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Original Article

Brain Stress Test for Assessing Risk for Hemodynamic Stroke

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ABSTRACT: ***Background:*** In patients with intracranial steno-occlusive disease (SOD), the risk of hemodynamic stroke depends on the post-stenotic vasodilatory reserve. Cerebrovascular reactivity (CVR) is a test for vasodilatory reserve. We tested for vasodilatory reserve by using $P_{ET}CO_2$ as the stressor, and Blood Oxygen Level Dependent (BOLD) MRI as a surrogate of blood flow. We correlate the CVR to the incidence of stroke after a 1-year follow-up in patients with symptomatic intracranial SOD. ***Methods:*** In this retrospective study, 100 consecutive patients with symptomatic intracranial SOD that had undergone CVR testing were identified. CVR was measured as % BOLD MR signal intensity/mmHg $P_{ET}CO_2$. All patients with normal CVR were treated with optimal medical therapy; those with abnormal CVR were offered revascularization where feasible. We determined the incidence of stroke at 1 year. ***Results:*** 83 patients were included in the study. CVR was normal in 14 patients and impaired in 69 patients ipsilateral to the lesion. Of these, 53 underwent surgical revascularization. CVR and symptoms improved in 86% of the latter. The overall incidence of stroke was 4.8 % (4/83). All strokes occurred in patients with impaired CVR (4/69; 2/53 in the surgical group, all in the nonrevascularized hemisphere), and none in patients with normal CVR (0/14). ***Conclusion:*** Our study confirms that CO_2-BOLD MRI CVR can be used as a brain stress test for the assessment of cerebrovascular reserve. Impaired CVR is associated with a higher incidence of stroke and normal CVR despite significant stenosis is associated with a low risk for stroke.

RÉSUMÉ : Étude de la vasoréactivité cérébrale dans l'évaluation du risque d'accident vasculaire cérébral hémodynamique. ***Contexte :*** Dans les cas de maladie sténo-occlusive (MSO) intracrânienne, le risque d'accident vasculaire cérébral (AVC) hémodynamique dépend de la réserve de vasodilatation en aval de la sténose. La réactivité vasculaire cérébrale (RVC) est une mesure de la réserve de vasodilatation. Celle-ci a été effectuée, dans l'étude, à l'aide de la pression partielle du CO_2 (pCO_2) en fin d'expiration utilisée comme agent stressant, et de l'IRM avec signal BOLD (Blood Oxygen Level Dependent) comme substitut du débit sanguin. Une corrélation a établie entre la RVC et l'incidence d'AVC au bout de un an de suivi chez les patients atteints d'une MSO intracrânienne symptomatique. ***Méthode :*** Il s'agit d'une étude rétrospective à laquelle ont participé 100 patients consécutifs qui présentaient une MSO intracrânienne symptomatique et qui ont été soumis à une mesure de la RVC, exprimée sous forme de pourcentage de l'intensité du signal BOLD en IRM/la pCO_2 en fin d'expiration, en mmHg. Tous les patients qui avaient une RVC normale ont été soumis au traitement médical optimal, tandis que ceux chez qui la RVC était anormale se sont vu offrir la revascularisation lorsque le traitement s'y prêtait. L'incidence des AVC a été déterminée au bout de un an. ***Résultats :*** Ont été retenus 83 patients dans l'étude. La RVC était normale chez 14 sujets et altérée chez 69 porteurs d'une lésion homolatérale. De ces derniers, 53 ont subi une revascularisation chirurgicale et, chez 86 % d'entre eux, on a observé une amélioration de la RVC ainsi qu'une diminution des symptômes. L'incidence globale des AVC s'est élevée à 4,8 % (4/83), et tous les accidents vasculaires sont survenus chez les patients ayant une RVC altérée (4/69; 2/53 dans le groupe de traitement chirurgical, tous du côté de l'hémisphère non revascularisé); aucun ne s'est produit chez les patients ayant une RVC normale (0/14). ***Conclusion :*** D'après les résultats de l'étude, la mesure de la RVC par IRM à l'aide du signal BOLD et de la pCO_2 peut servir d'étude de la vasoréactivité cérébrale pour l'évaluation de la réserve vasculaire cérébrale. Une RVC altérée est associée à une incidence plus élevée d'AVC, et une RVC normale, malgré une sténose importante, est associée à un faible risque d'AVC.

Keywords: Cerebrovascular reserve; MRI; Brain stress test; Stroke; CO_2; Hypercapnia

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Introduction

Hemodynamic stroke is a type of ischemic stroke secondary to hypoperfusion where blood flow is reduced to a critical level to cause ischemic injury.[1] In patients with steno-occlusive cerebrovascular diseases (SOD), both intracranial and extracranial, post-stenotic reduction in perfusion pressure and flow limitation results in regional hypoperfusion. However, autoregulation-related

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vasodilation and flow from the collateral circulation can compensate for reduced perfusion pressure. Hence, the risk of hemodynamic stroke in these patients depends on the post-stenotic vasodilatory reserve [2] and on the availability of recruitable flow through collateral blood vessels.[3] The presence of such recruitable flow markedly reduces the risk of stroke[4,5,6,7] and the need for revascularization.[8,9] However, in contrast to extracranial stenosis, recruitable collateral supply is limited in patients with intracranial stenosis and hence the incidence of hemodynamic stroke is higher. Cerebrovascular reactivity (CVR) is the measure of the change in cerebral blood flow (CBF) in response to a vasodilatory stimulus i.e., the measure of vascular reserve capacity. It measures the change in flow in the parenchymal vessels, i.e., the sum of flows from the feeding artery and collateral blood flow.[10,11] Over the past 10 years, we have developed a noninvasive, reproducible CVR brain stress test[12] to measure the cerebrovascular reserve in patients with symptomatic steno-occlusive disease (SOD) using a precisely controlled change in end-tidal (end-expiratory) partial pressure of CO_2 ($P_{ET}CO_2$) as a vasodilatory stimulus and the Blood Oxygen Level Dependent (BOLD) MRI signal as a semiquantitative surrogate of CBF.[13,14,15]

In this retrospective study, we examine the sensitivity of the brain stress test in identifying patients at risk for hemodynamic stroke. Secondarily, we examine the relationship between SOD and the pattern of CVR on the one hand, and the incidence of stroke on the other. We were particularly interested in the incidence of stroke after 1 year in a cohort of symptomatic patients who had similar degree of SOD but were discordant as to the presence of normal or impaired CVR. We hypothesized that in patients with similar degrees of stenosis, the CO_2 MRI brain stress test can help identify patients with impaired CVR and the incidence of stroke will be different between patients with normal CVR and impaired CVR.

Materials and Methods

Patients

The institutional ethics committee approved the study protocol (UHN REB #13-7168) and all patients provided written informed consent. Consecutive patients with angiographically (CT or MRI) demonstrated intracranial SOD (>70% stenosis or occlusion) who presented with transient ischemic attacks (TIA) or stroke were recruited for CVR testing within 3 months of their presentation. We excluded patients whose symptoms were suspected to be of extra-cranial SOD, cardiac (history of atrial fibrillation, valvular heart disease) and thromboembolic etiology. We screened patients for contraindication to MRI environment or hypercapnia (end-stage chronic obstructive pulmonary disease with CO_2 retention, intracranial hypertension).

CVR Measurement

The apparatus and technique for controlling the end-tidal pCO_2 ($P_{ET}CO_2$) have been described in greater detail elsewhere.[16,17] In brief, the subjects breathe without restriction while wearing an airtight light plastic mask. Gases are supplied via an automated gas blender running a feed-forward algorithm to target $P_{ET}CO_2$ and $P_{ET}O_2$ described by Slessarev et al (RespirAct™ Thornhill Medical Inc. Toronto, Canada).[17] The user enters the target end-tidal gas values and their durations. The RespirAct™ system then uses the algorithm to calculate the various gas concentrations and flows it will administer to the breathing circuit to attain the target end-tidal gas partial pressures. The gas sequence for CVR measurement consisted of two square wave hypercapnic stimuli (from baseline to baseline plus 10 mmHg) of 90- and 120-s duration, respectively. Iso-oxia (target $P_{ET}O_2$ of 100 mmHg) was maintained throughout. $P_{ET}CO_2$ and $P_{ET}O_2$ were monitored continuously, digitized, and recorded.

Imaging

MR imaging was performed on a 3T whole-body scanner (Signa HDx; GE Healthcare, Milwaukee, Wisconsin) with an 8-channel-phased array head coil for signal reception. Each patient was imaged with an identical CO_2-BOLD-CVR protocol preoperatively and postoperatively. Each CVR session included routine clinical acquisitions (sagittal T1-weighted, axial T2-weighted, axial T2-weighted FLAIR, and diffusion-weighted), an axial T1-weighted 3D spoiled gradient-echo acquisition (matrix size, 256 × 256; section thickness, 2.2 mm; intersection gap, 0) for anatomic coregistration, and an axial T2*-weighted single-shot gradient-echo echo-planar BOLD acquisition (flip angle, 85°; TR, 2000 ms; TE, 30 ms; Voxel size 3.75 × 3.75 × 5 mm; intersection gap, 2 mm; the number of frames, 255) during controlled changes in $PetCO_2$.

CVR Maps

MR imaging and $P_{ET}CO_2$ data were imported into the software AFNI (National Institutes of Health, Bethesda, Maryland; http://afni.nimh.nih.gov/afni). An AFNI algorithm was used to calculate head motion for each BOLD MR imaging acquisition. Each patient's whole-brain BOLD MR signal-intensity dataset was temporally shifted to the point of maximum correlation with the patient's $P_{ET}CO_2$ waveform to compensate for the delay of gas analysis resulting from transit time in the long gas sample line. The BOLD MR signal-intensity time waveform then underwent least-squares linear fitting to the $P_{ET}CO_2$-time waveform on a voxel-by-voxel basis, and CVR was calculated as the slope % BOLD-MR signal intensity per mm Hg $P_{ET}CO_2$. Anatomic images were automatically segmented into gray matter and white matter and transformed into Montreal Neurologic Institute space by using the software SPM8 (Welcome Department of Imaging Neuroscience, Institute of Neurology, University College, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Anatomic images were further segmented into anterior (ACA), middle (MCA) and posterior (PCA) cerebral vascular territories by using masks created from the atlas of Kretschmann and Weinrich[17]. Mean gray matter CVR was calculated for each of these segments, for each CVR study. The preoperative and postoperative routine T1- and T2-weighted images were reviewed to identify regions of parenchymal infarction or hemorrhage.

Treatment and Follow-up

Patients were offered revascularization on taking the full clinical and imaging picture into account. Patients with impaired or paradoxical CVR (areas with intracerebral steal) were offered revascularization. Surgical revascularization consisted of extracranial-intracranial (EC-IC) bypass using either a direct superficial temporal artery to middle cerebral artery (STA-MCA) bypass or indirect encephalo-dural–arterial synangiosis (EDAS). EDAS was performed if the STA-MCA bypass was not deemed to be technically achievable. Revascularization was carried out on the recently symptomatic side with impaired CVR. All patients were prescribed standard optimal medical therapy (OMT).[18,19] All patients had

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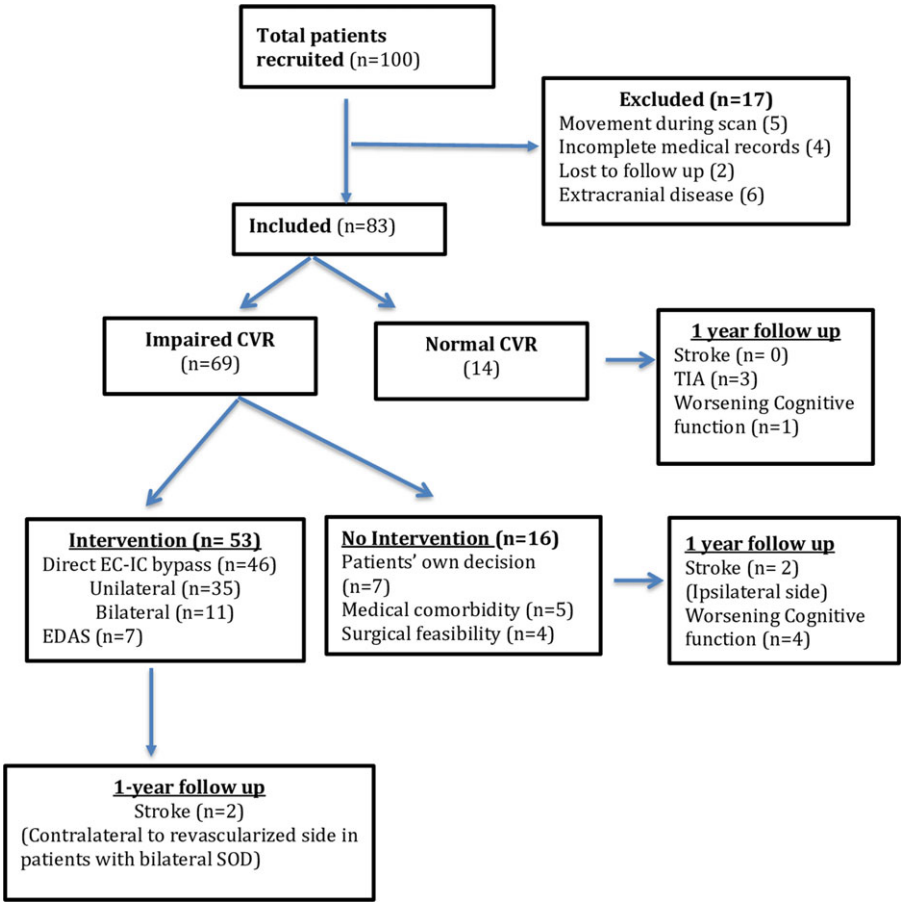

Figure 1: Flow chart with patient selection criteria and outcome. n – number, CVR – cerebrovascular reactivity, EC–IC – extracranial–intracranial, EDAS – encephalo-dural–arterial synangiosis, SOD – steno-occlusive disease. TIA – transient ischemic attack.

both clinical and radiological (structural imaging) follow-ups at 1 year. In addition, patients who had surgical revascularization had postoperative CVR at 3 months and 1 year. Clinical assessment included inquiring about a history of continued or new TIAs, strokes, seizures, or changes in neurological or cognitive function. The occurrence of stroke was diagnosed based on clinical presentation with radiological confirmation.

Performance Metrics and Data Analysis

Outcome Measures

The primary outcome was to identify patients with poor cerebrovascular reserve, a marker of high risk for hemodynamic stroke. Secondary outcomes include improvement in CVR with intervention, a correlation between improvements in CVR and clinical symptoms, and finally the incidence of stroke. We categorized patients as having either normal CVR or impaired CVR on the side ipsilateral to the vascular lesion on presentation. Impaired CVR consists of either reduced CVR or paradoxical or negative CVR. In our previous study from healthy volunteers ($n = 30$), mean (±SD) CVR in MCA territory was 0.30 ± 0.07 (%BOLD MR signal intensity per mm Hg of P_{ET} CO2).[20] We used 2 SD below normal CVR (0.16%) in the MCA territory as a cut-off threshold for reduced CVR. Improvement in CVR was defined as $a > 25\%$ increase in reactivity as compared to preoperative values. In patients with unilateral interventions, CVRs from the vascularized hemisphere were considered, and in patients who had bilateral interventions, the average CVR between the hemispheres was considered.

Data Analysis

Statistical analyses were performed using Graphpad Prism version 8.0, GraphPad Software, San Diego, California USA, and excel (Microsoft Corporation, USA). Demographics data were presented n (%) or mean (±SD) as appropriate. Descriptive statistics were used to measure the incidences of impaired CVR, interventions, response to intervention and the clinical outcome (stroke). A Mann–Whitney test was used to analyze the difference between CVR values between patients who had an intervention to those that did not have an intervention. A Wilcoxon matched-pairs signed rank test (two-sided, $\alpha = 0.05$) with Bonferroni correction was used for statistical analysis comparing the prerevascularization and postrevascularization CVR values. A Wilcoxon matched-pairs signed rank test (two-sided, $\alpha = 0.05$) with Bonferroni correction was used for statistical analysis comparing the prerevascularization and postrevascularization CVR values. Fisher's exact test (2 × 2 contingency table) was used to analyze the incidence of stroke between the normal CVR vs impaired CVR groups and the incidence of ipsilateral stroke with and without intervention in the impaired CVR group.

Results

We recruited 100 patients, with 17 patients excluded (Figure 1). The demographic data are presented in Table 1. The majority (71/83) of patients presented with TIA or ischemic stroke, and a small number ($n = 9$) of patients presented with hemorrhage which occurred in areas of neovascularization, especially in patients with moyamoya vasculopathy.

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Table 1: Patient demographics

	Total ($N = 83$)	Normal CVR ($N = 14$)	Impaired CVR ($N = 69$)	
			No Revascularization ($N = 16$)	Revascularization ($N = 53$)
Age (yrs) Mean (±SD)	46 ± 28	52.1 ± 18	55 ± 2	**42 ± 12**
Sex -Female (*n*) (%)	70(71%)	15 (65%)	10 (62.5%)	**45 (76%)**
Pathology (*n*)				
Moyamoya disease/syndrome	54	5	7	**42**
Atherosclerosis	29	10	9	**10**
Degree of stenosis				
70–90%	34	7	5	**22**
>90%	49	7	11	**31**
Site of stenosis				
Distal ICA/MCA	44/39	8/6	9/7	**27/26**
Unilateral/Bilateral	47/36	9/5	8/8	**40/13**
Clinical presentation				
TIA	51	14	11	**26**
Ischemic Stroke	20	5	3	**12**
Hemorrhage	9	2	1	**6**
Others (Dizziness, Seizures, Cognitive decline)	3	1	1	**1**

CVR – Cerebrovascular reactivity; n – number; Yrs – years; SD – Standard deviation; TIA – Transient Ischemic attacks; ICA – Internal carotid artery; MCA – Middle cerebral artery.

Table 2: Cerebrovascular reactivity values in the ipsilateral and the contralateral middle and anterior cerebral artery territories

	Ipsilateral		Contralateral	
	MCA	ACA	MCA	ACA
Normal CVR (24)	0.22 ± 0.006	0.19 ± 0.04	0.22 ± 0.05	**0.19 ± 0.04**
Impaired CVR (76)	0.06 ± 0.07	0.08 ± 0.09	0.13 ± 0.09	**0.11 ± 0.94**
Revascularization	0.05 ± 0.07	0.09 ± 0.09	0.13 ± 0.10	**011 ± 0.09**
No-Revascularization	0.07 ± 0.09	0.06 ± 0.07	0.14 ± 0.08	**0.10 ± 0.08**

Values (%BOLD MR signal intensity/mmHg of $P_{ET}CO_2$) are presented as mean ± SD. CVR – cerebrovascular reactivity; MCA – middle cerebral artery; ACA – anterior cerebral artery.

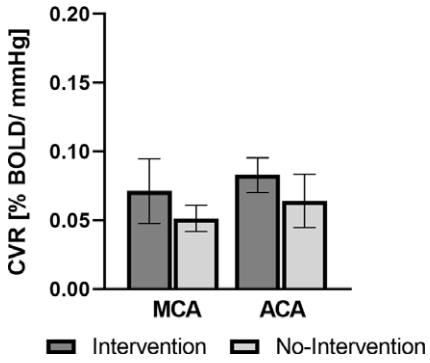

Figure 2: Bar graphs showing CVR with no surgical intervention (N = 16) compared to intervention (N = 53) in the middle cerebral artery (MCA) and Anterior cerebral artery (ACA) vascular territories. The CVR Mean (SD) values in the MCA territory were 0.05 (0.07) n = 53 in the intervention group, and 0.07 (0.1) n = 16 in the nonintervention group; the distributions in the two groups did not significantly differ (Mann–Whitney U = 410.5, P = 0.26 two-tailed). The CVR values in the ACA territory were 0.06 (0.08) n = 53 in the intervention group, and 0.08 (0.1) n = 16 in the nonintervention group; the distributions in the two groups did not significantly differ (Mann–Whitney U = 474.5, P = 0.74 two-tailed).

There were no reported adverse events during the test. The average (range) resting $P_{ET}CO_2$ was 37.4 (27–48) mmHg. Hypercapnia (resting + 10 mmHg) was achieved within 1.4 ± 1.3 mmHg (mean ± SD of) of the target in all patients. Fourteen patients showed normal CVR (0.21% ± 0.04%/mmHg) and impaired CVR (0.09 %± 0.06%/mmHg) was seen in 69 patients, predominantly in the middle and anterior cerebral artery territories. CVR values in MCA and ACA territories on the ipsilateral and contralateral sides are shown in Table 2.

Among the patients who had impaired CVR, 76% (53/69) underwent a revascularization procedure and the reminder (16/69) did not have revascularization (Figure 1). There were no significant differences in the preoperative CVR between the subjects who had an intervention and those who did not (Figure 2) [$P = 0.26$ for MCA and $P = 0.74$ for ACA (Mann–Whitney *U* test)]. In the postsurgery follow-up 86% (46/53) of patients showed improvement in the CVR at 1 year. There were no new symptoms in patients who had revascularization.

Pre- and post-revascularization CVR values are shown in Figure 3. Unilateral revascularization ($n = 35$) significantly improved the CVR in the ipsilateral MCA territory (mean ± SD 0.039 ± 0.069) to 0.100 ± 0.062 %BOLD/mm Hg, $P = 0.01$) (Figure 3). Seven patients showed no significant improvement in CVR after intervention [direct bypass (5), EDAS (2)]; however, they were clinically asymptomatic at 1 year.

The incidence of stroke in the cohort at 1 year was 4.8 % (4/83). All the strokes occurred in patients with impaired CVR (4/69) and none in patients with normal CVR despite no revascularization (Figure 4). However, it was not statistically significant (4/69 vs

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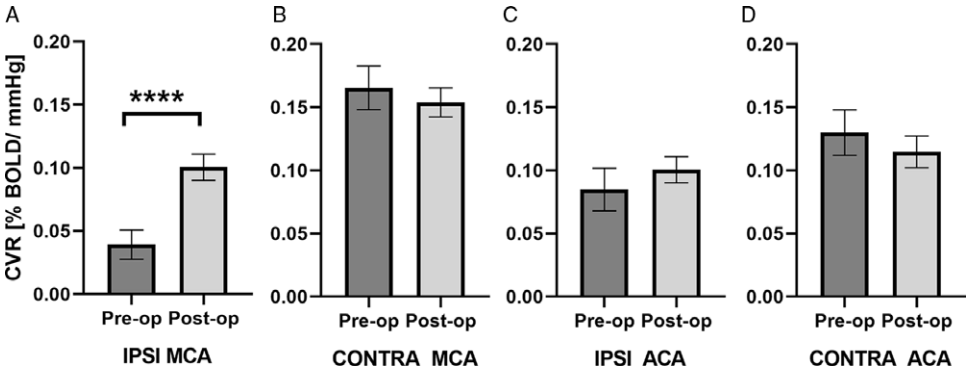

Figure 3: Preoperative versus postoperative CVR values in the (A) ipsilateral middle cerebral artery (MCA); (B) contralateral MCA; (C) ipsilateral anterior cerebral artery (ACA), and (D) contralateral ACA territory (N = 35). Bar graphs denote the mean (SEM) error bars. Four asterisks indicate a $P < 0.0001$, corrected for multiple comparisons.

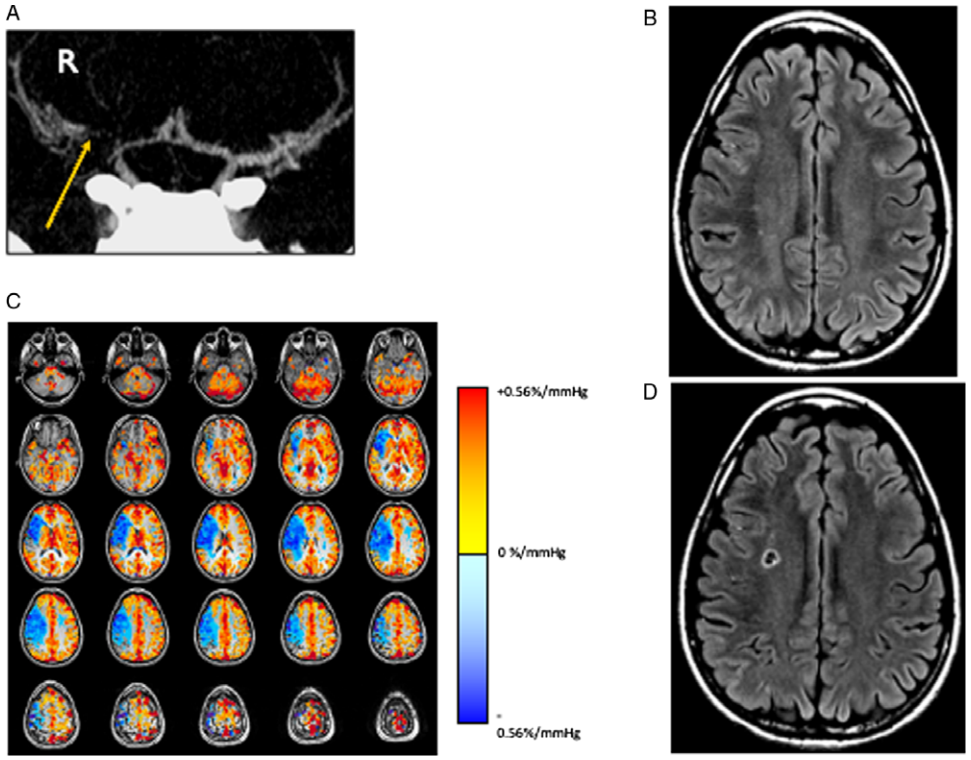

Figure 4: Example of a patient who presented with transient left face and upper and lower extremity paresthesia and weakness. (A) CT angiogram shows severe narrowing of the right middle cerebral artery (yellow arrow). (B) T2-weighted FLAIR image showed no evidence of brain infarct. (C) CVR study shows reduced (paradoxical) reactivity throughout the right MCA territory and preserved reactivity elsewhere. (D) 4-month follow-up MRI demonstrating a new infarct in the right MCA territory corresponding to the region of impaired CVR.

0/14 $p = 1.0$, Fisher's exact test)). Among the patients with impaired CVR, all the strokes happened on the nonrevascularized side; two strokes occurred in patients who had no revascularization and the other two occurred in the contralateral nonrevascularized side in patients with bilateral SOD who had ipsilateral revascularization. (4/16 vs 0/53 $p = 0.05$, Fisher's exact test). Note that all the strokes occurred in the area, which showed impaired CVR (Figure 4). Six (6/69, 8.7%) patients with impaired CVR and no revascularization had self-reported worsening of cognitive function at 1 year. Among the patients who had normal CVR, three patients (3/14, 21%) had episodes of TIA's (ipsilateral to SOD) and one patient (1/14, 7.1%) complained of worsening cognitive function at 1 year. There were no clinical strokes in this group.

Discussion

Our study confirms the previous findings[12,13] that 1) CO_2-BOLD MRI CVR can be used as a brain stress test for the assessment of cerebrovascular reserve in patients at risk for hemodynamic stroke. 2) Impaired CVR, a marker of the poor cerebrovascular reserve is associated with a higher incidence of stroke. 3) Normal CVR despite significant stenosis appears to be associated with a low risk of stroke.

In this study, we examined a cohort of symptomatic subjects with similar degrees of severe SOD (>70 % stenosis or occlusion). When subdivided according to a functional hemodynamic assay, the CVR, we found that 17% (14/83) of patients had a normal functional hemodynamic reserve. Their physicians, taking all clinical information into account, advised that they do not need revascularization, but be treated with OMT. At 1 year, none of these patients had a stroke. The remainder of the cohort did have reduced hemodynamic reserve as indicated by a reduction in CVR. The strokes occurred exclusively in this group. The subgroup that did not undergo revascularization had a higher incidence of stroke, though not statistically significant, than those that did. In addition, even in the group who had revascularization, two strokes occurred on the contralateral side with impaired CVR in patients with bilateral disease. We propose that patients, who have normal CVR, have a source of collateral blood flow that can be recruited to compensate for exhausted vasodilatory reserve, in

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the event of reductions in perfusion pressure or acute increased upstream obstruction, such as thrombosis. This collateral flow may not be as brisk or generous as that recruited by autoregulation in healthy vascular beds, but it appears that it is sufficient to maintain cellular integrity until blood flow readjusts and the neurological function returns, resulting in a TIA, rather than a stroke.

Clinical Implications

Assessing the cerebrovascular reserve capacity is important to determine the risk of hemodynamic stroke. Impaired CVR and stroke risk is not novel finding. In a systematic review and a meta-analysis, Gupta et al reviewed 1061 independent CVR tests in 991 patients and showed a significant positive relationship between impairment of CVR and development of stroke with an OR 3.86 (95% CI, 1.99–7.48).[20] They also found the association between CVR impairment and risk of stroke conserved across testing modalities (transcranial Doppler, positron emission tomography (PET), Single Photon Emission Computed Tomography (SPECT) and MR imaging techniques) as well as the nature of the vasodilatory stimulus (acetazolamide or variation in inspired CO2 levels).[20] However, our study showed that normal CVR despite hemodynamically significant SOD has a lower incidence of stroke at 1 year. Reinhard et al have previously shown that the presence of severe SOD was highly specific for the risk of stroke but not sensitive.[21] In line with this finding, our study shows that one needs both the presence of SOD and impaired CVR to be at risk for stroke. First, in our study, a quarter of the patients with good recruitable CVR were at low risk for stroke. It is important to identify these patients because surgical intervention would put them at risk of complications with no compensating reduction of the risk of stroke. Second, the low CVR in the remainder of the patients suggests their vascular lesion was poorly compensated by recruitable collateral flow, putting them at high risk for stroke. This suggests that an optimal clinical algorithm would best first identify those with SOD, and then identify those patients with high and low risk of stroke. Our data do not address whether abnormal CVR marks a high risk of stroke, but abundant studies suggest that this is the case. Our study does suggest that normal CVR would be a marker for a lower risk of stroke.

Randomization of SOD without further regard to identifying a low-risk group will result in an overestimation of the benefit of OMT, as this group will inevitably contain patients with good collateralization and low risk of stroke. It will also result in an underestimation of the benefit of the revascularization arm, as it would include surgical complications in the low-risk group where there will be no additional reduction of risk.[22] Interestingly, in patients who underwent revascularization, there is an improvement in CVR but their improvement is seldom to the mean normal range. Hence, these patients may continue to have chronic hypoperfusion or reduced recruitment of collateral flow.[23]

Limitations

Our study has several limitations. Firstly, unlike PET, arterial spin labelling (ASL) and phase-contrast MR angiography, BOLD does not directly measure CBF. The BOLD signal depends on several factors including cerebral metabolic rate, cerebral blood volume, and CBF, and hence, it can only provide an indirect nonquantitative measure of CBF provided other factors remain constant. These factors should always be considered during the interpretation of BOLD-CVR data. However, a previous study comparing ASL-CVR and BOLD-CVR has shown that even in patients with the SOD, the BOLD signal response to hypercapnia predominantly reflects changes in CBF.[15] Similarly, it has been shown recently that BOLD CVR corresponded well to CBF perfusion reserve measurements obtained with (^{15}O-) H_2O-PET, especially for detecting hemodynamic failure.[24] Secondly, this is a prospective observational study looking at a small number of patients considering the low incidence of stroke. However, the CVR benefits from the standardization of the stimulus. The small variability in the stimulus removes this confounder from the data increasing the specificity of the test. Thirdly, there was no randomization with regard to surgical interventions, leaving this as an observational study focusing on the outcome in patients with hemodynamically significant SOD yet normal CVR. The patients with abnormal CVR could not be randomized as they were recommended for revascularization based on previous evidence. There was a higher incidence (though statistically not significant) of stroke in patients with abnormal CVR whether or not they were revascularized. This suggests a strong effect size for abnormal CVR. Another limitation of this study is that patients were followed up for only 1 year, as this is our standard clinical practice. Longer follow-up may provide additional insights, especially in patients with normal CVR with severe SOD. In addition, only patients who had revascularization had follow-up CVR and observed improvement in CVR may partly reflect the natural history of the disease.

Conclusions

Our study confirms the prior findings that impaired CVR, a marker of the poor cerebrovascular reserve is associated with a higher incidence of stroke. Normal CVR despite significant stenosis appears to be associated with a low risk of stroke. This study further establishes that the noninvasive BOLD MRI CVR technique is sensitive and able to identify at-risk patients, and can therefore be more widely used.

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Disclosures. RespirAct™ is currently a noncommercial research tool assembled and made available by Thornhill Research Inc. (TRI), a spin-off company from the University Health Network, to research institutions to enable CVR studies. JAF is the Chief Scientist and JD is the Senior Scientist at (TRI), and JP, OS, and DJM have contributed to the development of RespirAct™ and have received payments from, or shares in, TRI.

Statement of authorship. LV, JF, and DJM designed the study. LV, CR, and LM analyzed the data and wrote the manuscript. LV, CR, LM, JP, OS, JD, JF, and DJM interpreted the data for the manuscript submission. LV, CR, LM, JP, OS, JD, MT, JF, and DJM contributed to the manuscript revision and reviewed and approved the submitted version.

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