Cerebral Hemodynamics in Acute Stroke: Pathophysiology and Clinical Implications

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TOPIC
REVIEW

Abstract

Background: The capacity of the brain to regulate its blood flow in order to meet metabolic demands and to compensate for acute and chronic changes in cerebral perfusion pressure (cerebral autoregulation) is an essential protecting mechanism against cerebral ischemia.

Methods: We reviewed existing data on methods of assessing cerebral blood flow and autoregulation.

Results: Cerebral autoregulation is mechanistically complex and depends on myogenic, neuronal, endothelial, and metabolic factors. There are numerous methods of estimating cerebrovascular reserve (CVR) non-invasively including Positive Emission Tomography (gold standard), Transcranial Doppler ultrasound, dynamic contrast-enhanced perfusion Magnetic Resonance Imaging, Single-Photon Emission Computed Tomography and Xenon Computed Tomography. Since each of these techniques has its advantages and disadvantages, selection of a specific method for CVR testing depends on availability, acquired experience in interpreting the study, required precision, and cost. Cerebral autoregulation may be impaired in patients with symptomatic or asymptomatic carotid stenosis or occlusion and is associated with a higher risk of stroke or transient ischemic attack (TIA) ipsilateral to the carotid artery disease.

Conclusion: Assessment of CVR can help stratify patients based on their risk of stroke or TIA and select patients who may benefit from revascularization therapies. Cerebral vasoreactivity testing may be useful to evaluate cerebral autoregulation after revascularization procedures as a surrogate endpoint of vascular events related to hypoperfusion or hyperperfusion.

Keywords: Regional cerebral blood flow, autoregulation, cerebral ischemia, cerebral blood volume, cerebral perfusion pressure
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A. Definition of cerebrovascular reserve and three-stage classification system of cerebral hemodynamics

Cerebrovascular reserve (CVR) refers to the capacity of the brain to increase cerebral blood volume (CBV) to maintain a constant regional cerebral blood flow (rCBF) in the face of low cerebral perfusion pressure (CPP). Regional cerebral blood flow is determined by the ratio of CPP to cerebrovascular resistance by the following formula.[1, 2]

$$rCBF = CPP / \text{vascular resistance} \quad (1)$$

CPP is related to systemic mean arterial pressure (MAP) and intracranial pressure (ICP) by the equation:

$$CPP = MAP - ICP \quad (2)$$

In healthy individuals, a constant rCBF is maintained over a wide range of CPP with mean rCBF values of approximately 50ml/100g/min. When rCBF values fall below 20ml/100g/min, ischemia occurs. Cerebral infarction develops at rCBF levels <8 ml/100g/min.
On the basis of the known physiologic responses of CBV, rCBF and oxygen extraction fraction (OEF) to reductions in global CPP, a non-invasive three-stage classification system for local hemodynamic status using non-invasive measurements has been proposed.[1, 2]
Stage 0
In this stage, CPP and OEF are within normal range. CBV and mean transit time (MTT) are not elevated, while the rCBF response to vasodilatory stimuli is normal.

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Stage 1

This stage is manifested by autoregulatory vasodilation of arterioles to maintain a constant rCBF when CPP is decreased. Consequently, MTT and CBV are increased, but OEF remains normal.

Stage 2

This is the stage of hemodynamic failure, where autoregulatory capacity is exceeded. There is an increase in OEF as CBF declines with respect to the cerebral metabolic rate of oxygen (CMRO2). This stage termed as "misery perfusion" can be divided in two phases: oligemia (decreased rCBF, increased OEF, and normal CMRO2) and ischemia (decreased rCBF, increased OEF, and decreased CMRO2).

B. Mechanisms underlying cerebrovascular reserve

The basis of CVR is complex and can be attributed to the following mechanisms.[1, 2]

Myogenic

The Bayliss effect (myogenic mechanism) postulates that smooth muscles of the resistance vessels respond to changes in the transmural pressure to increase or restrict the incoming flow. Thus, myogenic responses to changes in systemic blood pressure provide a mechanical basis for autoregulation

Chemical

Both hypoxia and hypercapnia are potent chemical cerebral vasodilators. More specifically, changes in pCO_2 cause changes in intracellular or extracellular pH, which in turn effect vascular smooth muscle tone.

Neuronal

Cerebral blood vessels receive both autonomic and general sensory innervation. Sympathetic stimuli constrict large arteries but dilate smaller downstream vessels. General sensory innervation from the trigeminal ganglion produces vasodilatory effects via calcitonin-gene-related-peptide (CGRP).

Metabolic

Whether exogenously administered or produced as a consequence of metabolic activity, the following vasoactive mediators are implicated in the maintenance of arteriolar tone:

Nitric oxide (constant and potent vasodilator);

Adenosine (increases in brain with hypotension and modulates vasodilation via K_{ATP} channels);

Endothelium-derived factors

C. Estimation of cerebrovascular reserve

Positive emission tomography (PET)

Positive emission tomography (PET) has been considered the gold standard for estimating CVR. Using oxygen-15 (O-15) labeled radiotracers, PET is able to give estimates of CBV, rCBF, $CMRO_2$ and MTT. Regional cerebral blood flow is related to CBV by the equation:

$$rCBF=CBV/MTT \quad (3)$$

Transcranial Doppler ultrasound (TCD)

Vasomotor reactivity (VMR) assessed by TCD using vasodilating or constricting stimuli is not a direct measure of autoregulation.[3] Brain autoregulation maintains rCBF constant with physiological variations in blood pressure. The changes in CO_2 concentration induce a vasomotor response that changes rCBF in parallel to the velocity changes. Thus, mean flow velocity (MFV) changes on TCD during normo-, hyper-, and hypo-capnia may prove a useful index of VMR and the capacity of smaller cerebral arteries to adapt to various stimuli.

The MFV modulation is most reliably and reproducibly measured by TCD at the M1-MCA segment during inhalation of different CO_2 concentrations. The end-expiratory CO_2 is measured by an infrared gas analyser and expressed as volume percentage. The baseline TCD recording should be obtained under normocapnia, or when breathing room air, and then during steady states when air is inhaled with CO_2 concentrations ranging from 2% to 6% given for 2-3 minutes each. Voluntary hyperventilation may be used to produce hypocapnia. TCD measurements of MFVs should be made during each steady state and during several (up to 20) cardiac cycles to minimize variations in MFV. The baseline MFV is considered 100% and is compared to velocity values obtained during hyper- and hypocapnia states. VMR is expressed as the percent change of M1-MCA MFV from the hypercapnic to the hypocapnic state.

Diamox is a potent and reversible inhibitor of carbonic anhydrase, however the mechanism by which it increases rCBF is still disputable since cerebral metabolic rate of oxygen and arterial blood pressure remain unaffected while arterial PCO_2 increases only slightly.

When administered intravenously, the effect of 1000 mg diamox (acetazolamide) bolus can be observed within 3 minutes with MFV reaching maximum values in 10 minutes. The peak effect lasts for 20 minutes. In normal subjects, a 35% increase in MFV is usually observed during hypercapnia. Administration of diamox may be associated with minor and transient side effects: dizziness, oral dysesthesia, tinnitus, and nausea. Since diamox belongs to the sulfanilamide group, any known allergy to sulfa- drugs is a contraindication to its use. Assessment of CO_2 reactivity requires special equipment which may not always be available. A more simple method of VMR assessment uses voluntary breath-holding. VMR is represented by the breath-holding index (BHI), which is the ratio of the percent MFV increase during hypercapnia over the time (seconds) of breath-holding. Baseline MFV are obtained during inhalation of room air followed by a 30 seconds breath-holding followed by a 4 seconds recording of the highest MFV (Figure 1). The efficacy of breath-holding can be assessed by a respiratory activity monitor. In normal subjects, BHI is usually greater than 1 (1.12+0.3, n=10, mean age 63+11 years). In asymptomatic individuals, BHI was 0.8+/-0.4 on the stenotic side before and 1.09+0.2 after carotid endarterectomy (CEA).

Dynamic contrast-enhanced perfusion magnetic resonance imaging

Dynamic contrast-enhanced perfusion magnetic resonance imaging (MRI) provides relative estimates of CBV derived from

perfusion images by tracking a bolus of paramagnetic contrast agent. However, it cannot provide absolute CBV measurements and may be inaccurate when there is breakdown of the blood brain barrier. An acetazolamide challenge can be administered with this technique to estimate vasodilatory capacity.

Single-photon emission computed tomography and xenon computed tomography

Technetium single-photon emission computed tomography (SPECT) and xenon computed tomography (CT) can also estimate rCBF. Xenon CT provides quantitative rCBF values, whereas values obtained from SPECT are relative values of rCBF change.

D. Pathophysiology of watershed infarction in internal carotid artery disease

Watershed infarcts involve the junction of the distal fields of two nonanastomosing arterial systems. Classic neuropathologic studies describe 2 distinct watershed areas.[4,5] (1) between the cortical territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA); and (2) in the white matter along and slightly above the lateral ventricle, between the deep and the superficial arterial systems of the MCA. The former, superficial areas have been commonly referred to as the cortical watershed (CWS), and the latter have been referred to as the internal watershed (IWS). In autopsy studies, CWS and IWS infarcts—also termed external and internal border-zone infarcts, respectively—together represent 10% of all brain infarcts. Based on the well-established notion that severe systemic hypotension can cause bilateral WS infarction, hemodynamic failure has been associated withWS infarcts in ICA disease. Susceptibility of the WS areas to ischemic injury is thought to result from their location of "distal field," where perfusion pressure is lowest, and repeated episodes of hypotension in the presence of severe ICA disease can precipitate WS infarcts.[4,5] The occasional occurrence of syncope at onset of WS stroke, and the typical clinical presentation of episodic, fluctuating, or progressive weakness of the hand, occasionally associated with upper limb shaking, are consistent with, and classically considered markers of, hemodynamic failure. This interpretation is further supported by radiological studies showing that WS infarcts distal to ICA disease are more likely to occur with an incomplete circle of Willis.

E. Symptomatic carotid stenosis or occlusion and impaired cerebrovascular reserve

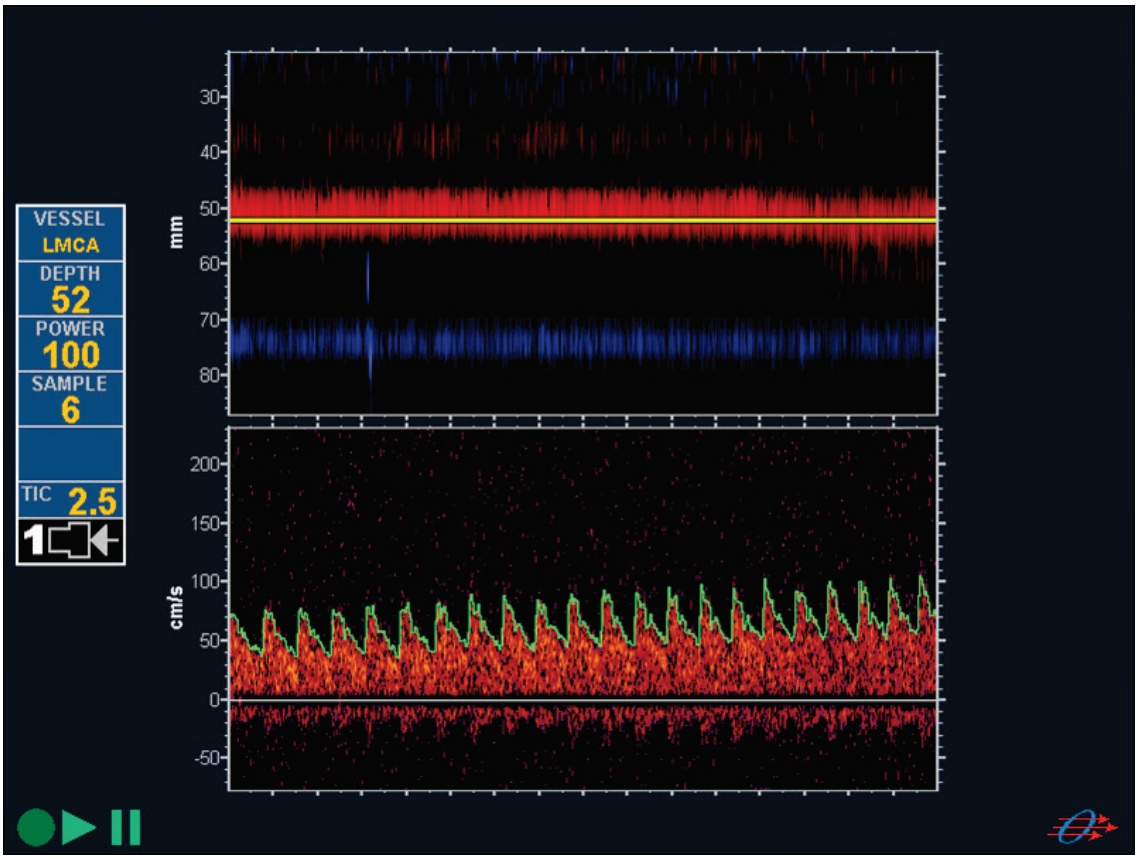

Figure 1.
Transcranial Doppler ultrasound-monitoring of the left middle cerebral artery shows gradual increase of Mean Flow Velocities (from a baseline of 46 cm/sec to 61 cm/sec) during voluntary breath holding of 30 seconds.

Patients with high-grade carotid stenosis or occlusion and poor hemodynamic reserve carry a high risk of subsequent stroke. Increased OEF, indicating stage II or greater hemodynamic failure, is a powerful independent predictor of stroke risk in patients with symptomatic stenosis or occlusion with an age-adjusted relative risk of 7.[6,7] These data provided the rationale for conducting the Carotid Occlusion Surgery Study (COSS), a large prospective multicenter trial that aimed at randomizing patients with carotid occlusion and stage II hemodynamic failure to superficial temporal artery-MCA bypass surgery plus best medical therapy versus medical therapy alone.[8] These findings from PET studies are in agreement with prospective reports evaluating status of CVR using SPECT or TCD.[9,10] Overall, these studies suggest that patients with reduced or exhausted vasodilatory capacity are at higher risk for subsequent stroke, although the risk appears substantially smaller than with misery perfusion, which reflects a more severe stage of hemodynamic impairment.

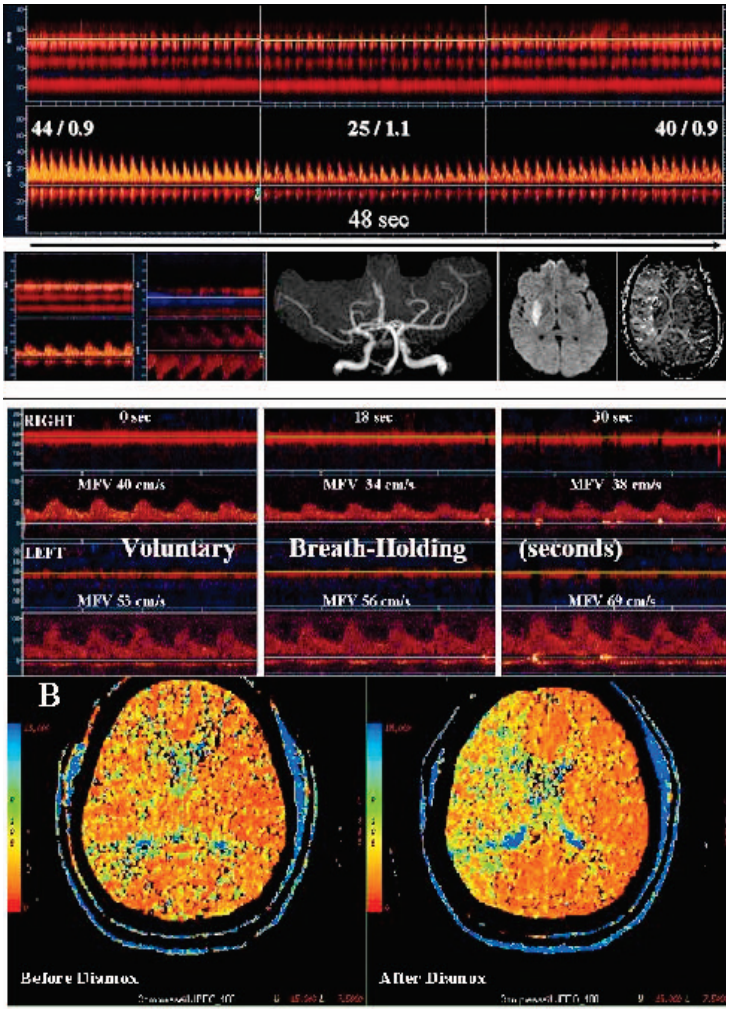

Figure 2.
A. Spontaneous velocity fluctuation with thrombolysis in brain ischemia (TIBI) 3 residual flow with embolic occlusion (MRA insert) and diffusion-perfusion mismatch (MRI insert). Bottom left, Thrombolysis in brain ischemia (TIBI) grade 3 waveform and flow diversion. Steal magnitude=[(25 cm/sec−44 cm/s)/44 cm/sec]x100=[−19/44] x100=−43.2%.
B. Bilateral MCA monitoring during BHI with a proximal internal carotid artery occlusion. Affected MCA MFV decreased at 18 s (middle frame). The steal magnitude was [(34 cm/s−40 cm/s)/40 cm/s]x100=[−6/40]x100=−15.0%. Increased flow on left nonischemic hemisphere and decreased right MCA flow indicating vasoparalysis on CT perfusion after Diamox. In this situation the pressure gradient within leptomeningeal collaterals may decrease and manifest as a deterioration of the patient's neurological status.

F. Asymptomatic carotid stenosis or occlusion and impaired cerebrovascular reserve

Although both the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) showed superiority of carotid endarterectomy over medical therapy alone, about 40 asymptomatic patients need to be treated to prevent 1 disabling or fatal stroke after 5 years.[11] Risk stratification, therefore may be helpful to identify patients who are appropriate for either medical therapy or an interventional approach. Asymptomatic carotid stenosis can be associated with poor CVR which is an independent predictor of stroke and TIA. In a prospective cohort of patients with asymptomatic carotid stenosis ≥70% the annual ischemic event rate was 4% in patients with normal CVR and 14% in patients with an abnormal breath holding index (≤0.69).[12] In addition, it has been postulated that abnormal CVR, reflecting collateral circulation status, is a better predictor of future stroke than the degree of carotid stenosis.

G. Carotid revascularization procedures and impaired cerebrovascular reserve

Hyperperfusion syndrome (HS) after carotid endarterectomy (CEA) consists of a classical clinical triad: transient focal deficits associated with ipsilateral migraine-like headache, seizures, and intracerebral hemorrhage (ICH).[1] The pathophysiology of the syndrome is still obscure, being probably related to the preoperative loss of vascular autoregulatory mechanisms in a chronically hypoperfused hemisphere. Although a degree of hyperperfusion seems to occur in most patients in the immediate postoperative period, clinically significant HS develops in only 1.4%-9%.[13] Several studies have demonstrated that in the acute period following CEA patients with symptoms or signs of cerebral hyperperfusion (headache, hemorrhage, seizure, focal deficits) had markedly elevated ipsilateral MCA MFV (>150%) compared with baseline values.[14] Reductions in arterial blood pressure can reduce MFV and alleviate symptoms. MRI perfusion weighted imaging has been successfully used in detecting relative increases in rCBF in patients who develop hyperperfusion syndrome.

H. Cerebral steal phenomenon and impaired cerebrovascular reserve

The concept of blood flow steal with arterial occlusions has been previously described. In brain, hemodynamic steals and shunts were identified with angiomas and subclavian artery lesions. Neurological symptoms linked to the cerebral blood flow steal were described with arterio-venous malformations or rare cases of symptomatic subclavian steal due to atheromatous disease, but not with an acute ischemic stroke due to thrombo-embolic occlusions.
Clinical deterioration following improvement is seen in about 15% of hyperacute stroke patients with most linked to an early arterial re-occlusion. However, recurrent neurological worsen-

ing followed by spontaneous improvement can occur without evidence of a proximal re-occlusion, edema extension or recurrent stroke. We recently described paradoxical changes in cerebral hemodynamics occurring spontaneously or in response to vasodilatory stimuli. Although velocity does not equate with flow, changes in MFV at a constant angle of insonation reflect changes in flow volume. In patients with persisting proximal arterial occlusions, hypercapnia can paradoxically decrease the residual MFV in the affected vessel at the expected time of normal brain vasodilation when blood flow is shifted to non-ischemic areas. We termed this "reversed Robin Hood syndrome" for analogy with "rob the poor to feed the rich".[15]

This steal is detectable and measurable by spectral Doppler in the MCA (Figure 2). Bilateral TCD monitoring can identify acute stroke patients with paradoxical velocity responses to hypercapnia or other vaso-active stimuli. Perhaps, these stroke patients could be a target group who may potentially benefit from non-invasive ventilatory correction for reduction of new vascular events after stroke or from arterial blood pressure manipulations to reverse hypoperfusion with an experimental induced hypertension or the so-called "let-it-ride" approach within blood pressure limits acceptable by current guidelines.

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