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Effect of Intracranial Stenosis Revascularization on Dynamic and Static Cerebral Autoregulation

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Abstract

Introduction—Severe intracranial stenosis might lead to acute cerebral ischemia. It is imperative to better assess patients who may benefit from immediate reperfusion and blood pressure management to prevent injury to peri-infarct tissue.

Methods—We assessed cerebral autoregulation using static and dynamic methods in an 81-year-old woman suffering acute cerebral ischemia from severe intracranial stenosis in the petrous segment of the left internal carotid artery (LICA).

Results—Static cerebral autoregulation, which is evaluated by magnetic resonance imaging and magnetic resonance perfusion studies showed a progression of infarcts and a large perfusion–diffusion mismatch in the entire LICA territory between the second and third days after onset despite maximized medical therapy. Dynamic methods, including transfer function analysis and mean velocity index, demonstrated an increasingly impaired dynamic cerebral autoregulation (DCA) on the affected side between these days. Revascularization through acute intracranial stenting resulted in improved perfusion in the LICA territory and normalization of both dynamic and static cerebral autoregulation.

Conclusion—Thus, DCA, a noninvasive bedside method, may be useful in helping to identify and select patients with large-vessel flow-failure syndromes that would benefit from immediate revascularization of intracranial atherosclerotic disease.

Keywords

Cerebral autoregulation; intracranial stenosis; stent; acute cerebral ischemia; transcranial Doppler ultrasonography; transfer function analysis

INTRODUCTION

Cerebral autoregulation is a mechanism of the brain that enables it to maintain relatively stable cerebral blood flow despite variable cerebral perfusion pressure [1,2]. Impaired autoregulation in patients with acute cerebral ischemia may cause cerebral blood flow and perfusion to be dependent on systemic blood pressure, resulting in infarct extension from hypoperfusion of the peri-infarct tissue, or edema and hemorrhagic transformation caused

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by high cerebral perfusion pressure and reperfusion injuries. Assessing cerebral autoregulation in these patients may allow clinicians to better select those who might require immediate revascularization and active management of blood pressure to prevent the consequences of impaired perfusion.

METHODOLOGIES AND IMPORTANCE

Cerebral autoregulation can be assessed by dynamic methods or static methods. Static cerebral autoregulation methods assess the cerebral autoregulatory capacity by measuring cerebrovascular reserve under steady-state hemodynamic conditions. By measuring the cerebrovascular reserve when the brain is in a physiologic baseline condition and comparing it to measurements made following a physiologic perturbation or impairment, after a new baseline has been established, static methods provide an overall assessment of cerebral autoregulation. Positron emission tomography, computed tomographic perfusion imaging, and magnetic resonance perfusion imaging (MRP) are examples of static methods. Unlike dynamic methods, these physiologic imaging modalities do not yield information about the body's ability to regulate cerebral perfusion pressure on a moment-to-moment basis, but they are noninvasive and can be implemented in clinical practice.

Dynamic cerebral autoregulation (DCA) techniques, on the other hand, noninvasively measure spontaneous beat-to-beat fluctuations in cerebral blood flow velocity (CBFV) and blood pressure using transcranial Doppler ultrasonography (TCD) [3]. The pressure–flow relationship can be observed by analyzing the two blood pressure signals at various discrete times called the time domain, or at a frequency of interest, the frequency domain. Transfer function analysis (TFA) is a frequency domain method that assesses DCA by measuring the independence of the low-frequency oscillations of systemic blood pressure and CBFV through the phase shift (PS) [4]. The mean velocity index, Mx, is a time-domain method that measures DCA by calculating a time averaged Pearson correlation coefficient between the two signals [5]. Both DCA parameters are primarily used as research tools. Details regarding mathematical calculations have been previously described [6].

Although several studies of DCA in patients with carotid stenosis and acute ischemic have been performed [7,8], data is currently limited on patients with intracranial atherosclerotic disease. Herein, we report the first concomitant use of TFA and MRP before and after cerebral revascularization in a patient suffering acute cerebral ischemia from severe intracranial atherosclerotic stenosis.

INTERVENTION AND RESULTS

An 81-year-old right-handed woman with a past medical history of hypertension, hyperlipidemia, coronary artery disease, and type 2 diabetes mellitus presented to an outside hospital following an episode of acute aphasia. She reported "not feeling right" at dinner and shortly thereafter began to exhibit slurred speech and lack of coordination on her right hand. Emergency medical services were called and after confirming a normal glucose level, she was immediately transported to the Emergency Department of the outside hospital five hours after symptom onset. Upon arrival, her blood pressure was 157/89 mmHg, temperature was 36.7°C, heart rate was 80 beats per minute, and EKG confirmed normal sinus rhythm. Initial NIH stroke scale (NIHSS) score was 8, accounting for aphasia, mild lower right facial weakness, and right-sided hemiparesis. A noncontrast head CT showed no acute pathology and mild periventricular white matter disease. The patient was admitted and started on aspirin and high dose statin. Magnetic resonance imaging (MRI) demonstrated scattered left cerebral hemisphere infarctions in the watershed territories. MR angiography revealed nonocclusive stenosis in the left internal carotid artery (LICA). After slight improvement in initial symptoms, she developed acute worsening of her nonfluent aphasia and complete right-sided hemiplegia. Arrangements were made to transfer the patient to our hospital.

On arrival to the Neurological Intensive Care Unit, she had a heart rate of 75 with regular rhythm, elevated blood pressure of 162/94 mmHg, and NIHSS score of 9 for acute aphasia, facial droop, right-sided visual neglect, and right-sided weakness. Noncontrast head CT was obtained revealing scattered hypodensities in the watershed areas without hemorrhagic conversion. CT angiography demonstrated severe stenosis at the intrapetrous portion of the LICA. Given the patient's fluctuating deficits in the context of a severe stenosis large-vessel flow-failure syndrome was suspected and hypertensive therapy trial was attempted following our institutional protocol. Systolic blood pressure was augmented with phenylephrine in twenty-percent increments of baseline every 30 min up to 210 mmHg without evidence of clinical improvement. Therefore, phenylephrine was stopped and dual antiplatelet therapy combined with a high statin dose was initiated.

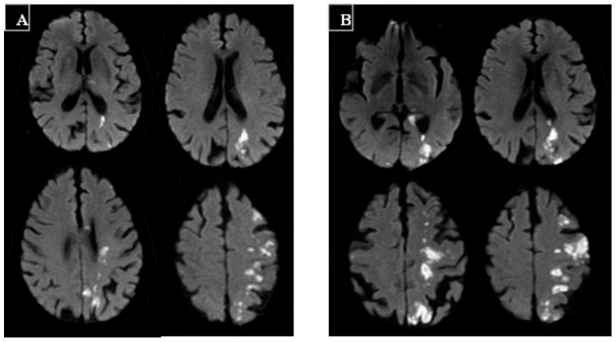

Figure 1. Findings on MRI: DWI performed (A) at admission and (B) at day 2 after symptom onset revealed an increased number of lesions in the left middle cerebral artery–anterior cerebral artery and left middle cerebral artery–posterior cerebral artery watershed territories (arrowheads) as well as the left middle cerebral artery territory along the cerebral convexity (arrow). All DWI lesions showed concomitant decreases in the apparent diffusion coefficient map consistent with ischemia (not shown).

On the second day, the patient exhibited worsening aphasia, right arm and leg hemiplegia, and neglect, and she followed neither verbal nor visual commands constituting a NIHSS of 18. Repeat brain MRI showed an increased number of diffusion-weighted imaging (DWI) lesions in the LICA territory compared to the admission MRI (Figure 1). MR perfusion images obtained using intravenous bolus injection of gadolinium contrast, and dynamic susceptibility-weighted contrast technique revealed a large perfusion–diffusion mismatch in the entire left ICA territory (Figure 2).

The patient continued to exhibit fluctuating symptoms in the Neurological Intensive Care Unit and on day 5, she underwent a transfemoral catheter cerebral angiogram that confirmed over 90% atherosclerotic stenosis in the distal cervical and proximal petrous segments of the LICA. She immediately underwent an angioplasty followed by a PROMUS metal stent placement with gradual improvement of her aphasia and weakness over several hours following the procedure. Repeated MRP one day later demonstrated improved perfusion of the territory at risk (Figure 3).

Following completion of MRP, DCA was monitored at the bedside during her second and third day after stroke, and immediately after postrevascularization by insonating both middle cerebral arteries cerebral blood flow velocities using TCD and measuring systemic blood pressure obtained through a radial arterial catheter. A posterior analysis of both physiological signal revealed

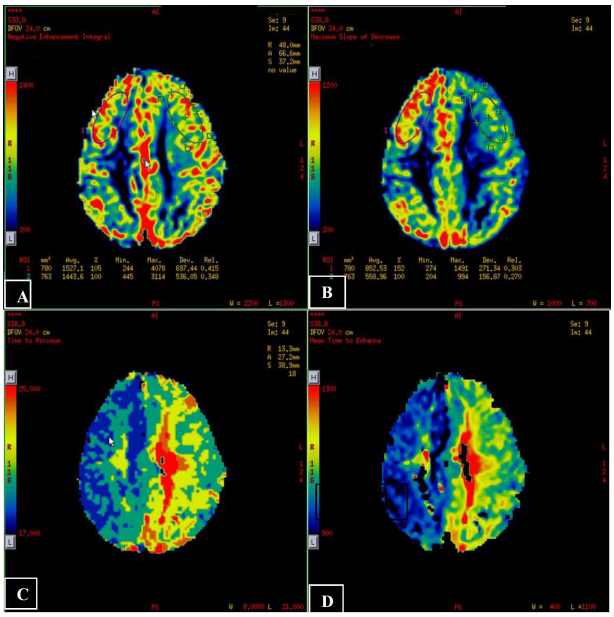

Figure 2. MRP findings: (A) the maps labeled "negative enhancement integral" are proportionate to relative cerebral blood volume (rCBV); (B) the maps labeled "maximum slope of decrease" are proportionate to relative cerebral blood flow (rCBF); (C) "Time to minimum" indicates the time the contrast passes though the large arteries and reach the region of interest (TTP); (D) "mean time to enhance" indicates the time that the contrast agent passes through micro-vessels (MTT). Ellipses (red and green) represent the region of interest from all the above parameters are estimated. In our patient, rCBF in the left cerebral hemisphere/frontal lobe is diminished compared to the rCBF of the right frontal lobe. But the rCBV of the right and left hemispheres is similar. Perfusion to the left side is delayed relative to the right as evidenced by the prolonged relative transit times (MTT and TTP). So, rCBV is being maintained on the left by collateral flow. Since collateral routes take longer to reach the territory at risk, blood flow to the left is delayed relative to the right. Since the decrease in flow is remarkably larger than the infarcted regions representing a left ICA perfusion–diffusion mismatch with large territory at risk.

that both PS and Mx indicated impaired initial DCA with subsequent improvement postrevascularization (Figure 4).

Patient was discharged to acute rehabilitation on day 14 with NIHSS score of 9 exhibiting nonfluent aphasia and right hemiparesis and mild neglect. She was still unable to ambulate. A 6-month follow-up evaluation in the stroke clinic revealed NIHSS of 5 with mild aphasia and hemiparesis. At that time, she was able to walk with assistance. No complications had occurred in the interim.

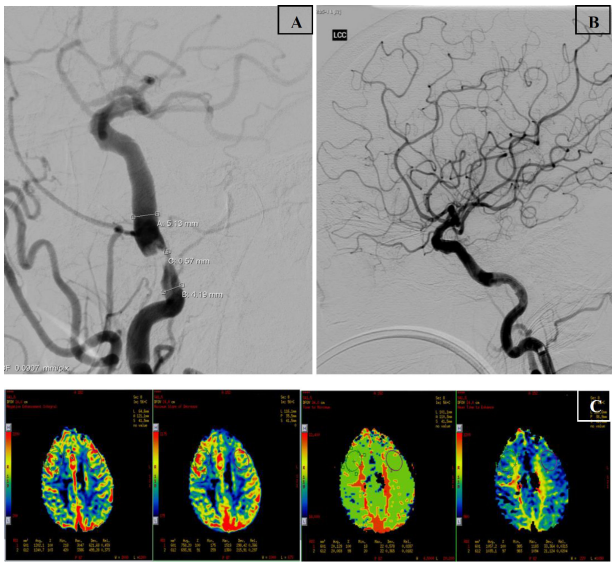

Figure 3. Pre- and post-revascularization angiogram and MR Perfusion: (A) diagnostic digital subtraction angiogram of the distal ICA revealing over 90% atherosclerotic flow-limiting stenosis at the high cervical to the petrous portion, (B) postrevascularization DCA oblique distal L ICA injection showing a successful recanalization of the petrous stenosis after angioplasty and stent deployment, (C) poststenting MR PWI maps again showing equalization of (from left to right) the rCBV, rCBF, TTP, and MTT in the territory at risk.

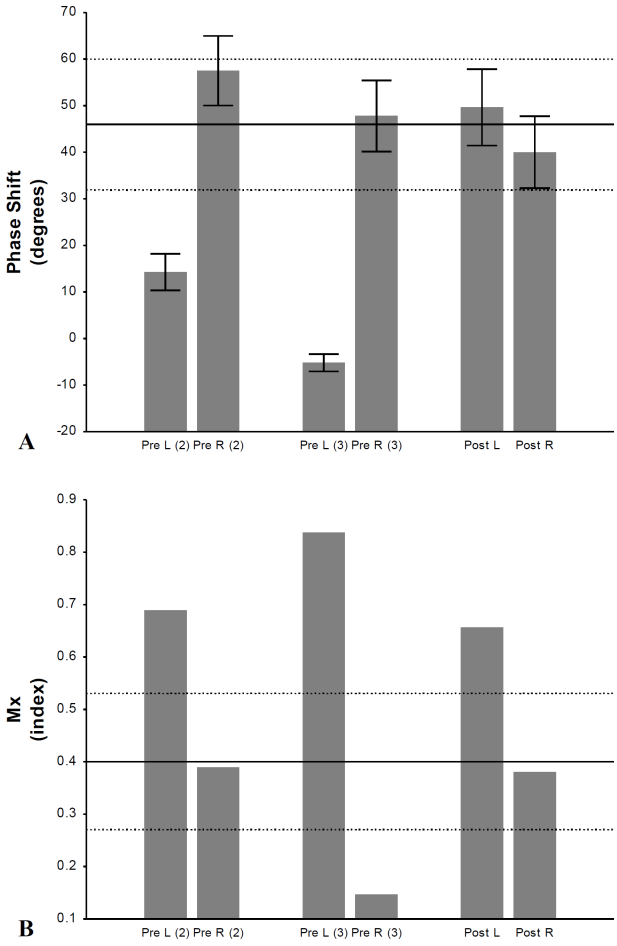

Figure 4. DCA measured by PS Means and Standard: (A) TFA showed a decrease in PS on the affected side (left) on days 2 (1) that subsequently further decrease at day 3 (2) after stroke onset. This decrease indicates worse DCA that was consistent with the increased in number of infarcts on MRI (see Figure 1) at the L ICA territory and the patient's symptoms of worsening aphasia and right-sided weakness. A marked left PS increase postrevascularization is observed from an average PS of –5.21 ± 1.97 degrees on the left MCA and 47.79 ± 7.20 degrees on the right MCA on the 2nd day of measurement, prior to revascularization (pre), to an average PS of 49.62 ± 8.64 on the left MCA and 40.02 ± 8.13 degrees on the right MCA, poststenting (post), (B) Mx analysis showed an initial 0.15 units increase in Mx on the affected side from measurement 1 to 2 before stent placement signifying a worsening on the autoregulatory status. Only a mild decrease of 0.18 unit postrevascularization was seen indicating a partial improvement, but not complete normalization when compare to the unaffected side. Normal values for PS and Mx in healthy individuals are considered 46 ±14 and 0.4 ± 0.13, respectively (straight and dashed lines, respectively). Details regarding mathematical calculations have been previously described [6].

CONCLUSION

This case report represents the first case of bedside measurement of DCA using TFA in parallel with MRP, a static cerebral autoregulation method routinely used in clinical practice after endovascular recanalization of a severe intracranial stenosis. Both methodologies reported drastic impairment of cerebral autoregulation on the symptomatic vascular territory that, while being treated with maximized medical therapy, it was associated with further neurological deterioration and increase in the number of DWI lesions. After endovascular recanalization was instituted using an intracranial balloon-mounted stent, we observed an immediate improvement not only clinically, but also physiologically with a near normalization PS and extinction of the diffusion–perfusion mismatch. Mx, in contrast, demonstrated only a partial improvement but remained mildly elevated postrecanalization.

Large-artery intracranial occlusive disease is a common cause of ischemic stroke associated with a high risk of recurrence [9]. Recent data from a multicenter randomized control trial suggest that aggressive medical therapy

using dual antiplatelet therapy, a statin, and aggressive control of the risk factors is superior in to percutaneous transluminal angioplasty and stenting in preventing early stroke or death in patients with a recent transient ischemic attack or stroke [10]. All patients who had a transient ischemic attack or nondisabling stroke attributed to a verified angiographic stenosis >70% stenosis in a proximal intracranial vessel were included in the study. Importantly, no other neurophysiological parameters to assess compensatory mechanisms and ultimately, adequacy of the cerebral blood flow were considered before treatment randomization. The repercussion of this data has reasonably created a skeptical attitude toward invasive revascularization as a treatment for intracranial stenosis.

Cerebral autoregulation reflects the intrinsic ability of the cerebral vasculature to guarantee downstream blood supply; and therefore, might exemplify an optimal method to evaluate cerebral hemodynamic impairment in real time [11]. Studies in severe carotid disease demonstrated that DCA was significantly impaired in patients with asymptomatic stenosis and prognostic of subsequent ipsilateral stroke [8]. Similarly to our patient, recanalization using endarterectomy or endovascular stenting demonstrated an immediate normalization of PS and Mx parameters that persisted after subsequent follow-up [7].

A subgroup analysis of 287 angiograms of patients with intracranial atherosclerosis with >50% luminal stenosis included in the Warfarin–Aspirin Intracranial study demonstrated that the variability of compensatory mechanism through collateral flow might offset the detrimental effect of stenosis and be associated with resultant infarct size and subsequent stroke risk [12]. In fact, extensive collateral flow diminished the risk of subsequent stroke in patients with severe intracranial stenosis (70%–99%) whilst increases the risk of in patients with milder ones (50%–69%) [13]. Thus, hemodynamic downstream failure and leptomeningeal collateral circulation may exert complex interactions with the anatomic stenosis to predict the risk that cannot be inferred by mere inspection of the luminal compromise. Moreover, when leptomeningeal collaterals were quantified in parallel with TFA in patient with severe carotid stenosis, DCA was found to be significantly impaired when leptomeningeal collateral pathways were recruited. In contrast, DCA tended to be preserved when anterograde flow from contralateral anterior cerebral or posterior communicating artery was present [14]. Thus, the inability of the arterioles to regulate downstream the stenosis might represent an additional pathophysiological route to further distinguishing stenosis relatively unstable that requires prompt treatment.

Our report illustrates an example where aggressive medical therapy might not be sufficient to prevent further ischemic events during the acute phase. Additionally, it describes for the first time the TCD-derived dynamic autoregulatory status after stroke due to large-artery intracranial stenosis, its correlation with MRP, a physiology-based modality frequently used in routine clinical practice. Factors beyond angiographic anatomic measures of maximal stenosis that incorporate information about cerebral hemodynamic and its compensatory mechanisms urge to be used to improve on patient selection for endovascular recanalization treatment. DCA, thus, represents an efficient, non-invasive method of determining real-time cerebral autoregulation status that might aid to determine the course of intracranial atherosclerotic disease.

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