signal intensity S(0) prior to the arrival of contrast agent an injection delay of 10 seconds was applied. Eighty single-shot, gradient-echo, echo-planar images, were obtained in each of the slices during the 2'11 minute acquisition time.

CVR study

CVR imaging consisted in BOLD sensitive T2* WI GRE EPI acquisition (32 axial slices, slice thickness=4mm, TR/TE/α: 3000/35ms/90°, 64x64 matrix, FOV=256x256 mm, 240 dynamics) with a whole brain coverage. Hypercapnic challenge was conducted according to the following block-designed paradigm [air(1')–hypercapnia(2')–air(1')]×3, for a total duration of 12 minutes. Each participant was exposed alternatively to medical air and to a hypercapnic normoxic gas mixture (CO_2 (8%), O_2 (21%), and N_2 (71%) through a non-rebreathing face mask. Physiological parameters, including end-tidal CO_2 pressure ($PetCO_2$), arterial oxygen saturation, breath frequency and heart rate were monitored using a MR compatible device (Maglife, Schiller medical). This protocol induces an increase $PetCO_2$ about 10 mm Hg, recorded via nasal cannula.

Images processing and analyses

Data analysis was performed with Amigo, an in-house post-processing suite written in Python 3.6 using Matlab (MathWorks, Inc., Natick, MA, USA) and SPM12 (SPM, Wellcome Department of Imaging Neuroscience).

Anatomical data

White and gray matters (GM) were segmented through the 3D GRE T1 sequence using the standard space tissue probability maps from SPM12. GM maps were spatially normalized to the Montreal Neurologic Institute (MNI) T1-weighted template and resampled at 2x2x2mm

resolution. GM maps were further smoothed with a 6-mm Gaussian Kernel for Regions of Interest (ROI) analyses.

Basal perfusion data

Basal perfusion images preprocessing consisted in coregistration, 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) maps were then calculated pixel-wise with a deconvolution approach based on a singular value decomposition using a tracer arrival timing insensitive method and an automatic regularization of oscillations[33]. The relative Cerebral Blood Volume (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%. The MTT maps were estimated from the area under the curve and from the time to maximum of the deconvolved function respectively. CBF was calculated as the ratio CBV/MTT from the central volume theorem. The excluded voxels from the computation were averaged with the nearby voxels.

CVR data

BOLD CVR images preprocessing consisted in coregistration, 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 $PetCO_2$ in mmHg as a physiological regressor. CVR maps were expressed as percent change of BOLD signal per mmHg change of $PetCO_2$ (%BOLD/ $PetCO_2$ mmHg). Illustrative case is shown in Figure 1.

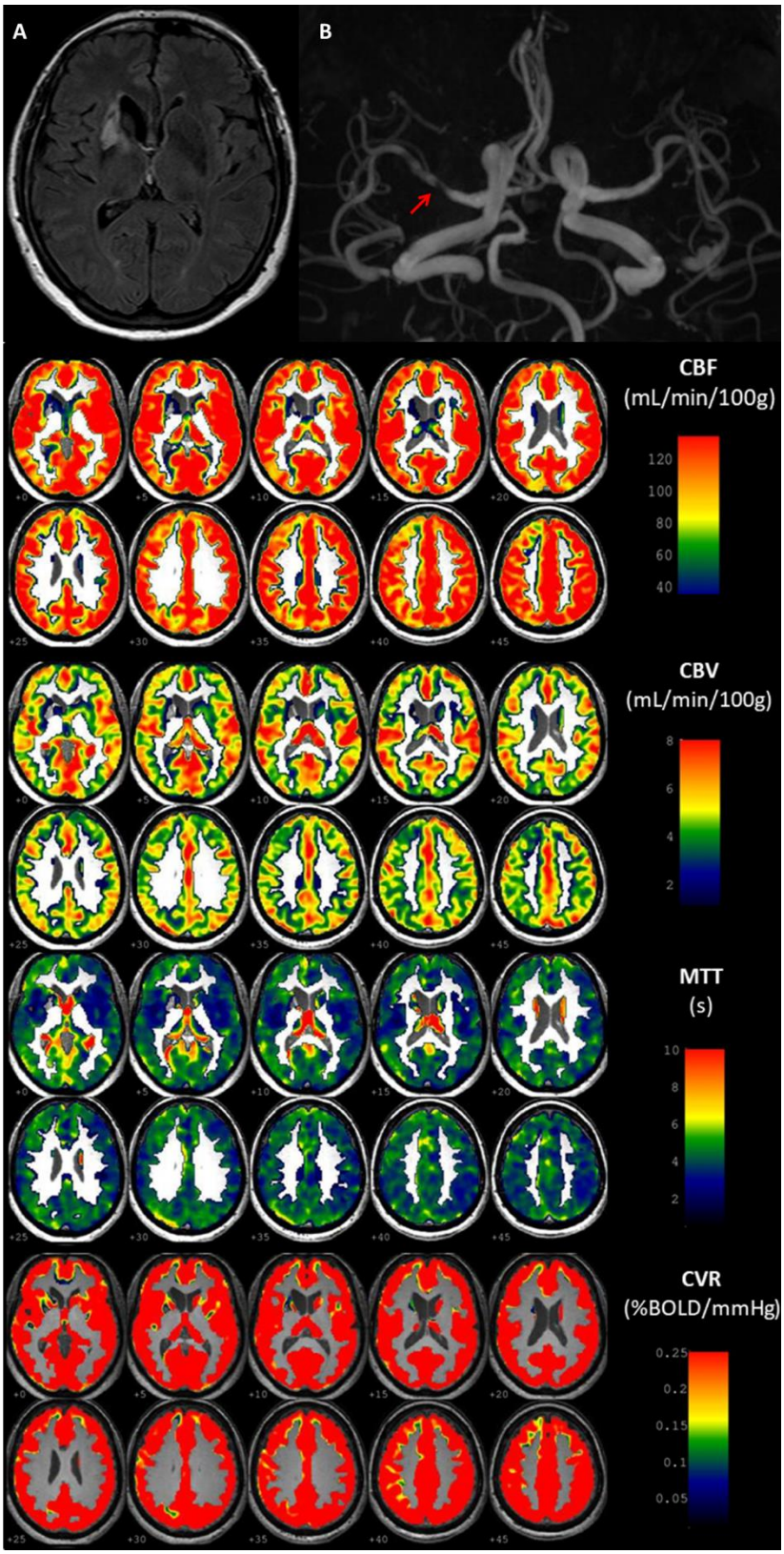


Figure 1: FLAIR-T_2 weighted image (A), Time-Of-Flight weighted image (B), basal perfusion parameters and CVR maps in 68-year woman referred for symptomatic right MCA stenosis in red arrow, without ischemic recurrence (radiological convention).

ROI analyses

Vascular territories ROIs were obtained by using a standard set of vascular ROIs[34] masked by smoothed GM maps, giving individual ROIs in the territories of the middle (MCA), anterior (ACA), and posterior (PCA) cerebral arteries (Figure 2).

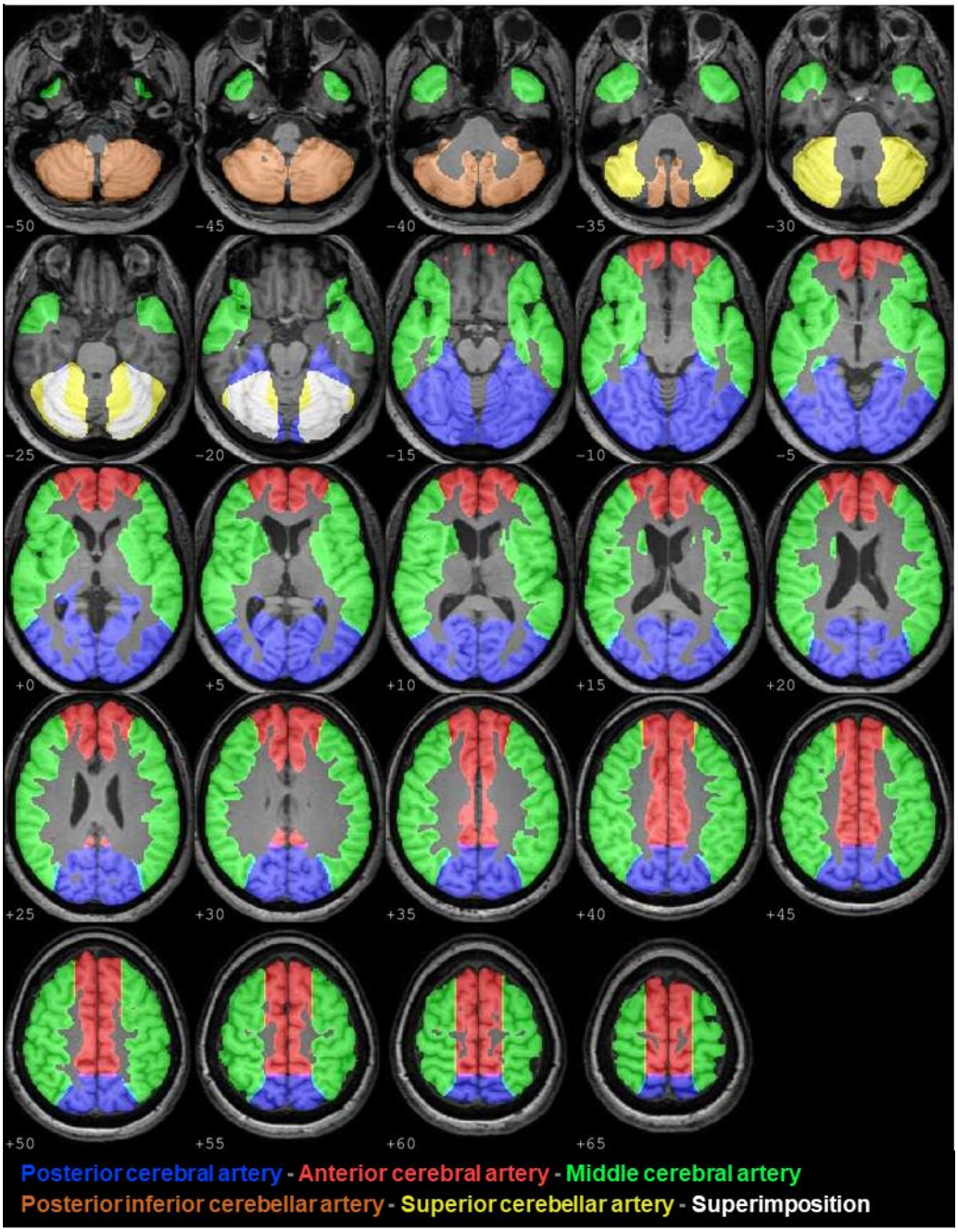


Figure 2: Individual regions of interest in major cerebral arteries territories.

We conducted ROI analyses on each basal perfusion parameter and CVR maps. For each parameter, we calculated mean values and a laterality index (LI), e.g. for CVR in MCA territory LI CVR_{MCA} = (Left_CVR_{MCA} – Right_CVR_{MCA}) / (Left_CVR_{MCA} + Right_CVR_{MCA}). A positive value of LI representing left-hemisphere dominance and negative value a right-hemisphere dominance. The intermediate values reflect varying degrees of laterality. In our analyses we used the absolute values of LI (|LI|). We also defined 2 groups based on |LI| CVR_{MCA}: NORMAL CVR_{MCA} for |LI| CVR_{MCA} < 0.08; IMPAIRED CVR_{MCA} for |LI| CVR_{MCA} ≥ 0.08[35]. Calculation of a LI was also used for all basal perfusion parameters (CBF, CBV, or MTT) and in other ROI.

Statistical analyses

Analyses were performed using the SPSS 20.0. Non-parametric statistics were conducted because of small sample sizes. Intergroup comparisons were conducted using Mann-Whitney U tests. Relationship between CVR_{MCA} status and recurrent ipsilateral ischemic event was determined using Kaplan–Meier analysis with log rank comparison. Correlations between basal perfusion parameters and CVR_{MCA} were assessed by Spearman's ρ correlation coefficient. All tests were two-tailed and a p value < 0.05 was considered statistically significant.

RESULTS:

Twenty-one patients satisfied inclusion criteria. No adverse reaction to the Gadolinium-dota administration and to hypercapnic stimulus was reported. Two patients were excluded because of incomplete protocol realization secondary to discomfort due to the face mask within the head coil (n=1) and inappropriate hypercapnic stimulus (n=1), leaving 19 patients for further analyses. Finally, 13 men and 6 women were included, with a mean age of 61.0 years (SD ±12.5). Clinical and biological baseline characteristics are presented in Table 1. IAS were located on right MCA (n=9), left MCA (n=5), right ICA (n=3), left ICA (n=2). Qualifying events were stroke (n=15) and TIA (n=4).

	IAS patients (n=19)
Age in years	61.0±12.5
Men	13
History of hypertension	10
History of lipid disorder	11
Smoking	8
Diabetes	5
History of coronary artery disease	2
Low-density lipoprotein cholesterol (g/L)	1.1±0.4
High-density lipoprotein cholesterol (g/L)	0.5±0.3
Total cholesterol (g/L)	1.9±0.4
Triglycerid (g/L)	1.4±0.6
Glycosylated haemoglobin (%)	6.9±2.5
Overweigh or obesity (body-mass index > 25)	5
Qualifying event	
- Stroke	15
- TIA	4
NIHSS at entrance (median [IQR])	2 [0.5-3]
mRS at discharge (median [IQR])	2 [0-2]
On antithrombotic therapy at qualifying event	4
On antihypertensive therapy at qualifing event	9
On lipid-lowering therapy at qualifiying event	5
On diabetic therapy at qualifiying event	4
Symptomatic qualifying artery	
- ICA	5
- MCA	14
Follow-up duration in years	3.6±1.4
mRS follow-up (median [IQR])	1 [0-1.5]

Table 1: Clinical and biological baseline characteristics. Data are mean ±standard deviation. IAS=intracranial atherosclerotic stenosis, TIA=transient ischemic attack, MCA=first segment of middle cerebral artery, ICA=internal carotid artery, NIHSS=National Institutes of Health Stroke Scale, mRS=modified Rankin Scale, [IQR]=interquartile range.

During follow-up (mean±SD=3.57±1.43 years), we identified 2 groups: 12 patients had a single ischemic qualifying event (SINGLE), and 7 patients experienced a recurrent ipsilateral ischemic event (RECURRENT), of which 3 strokes and 4 TIA (Table 2). Overall annual risk of recurrent ipsilateral ischemic event was 18.4% per year. An ischemic event out of the qualifying IAS territory occurred in 3 patients (2 in RECURRENT group and 1 in SINGLE group). No intracranial hemorrhage was detected on follow-up. One death caused by acute pulmonary edema was reported at 3.5 years follow-up for a patient from SINGLE group. Annual risk of recurrent combination of all ischemic events and death was 24.2% per year.

N°	Age (years)	Sex	Qualifying event	Location of stenosis	|LI| CVR_{MCA}	Days to recurrent event	Details of recurrent event
1	80	F	Stroke	MCA	0.05	84	TIA
2	63	F	Stroke	MCA	0.12	182	TIA
3	63	M	Stroke	MCA	0.12	24	Stroke
4	72	M	TIA	ICA	0.13	110	TIA
5	64	M	Stroke	ICA	0.14	173	Stroke
6	84	F	TIA	MCA	0.19	2	TIA
7	62	M	Stroke	MCA	0.20	9	Stroke

Table 2: Summary details of RECURRENT patients. |LI|CVR_{MCA}=absolute value of laterality index of cerebrovascular reactivity in middle cerebral artery territories, other abbreviations are defined in Table 1.

Comparisons between SINGLE and RECURRENT groups

When compared with SINGLE, RECURRENT patients were older (69.5±9.1. vs 56.1±11.8 p=0.04). There were no differences among other clinical and biological data (Table 3).

	SINGLE group (n=12)	RECURRENT group (n=7)	*p* value
Age in years	56.1±11.8	69.5±9.1	0.04
Men	9	4	0.54
History of hypertension	5	5	0.3
History of lipid disorder	8	3	0.43
Smoking	6	2	0.48
Diabetes	3	2	0.9
History of coronary artery disease	1	1	0.84
Low-density lipoprotein cholesterol (g/L)	1.2±0.4	1±0.3	0.17
High-density lipoprotein cholesterol (g/L)	0.4±0.1	0.6±0.4	0.2
Total cholesterol (g/L)	1.9±0.5	1.9±0.3	0.86
Triglycerid (g/L)	1.4±0.6	1.5±0.7	0.84
Glycosylated haemoglobin (%)	7.0±2.9	6.9±1.7	0.48
Overweigh or obesity (body-mass index > 25)	4	1	0.54
Qualifying event			
- Stroke	10	5	0.71
- TIA	2	2	
NIHSS at entrance (median [IQR])	3[1-1.5]	1[0-2.5]	0.23
mRS at discharge (median [IQR])	2[0.8-2]	1[0-2]	0.3
On antithrombotic therapy at qualifying event	3	1	0.71
On antihypertensive therapy at qualifing event	5	4	0.59
On lipid-lowering therapy at qualifiying event	4	1	0.54
On diabetic therapy at qualifiying event	2	2	0.71
Symptomatic qualifying artery			
- ICA	3	2	0.9
- MCA	9	5	
Follow-up duration in years	3.8±1.3	3.2±1.7	0.38
mRS follow-up (median [IQR])	0.5[0.5-1.3]	1[0.5-1.5]	0.59

Table 3: Clinical and biological baseline characteristics of SINGLE and RECURRENT groups. Patients who experiment recurrent ipsilateral ischemic event are significantly older than SINGLE patients. Data are mean ± standard deviation. Abbreviations are defined in Table 1.

RECURRENT patients had higher |LI| CVR_{MCA} (0.14±0.05 vs 0.05±0.03, p=0.001). There were no differences among |LI| CVR in other arterial territories. Subtle intergroup differences in basal perfusion parameters did not reach significance (Table 4).

		SINGLE group (n=12)	RECURRENT group (n=7)	*p* value
|LI| CVR	MCA	**0.05**±0.03	**0.14**±0.05	0.001
	ACA	**0.04**±0.04	**0.05**±0.06	0.23
	PCA	**0.04**±0.03	**0.04**±0.02	0.54
|LI| CBF	MCA	**0.07**±0.05	**0.11**±0.06	0.23
	ACA	**0.07**±0.05	**0.04**±0.02	0.38
	PCA	**0.03**±0.02	**0.02**±0.02	0.97
|LI| CBV	MCA	**0.04**±0.03	**0.03**±0.03	0.54
	ACA	**0.04**±0.03	**0.03**±0.03	0.26
	PCA	**0.03**±0.03	**0.03**±0.02	0.97
|LI| MTT	MCA	**0.07**±0.03	**0.10**±0.07	0.43
	ACA	**0.05**±0.03	**0.05**±0.04	0.65
	PCA	**0.03**±0.03	**0.02**±0.02	0.38

Table 4: Laterality indices between SINGLE and RECURRENT groups for each vascular ROI and each hemodynamic parameter (cerebrovascular reactivity, basal perfusion parameters). The |LI| CVR_{MCA} is significantly increased in patients who experiment recurrent ipsilateral ischemic event, other hemodynamic parameters differ between these two groups. Data are mean ± standard deviation. |LI|=absolute value of laterality index, CVR=cerebrovascular reactivity, CBF=cerebral blood flow, CBV=cerebral blood volume, MTT=mean time transit, ACA=anterior cerebral artery territories, PCA=posterior cerebral artery territories, other abbreviations are defined in Table 1.

Illustrative cases are shown in Figure 3.

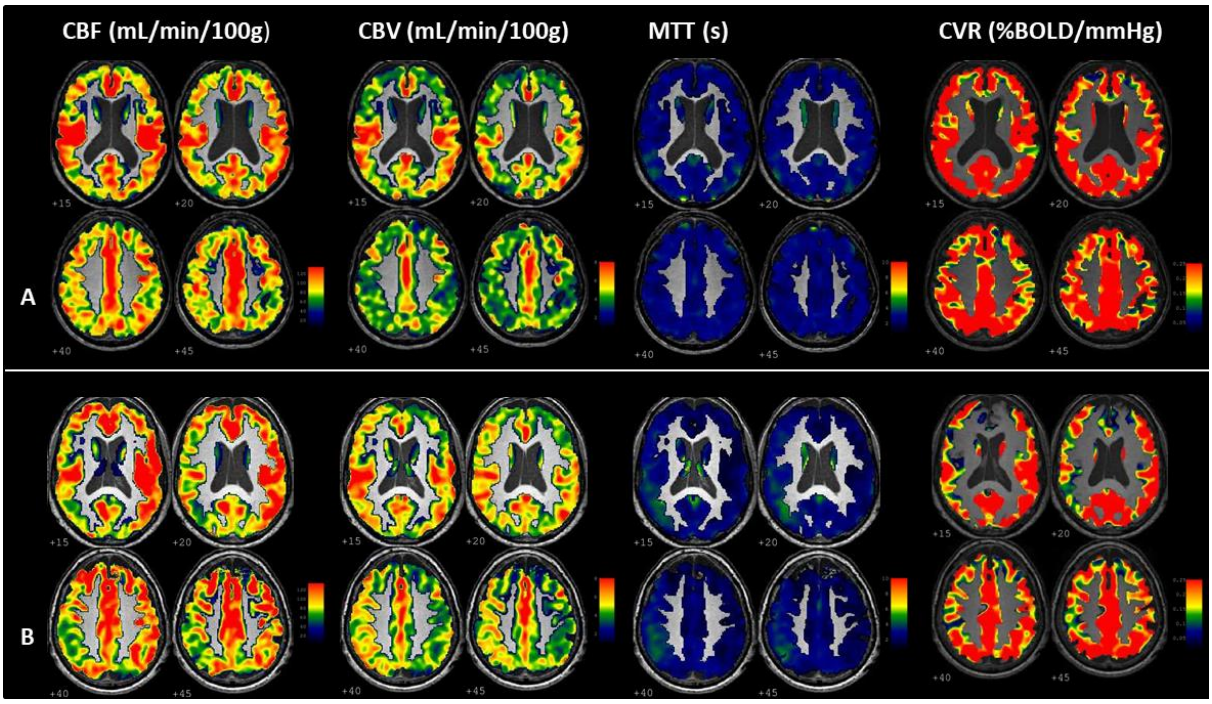


Figure 3: Basal perfusion parameters and CVR maps in patients referred for symptomatic right MCA severe stenosis (radiological convention). Upper row: 65-years man without ischemic recurrence (SINGLE group). Both basal perfusion (CBF, CBV, MTT) and CVR_{MCA} were symmetrical: |LI| CBF_{MCA}=0.00, |LI| CBV_{MCA}=0.00, |LI| MTT_{MCA}=0.01, |LI| CVR_{MCA}=0.02 (NORMAL CVR_{MCA}). Lower row: 83-years woman with 2 recurrent transient ischemic attacks (RECURRENT group). Autoregulation with increased CBV failed to maintain CBF symmetrical. Additionally, CVR decreased downstream MCA stenosis: |LI| CBF_{MCA}=0.18, |LI| CBV_{MCA}=0.06, |LI| MTT_{MCA}=0.22, |LI| CVR_{MCA} = 0.19 (IMPAIRED CVR_{MCA}).

Comparisons between IMPAIRED and NORMAL CVR_{MCA} groups

Among all patients, 11 patients had NORMAL CVR_{MCA}, and 8 had IMPAIRED CVR_{MCA}. There were no intergroup differences among clinical and biological baseline data (Table 5).

	NORMAL CVR_{MCA} group (n=11)	IMPAIRED CVR_{MCA} group (n=8)	*p* value
Age in years	58.3±13.1	64.8±11.4	0.27
Men	7	6	0.72
History of hypertension	5	5	0.55
History of lipid disorder	6	5	0.78
Smoking	5	3	0.78
Diabetes	2	3	0.49
History of coronary artery disease	0	2	0.4
Low-density lipoprotein cholesterol (g/L)	1.3±0.4	1.0±0.4	0.13
High-density lipoprotein cholesterol (g/L)	0.5±0.1	0.6±0.4	0.72
Total cholesterol (g/L)	2.0±0.4	1.9±0..4	0.76
Triglycerid (g/L)	1.4±0.5	1.6±0.8	0.60
Glycosylated haemoglobin (%)	6.3±1.5	6.5	0.21
Overweigh or obesity (body-mass index > 25)	4	1	0.4
Qualifying event			
- Stroke	9	6	0.84
- TIA	2	2	
NIHSS at entrance (median [IQR])	1 [0.5-3]	2 [0.8-2]	0.44
mRS at discharge (median [IQR])	2 [0-2]	1 [0.8-2.3]	0.66
On antithrombotic therapy at qualifying event	2	2	0.84
On antihypertensive therapy at qualifing event	5	4	0.9
On lipid-lowering therapy at qualifiying event	3	2	0.97
On diabetic therapy at qualifiying event	1	3	0.31
Symptomatic qualifying artery			
- ICA	2	3	0.49
- MCA	9	5	
Follow-up duration in years	3.6±1.4	3.5±1.6	0.78
mRS follow-up (median [IQR])	0 [0-1]	1 [0.8-2.3]	0.27

Table 5: Baseline characteristics of NORMAL and IMPAIRED CVR_{MCA} groups. Clinical and biological data are similar between patients with and without CVR impairment downstream the intracranial stenosis. Data are mean ± standard deviation. CVR_{MCA}=cerebrovascular reactivity on middle cerebral artery territories, other abbreviations are defined in Table 1.

The occurrence of recurrent ipsilateral ischemic event in IMPAIRED CVR_{MCA} (n=6/8) was more frequent than in NORMAL CVR_{MCA} group (n=1/11) with different survival curves (p=0.003) (Figure 4).

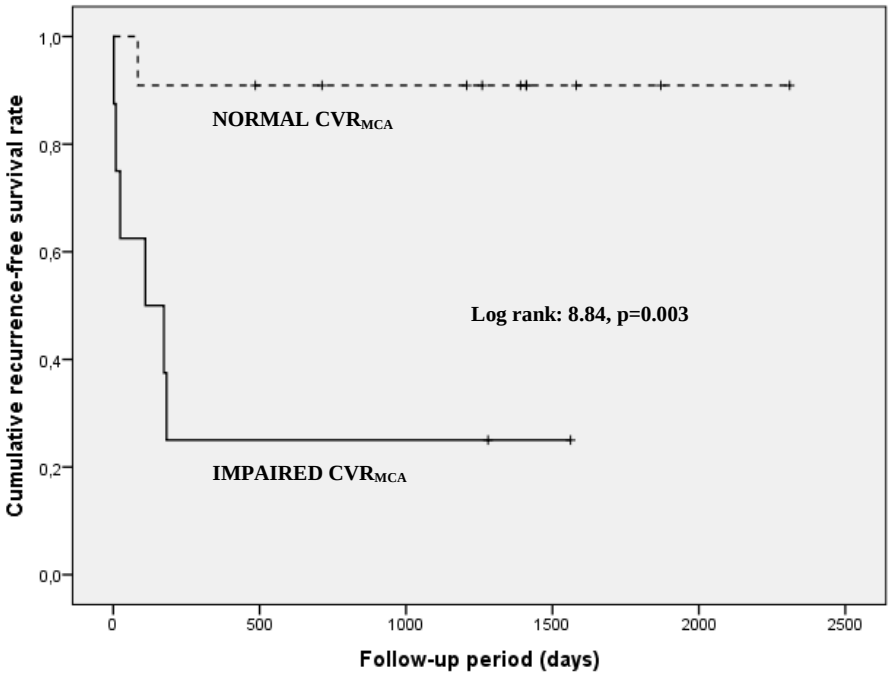


Figure 4: Kaplan-Meier survival curves illustrating the relationship between CVR_{MCA} and the occurrence of ipsilateral ischemic event**.** The vertical cross-lines indicates patient whose data were censored due to study end, death, or recurrent ischemic event.

The annual risk of recurrent ipsilateral ischemic event was higher in IMPAIRED CVR_{MCA} group compared to NORMAL CVR_{MCA} group (39.1%/year vs 3.4%/year, *p*=0.012). There were neither differences among |LI| CVR in other arterial territories nor in other basal perfusion parameters (Table 6).

		NORMAL CVR_{MCA} group (n=11)	IMPAIRED CVR_{MCA} group (n=8)	*p* value
|LI| CVR	MCA	**0.04**±0.02	**0.14**±0.04	<0.001
	ACA	**0.04**±0.04	**0.06**±0.05	0.44
	PCA	**0.04**±0.03	**0.04**±0.02	0.17
|LI| CBF	MCA	**0.08**±0.05	**0.10**±0.06	0.49
	ACA	**0.07**±0.05	**0.04**±0.02	0.55
	PCA	**0.03**±0.02	**0.02**±0.02	0.44
|LI| CBV	MCA	**0.03**±0.02	**0.05**±0.03	0.27
	ACA	**0.04**±0.03	**0.03**±0.03	0.78
	PCA	**0.03**±0.03	**0.03**±0.02	0.90
|LI| MTT	MCA	**0.07**±0.03	**0.11**±0.06	0.11
	ACA	**0.06**±0.03	**0.04**±0.04	0.24
	PCA	**0.03**±0.03	**0.02**±0.02	0.44

Table 6: Laterality indices between NORMAL and IMPAIRED CVR_{MCA} groups for each vascular ROI and each hemodynamic parameter (cerebrovascular reactivity, basal perfusion parameters). Except |LI| CVR_{MCA}, no other hemodynamic parameters differ significantly between these two groups. Data are mean ± standard deviation. Abbreviations are defined in Table 4.

CVR_{MCA} and basal perfusion parameters correlations

We found a positive correlations between LI CVR_{MCA} and LI CBF_{MCA} (ρ=0.89, *p*=0.007 vs ρ=0.59, *p*=0.043) for RECURRENT and SINGLE patients, respectively (Figure 5). A significant negative correlation was found between LI CVR_{MCA} and LI MTT_{MCA} in RECURRENT group (ρ=-0.86, p=0.014) but not significant in SINGLE group (ρ=-0.47, p=0.12). For both groups, LI CVR_{MCA} was not significantly correlated with LI CBV_{MCA}.

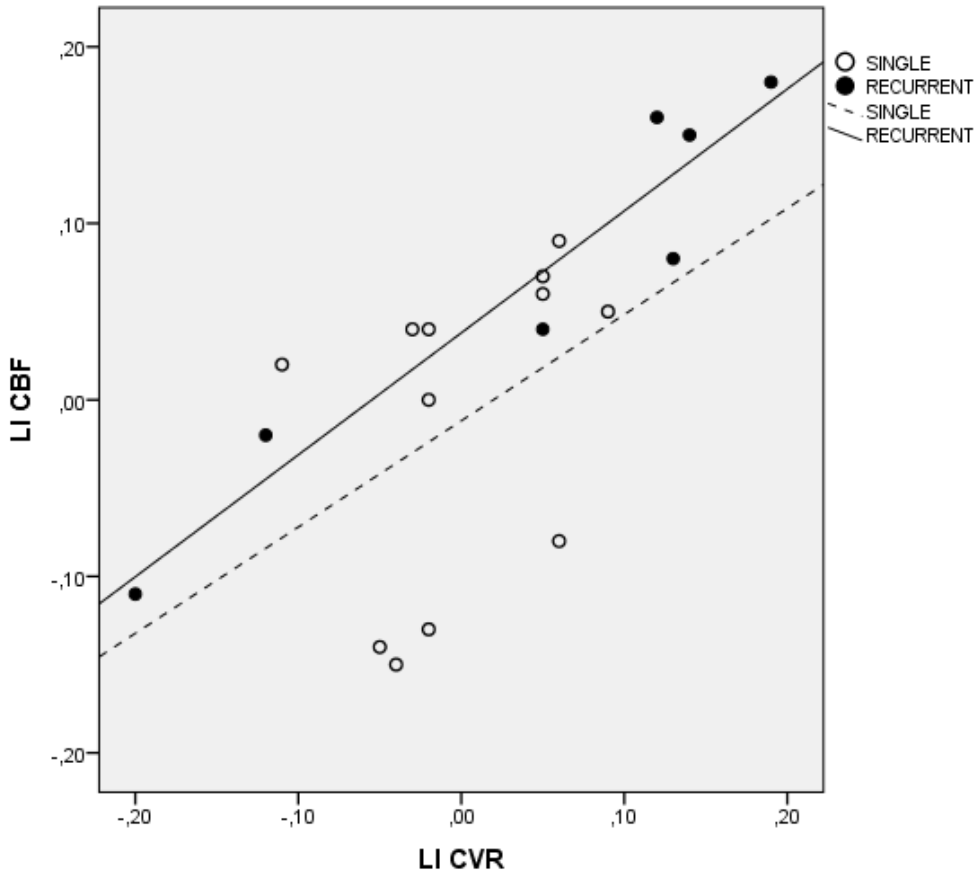


Figure 5: Positive correlations between LI CBF and LI CVR from middle cerebral artery territories (ρ=0.89, *p*=0.007 vs ρ=0.59, *p*=0.043) for RECURRENT and SINGLE patients with intracranial stenosis, respectively.

DISCUSSION:

In patients with symptomatic intracranial atherosclerotic stenosis, recurrent ischemic events occur despite optimal medical therapy. Additional treatments such as endovascular angioplasty and stenting are still not validated. Indeed, large trials failed to demonstrate significant clinical benefits when compared to higher risks of mordibity and mortality. To further address additional therapy, the estimation of cerebrovascular reserve may help to better identify patients at higher risk of stroke recurrence. In our observational study, we showed that 1°) patients with recurrent ischemic events have an impaired CVR downstream the IAS, using BOLD fMRI with hypercapnic challenge; 2°) patients with abnormal CVR defined by a laterality index ≥0.08 are at higher risk of recurrent ischemic events. These results emphasized the potential role of CVR fMRI to select patients for additional treatment.

In our study, the global rate of recurrence of ischemic event was 37%, similar to 38% observed in GESICA study[6]. The annual rate of stroke downstream the qualifying IAS was also close to 18% reported in the severe IAS subgroup of WASID trial, but higher than 12% in the SAMMPRIS trial[4,9]. We used identical restrictive inclusion and exclusion criteria. This led to analyze a much smaller population in our monocentric study. However, clinical baseline characteristics were similar. In SAMMPRIS, a more intensive control of cardiovascular risk factors, based on a tight clinical and biological follow-up and a lifestyle modification program may explain this difference[9].

We identified a high-risk subgroup, i.e. patients with IMPAIRED CVR_{MCA} had a rate of ipsilateral recurrent ischemic event of 39%/year when compared to 3%/year in NORMAL

CVR_{MCA} patients. The 13x higher rate in patients with CVR impairment advocates for a tight relationship. Reduced CVR has been identified as a strong and independent predictor on stroke recurrence in steno-occlusive diseases, using multivariate analysis among other variables (cardiovascular risk factors, degree of stenosis)[28,36,37]. Most of these CVR studies used TDS with several advantages, such as high temporal resolution, arterial velocity quantification, non-invasiveness, cost, and availability, and limitations such as insonation window access, interoperator variability, absence of parenchymal imaging. Functional brain imaging techniques using SPECT, and MRI have been proposed to explore whole brain CVR[17,18]. However, fMRI studies on steno-occlusive diseases were heterogeneous with extracranial and/or stenosis or occlusion, and with different etiologies such as atheromatous or moya-moya[15,24,29,30,38,39]. Our study is the first one to evaluate CVR using fMRI in a homogeneous group of patients with symptomatic atherosclerotic stenosis of a major intracranial artery, like in large randomized trials[4,9].

BOLD fMRI with hypercapnic challenge has been shown as a safe and reliable brain imaging technique to estimate cerebrovascular reserve[29,30]. 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[24,40]. In our experience, CVR fMRI using ASL remains difficult to implement in clinical work-flow, mostly limited by a poor signal to noise ratio, a lower temporal resolution (8 sec between 2 pairs of tag-control images), a critical sensitivity to labeling temporal parameters with aging and arterial transit time asymmetry *a fortiori* downstream IAS, sophisticated postprocessing that requires parametric assumptions and signal corrections for “absolute” CBF quantification[41,42].

Because of the variability of basal perfusion and CVR, we chose to estimate these parameters independently, to calculate LI to minimize interindividual amplitude effects, and to test their relationships[23]. Using classical LI, as defined for hemispheric lateralization for language, we previously shown that 95% of 100 healthy subjects, had CVR $|LI|<0.08$[35]. In the present study, all RECURRENT patients but one had a CVR $|LI|\geq 0.08$. Based on both of these results, IMPAIRED CVR_{MCA} had a much higher risk of ischemic event, suggesting a reliable threshold to select patients at high risk in a future prospective study. However, the asymmetry characterization is less relevant and limits results interpretation in case of bilateral stenosis. Thus, absolute CVR quantification would be helpful to further address these limitations, although physiological and pathological confounds account for a large inter-individual variability [18,24,35].

In a previous study, basal CBF decrease and CVR impairment explained decreased parenchymal oxygenation, suggesting chronic low grade ischemia in patients with symptomatic IAS[23]. Here, CBF and CVR asymmetry were correlated in both RECURRENT and SINGLE patients. The correlation coefficient was higher in the RECURRENT group. However the small groups' size did not allow to conduct appropriate statistical comparison. Despite these relationships, CVR asymmetry was the only significant parameter which differed across RECURRENT and SINGLE groups.

In fact, most recurrent ischemic events downstream IAS occurred during the first year after qualifying event, in line with large clinical trials[4,9]. This observation suggests time-dependent changes of the plaque under aggressive medical management, collateral supply development, and adaptive cerebrovascular reserve increase. Indeed, IAS are dynamic and

degree of stenosis may progress or regress over time[43]. The risk of new stroke is attenuated after 1 year by the stabilization of vulnerable plaque, and development of collateral circulation[44]. Intensive medical management should therefore accelerate these different protective processes[45,46]. Beside structural changes of vascularization, functional changes of arterial supply may also occur. Several cases of spontaneous improvement of cerebrovascular reserve were reported using SPECT[47]. 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, and to monitor natural evolution of CVR and basal perfusion.

Additionally to hemodynamic ischemic event related to CVR impairment, artery-to-artery embolism, *in situ* thrombo-occlusion, and occlusion of perforating arteries are other key pathophysiological mechanisms underlying cerebral ischemia in patients with IAS[48]. Dual antiplatelet therapy and restrictive medical management of cardiovascular factors decrease the risk of disability and death following recurrent stroke in and out the stenosis territory over extended follow-up[9]. Indeed, stroke out the qualifying artery territory and cardiovascular death also occurred, as in large trials[4,6–9], in 4 patients out of 19, independently of CVR_{MCA} status.

Given to our results, prevention of stroke recurrence within the first year remains the most critical therapeutic challenge after the acute stroke management. CVR fMRI would be useful to select high-risk patients and to may help to justify peri-procedural adverse events related to additional invasive treatment. We suggest that future therapeutic trials on endovascular

techniques using stents[49] or angioplasty alone[50], should be first conducted on IAS patients with CVR impairment, only.

CONCLUSION:

Symptomatic intracranial atherosclerotic stenosis is associated with high rates of subsequent stroke and cerebrovascular mortality. Prevention of recurrent ischemic events remains challenging. Using noninvasive CVR BOLD fMRI, LI CVR_{MCA} derived from asymmetric BOLD signal change, elicited by hypercapnic stimulus, shows that CVR impairment is observed in more than 40% of patients with unilateral symptomatic IAS. An increased |LI| CVR_{MCA} is associated with a major risk of ipsilateral recurrent ischemic event. CVR_{MCA} impairment is more frequent in patients with recurrent versus single event. CVR impairment significantly shortens event-free survival during the first year, despite optimal medical management. CVR status should be considered to identify among IAS patients those at a higher risk of recurrent ischemic event and to select those who may benefit from additional treatment, such as endovascular procedures.

BIBLIOGRAPHY

1. Sacco, R. L., Kargman, D. E., Gu, Q. & Zamanillo, M. C. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke* **26,** 14–20 (1995).
2. White, H. *et al.* Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* **111,** 1327–1331 (2005).
3. Wong, L. K. S. Global burden of intracranial atherosclerosis. *Int. J. Stroke Off. J. Int. Stroke Soc.* **1,** 158–159 (2006).
4. Chimowitz, M. I. *et al.* Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N. Engl. J. Med.* **352,** 1305–1316 (2005).
5. Holmstedt, C. A., Turan, T. N. & Chimowitz, M. I. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol.* **12,** 1106–1114 (2013).
6. Mazighi, M. *et al.* Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology* **66,** 1187–1191 (2006).
7. Weber, R., Kraywinkel, K., Diener, H.-C. & Weimar, C. Symptomatic Intracranial Atherosclerotic Stenoses: Prevalence and Prognosis in Patients with Acute Cerebral Ischemia. *Cerebrovasc. Dis.* **30,** 188–193 (2010).
8. Famakin, B. M. *et al.* Causes and severity of ischemic stroke in patients with symptomatic intracranial arterial stenosis. *Stroke J. Cereb. Circ.* **40,** 1999–2003 (2009).
9. Chimowitz, M. I. *et al.* Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. *N. Engl. J. Med.* **365,** 993–1003 (2011).
10. Zaidat, O. O. *et al.* Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* **313,** 1240–1248 (2015).

11. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. *N. Engl. J. Med.* **313,** 1191–1200 (1985).

12. Powers, W. J. *et al.* Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. *JAMA* **306,** 1983–1992 (2011).

13. Hoak, D. A. & Lutsep, H. L. Management of Symptomatic Intracranial Stenosis. *Curr. Cardiol. Rep.* **18,** 83 (2016).

14. Attyé, A. *et al.* Normalization of cerebral vasoreactivity using BOLD MRI after intravascular stenting. *Hum. Brain Mapp.* **35,** 1320–1324 (2014).

15. Mandell, D. M. *et al.* Quantitative Measurement of Cerebrovascular Reactivity by Blood Oxygen Level-Dependent MR Imaging in Patients with Intracranial Stenosis: Preoperative Cerebrovascular Reactivity Predicts the Effect of Extracranial-Intracranial Bypass Surgery. *Am. J. Neuroradiol.* **32,** 721–727 (2011).

16. Waters, M. F. *et al.* Factors Associated With Recurrent Ischemic Stroke in the Medical Group of the SAMMPRIS Trial. *JAMA Neurol.* 1–8 (2016). doi:10.1001/jamaneurol.2015.4315

17. Gupta, A. *et al.* Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke J. Cereb. Circ.* **43,** 2884–2891 (2012).

18. Krainik, A. *et al.* Functional imaging of cerebral perfusion. *Diagn. Interv. Imaging* **94,** 1259–1278 (2013).

19. Mchedlishvili, G. Physiological mechanisms controlling cerebral blood flow. *Stroke* **11,** 240–248 (1980).

20. Powers, W. J. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann. Neurol.* **29,** 231–240 (1991).

21. Krainik, A., Hund-Georgiadis, M., Zysset, S. & von Cramon, D. Y. Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. *Stroke J. Cereb. Circ.* **36,** 1146–1152 (2005).

22. Conklin, J. *et al.* Mapping white matter diffusion and cerebrovascular reactivity in carotid occlusive disease. *Neurology* **77,** 431–438 (2011).

23. Bouvier, J. *et al.* Reduced $CMRO_2$ and cerebrovascular reserve in patients with severe intracranial arterial stenosis: a combined multiparametric qBOLD oxygenation and BOLD fMRI study. *Hum. Brain Mapp.* **36,** 695–706 (2015).

24. Smeeing, D. P. J., Hendrikse, J., Petersen, E. T., Donahue, M. J. & de Vis, J. B. Arterial Spin Labeling and Blood Oxygen Level-Dependent MRI Cerebrovascular Reactivity in Cerebrovascular Disease: A Systematic Review and Meta-Analysis. *Cerebrovasc. Dis. Basel Switz.* **42,** 288–307 (2016).

25. Herold, S. *et al.* Assessment of cerebral haemodynamic reserve: correlation between PET parameters and CO2 reactivity measured by the intravenous 133 xenon injection technique. *J. Neurol. Neurosurg. Psychiatry* **51,** 1045–1050 (1988).

26. Chen, J. *et al.* Impaired dynamic cerebral autoregulation and cerebrovascular reactivity in middle cerebral artery stenosis. *PloS One* **9,** e88232 (2014).

27. Pindzola, R. R., Balzer, J. R., Nemoto, E. M., Goldstein, S. & Yonas, H. Cerebrovascular Reserve in Patients With Carotid Occlusive Disease Assessed by Stable Xenon-Enhanced CT Cerebral Blood Flow and Transcranial Doppler. *Stroke* **32,** 1811–1817 (2001).

28. Ogasawara, K., Ogawa, A. & Yoshimoto, T. Cerebrovascular Reactivity to Acetazolamide and Outcome in Patients With Symptomatic Internal Carotid or Middle Cerebral Artery Occlusion. *Stroke* **33,** 1857–1862 (2002).

29. Donahue, M. J. *et al.* Routine Clinical Evaluation of Cerebrovascular Reserve Capacity Using Carbogen in Patients With Intracranial Stenosis. *Stroke* **45,** 2335–2341 (2014).

30. Spano, V. R. *et al.* CO2 blood oxygen level-dependent MR mapping of cerebrovascular reserve in a clinical population: safety, tolerability, and technical feasibility. *Radiology* **266,** 592–598 (2013).

31. Fierstra, J. *et al.* Measuring cerebrovascular reactivity: what stimulus to use? *J. Physiol.* **591,** 5809–5821 (2013).

32. Samuels, O. B., Joseph, G. J., Lynn, M. J., Smith, H. A. & Chimowitz, M. I. A standardized method for measuring intracranial arterial stenosis. *AJNR Am. J. Neuroradiol.* **21,** 643–646 (2000).

33. Wu, O. *et al.* Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. *Magn. Reson. Med.* **50,** 164–174 (2003).

34. Tatu, L., Moulin, T., Vuillier, F. & Bogousslavsky, J. Arterial territories of the human brain. *Front. Neurol. Neurosci.* **30,** 99–110 (2012).

35. Boudiaf, N. *et al.* BOLD fMRI of cerebrovascular reactivity in the middle cerebral artery territory: A 100 volunteers' study. *J. Neuroradiol. J. Neuroradiol.* **42,** 338–344 (2015).

36. Markus, H. & Cullinane, M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain J. Neurol.* **124,** 457–467 (2001).

37. Reinhard, M. *et al.* Cerebrovascular reactivity predicts stroke in high-grade carotid artery disease. *Neurology* **83,** 1424–1431 (2014).

38. Goode, S. D., Altaf, N., Munshi, S., MacSweeney, S. T. R. & Auer, D. P. Impaired Cerebrovascular Reactivity Predicts Recurrent Symptoms in Patients with Carotid Artery Occlusion: A Hypercapnia BOLD fMRI Study. *Am. J. Neuroradiol.* **37,** 904–909 (2016).

39. Haller, S. *et al.* Reduced cerebrovascular reserve at CO2 BOLD MR imaging is associated with increased risk of periinterventional ischemic lesions during carotid endarterectomy or stent placement: preliminary results. *Radiology* **249,** 251–258 (2008).

40. Villien, M. *et al.* Changes in cerebral blood flow and vasoreactivity to CO2 measured by arterial spin labeling after 6days at 4350m. *NeuroImage* **72,** 272–279 (2013).

41. Vincent, T. *et al.* Bayesian joint detection-estimation of cerebral vasoreactivity from ASL fMRI data. *Med. Image Comput. Comput.-Assist. Interv. MICCAI Int. Conf. Med. Image Comput. Comput.-Assist. Interv.* **16,** 616–624 (2013).

42. Villien, M. *et al.* Per-subject characterization of bolus width in pulsed arterial spin labeling using bolus turbo sampling. *Magn. Reson. Med.* **69,** 1677–1682 (2013).

43. Akins, P. T., Pilgram, T. K., Cross, D. T. & Moran, C. J. Natural history of stenosis from intracranial atherosclerosis by serial angiography. *Stroke* **29,** 433–438 (1998).

44. Liebeskind, D. S. *et al.* Collaterals dramatically alter stroke risk in intracranial atherosclerosis. *Ann. Neurol.* **69,** 963–974 (2011).

45. Sander, K., Hof, U., Poppert, H., Conrad, B. & Sander, D. Improved Cerebral Vasoreactivity After Statin Administration in Healthy Adults. *J. Neuroimaging* **15,** 266–270 (2005).

46. Sterzer, P. *et al.* Pravastatin Improves Cerebral Vasomotor Reactivity in Patients With Subcortical Small-Vessel Disease. *Stroke* **32,** 2817–2820 (2001).

47. Hasegawa, Y., Yamaguchi, T., Tsuchiya, T., Minematsu, K. & Nishimura, T. Sequential change of hemodynamic reserve in patients with major cerebral artery occlusion or severe stenosis. *Neuroradiology* **34,** 15–21 (1992).

48. van den Wijngaard, I. R. *et al.* Treatment and imaging of intracranial atherosclerotic stenosis: current perspectives and future directions. *Brain Behav.* **6,** n/a-n/a (2016).

49. Ding, D., Starke, R. M., Crowley, R. W. & Liu, K. C. Role of stenting for intracranial atherosclerosis in the post-SAMMPRIS era. *BioMed Res. Int.* **2013,** 304320 (2013).

50. Dumont, T. M. *et al.* Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective Phase I study. *J. Neurosurg.* 1–8 (2016). doi:10.3171/2015.8.JNS15791

THESE SOUTENUE PAR :

PAPASSIN Jérémie

TITRE:

Altération de la vasoréactivité cérébrale en IRMf hypercapnique chez les patients présentant une sténose artérielle intracrânienne symptomatique d'origine athéromateuse à haut risque de récidive.

RESUME :

Introduction: Malgré un traitement médical optimal, le risque de récidive dans les sténoses artérielles intracrâniennes symptomatiques (SAIS) d'origine athéromateuse est élevé. Une altération de la vasoréactivité cérébrale (CVR) pourrait être impliquée. L'étude en IRM fonctionnelle BOLD hypercapnique de la CVR permettrait d'identifier les patients à haut risque de récidive, afin de proposer des traitements complémentaires plus invasifs comme l'angioplastie transluminale percutanée avec stent intracrânien.

Méthodes: Nous avons étudiés les relations statistiques entre les données cliniques et biologiques individuelles, la récidive d'évènement ischémique et la CVR dans les territoires de l'artère cérébrale moyenne (ACM) rapportée par un index de latéralité (IL), pour 19 patients avec une SAIS de l'ACM ou de l'artère carotide interne.

Résultats: Huit patients (42%) avaient un IL CVR_{ACM} anormal ($|IL|$ $CVR_{ACM} \geq 0.08$). Avec un suivi moyen de 3.6 ans, la récurrence d'évènement ischémique était plus fréquente et plus précoce dans le groupe CVR_{ACM} altérée (n = 6/8) que dans le groupe CVR_{ACM} normale (n = 1/11) avec des courbes de survie significativement différentes (log rank, p = 0.003). Les caractéristiques cliniques étaient similaires entre les deux groupes.

Conclusion: Une altération de la CVR en IRMf hypercapnique est associée à un risque élevé de récidive pour les patients avec une SAIS d'origine athéromateuse. La cartographie de la CVR pourrait être utilisée pour sélectionner les patients à haut risque de récidive, afin de discuter un traitement complémentaire.

VU ET PERMIS D'IMPRIMER
Grenoble, le 21/09/2017

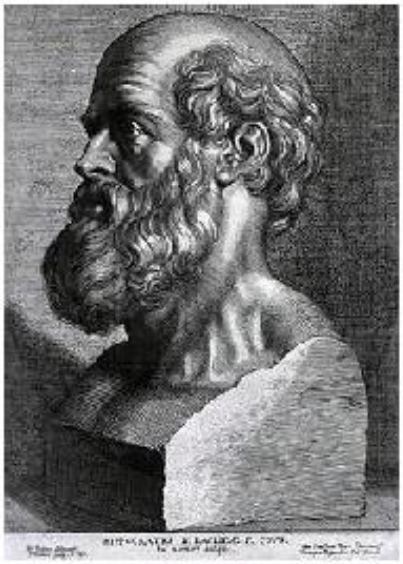
LE DOYEN

J.P. ROMANET

Pour la Présidente
et par délégation
Le Doyen de Médecine
Pr. Jean-Paul ROMANET

LE PRESIDENT DE LA THESE

M. MAZIGHI



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Impaired cerebrovascular reactivity assessed by BOLD hypercapnic fMRI is associated with increased risk of stroke in patients with symptomatic intracranial atherosclerotic stenosis

***Introduction*:** Despite intensive medical management, intracranial atherosclerotic stenosis (IAS) remains at risk of recurrent ischemic events. Impaired cerebrovascular reserve is suggested to explain hemodynamic stroke. Cerebrovascular reactivity assessed by hypercapnic challenge using BOLD functional MRI (CVR BOLD fMRI) has been proposed to estimate cerebrovascular reserve and to identify patients at higher risk. To discuss patients' selection for additional therapy such as intracranial angioplasty and stenting, we studied the relationships between baseline characteristics of patients with unilateral symptomatic IAS, recurrence of ischemic events, and CVR BOLD fMRI.

***Subjects and methods*:** Nineteen patients with symptomatic unilateral IAS of middle cerebral artery (MCA) or internal carotid artery were selected. We calculated statistical relationships between individual clinical and biological baseline characteristics, recurrent ischemic events, basal perfusion estimated by dynamic susceptibility contrast MRI, and CVR BOLD fMRI measured in MCA territories (CVR_{MCA}), and reported using laterality indices (LI).

***Results*:** Eight patients (42%) had an abnormal LI CVR_{MCA} ($|LI|$ $CVR_{MCA} \geq 0.08$). During a mean follow-up of 3.6 years, recurrent ischemic events occurred within the first year. They were more frequent in impaired CVR_{MCA} group (n=6/8) than in normal CVR_{MCA} group (n=1/11), with different survival curves (log rank, p=0.003). Baseline characteristics were similar in both groups.

***Conclusion*:** Impaired CVR assessed by BOLD hypercapnic fMRI is associated with increased risk of stroke in patients with symptomatic IAS. CVR mapping should be proposed to select high-risk patients in order to discuss additional treatment.