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Dissociation among hemodynamic measures in asymptomatic high grade carotid artery stenosis

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Abstract

Background—Cerebral blood flow (CBF) regulation is a critical element in cerebrovascular pathophysiology, particularly in large vessel disease, but the best method to use for hemodynamic assessment is not clear. We examined 4 different blood-flow related measures in patients with unilateral high-grade carotid artery disease, assessing asymmetry between the occluded vs non-occluded side, and the correlations among the measures.

Methods—Thirty-three patients (age 50-93, 19M) with unilateral 80-100% ICA occlusion but no stroke underwent: 1) mean flow velocity (MFV) in both middle cerebral arteries by transcranial Doppler (TCD), 2) quantitative resting CBF using pseudo-continuous arterial spin labeling (pCASL) MRI, 3) Vasomotor reactivity (VMR) in response to 5% CO₂ inhalation, and 4) Dynamic cerebral autoregulation (DCA) assessing the counter-regulation of blood flow to spontaneous changes in blood pressure using TCD monitoring and finger photoplethysmography. Paired T-tests and Pearson correlations assessed side-to-side differences within each measure, and correlations between measures.

Results—CBF ($p=.001$), MFV ($p<.001$), VMR ($p=.008$), and DCA ($p=.047$) all showed significantly lower values on the occluded side. The 4 measures were independent of each other on correlation analysis, even when controlling for age and anterior circle of Willis collateral (all partial correlations $<.233$ and p -values $>.468$).

Conclusions—These 4 measures showed high sensitivity to the occluded carotid artery, but their dissociation suggests that any given measure only partially characterizes the hemodynamic state. Additional research is needed to explore the multifaceted biology of cerebral blood flow regulation.

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Keywords

carotid artery stenosis; cerebral blood flow; cerebral hemodynamics; autoregulation; transcranial Doppler; arterial spin labeling

1. Introduction

Adequate blood flow regulation is required for normal brain function and to prevent cerebral ischemia. Blood flow and its correlates can be measured using a variety of techniques, and there are a number of conditions, such as high-grade carotid occlusive disease, in which several hemodynamic measures have been promoted for diagnostic and prognostic use. There has been no consensus as to the best method for hemodynamic assessment, however, and there is continued debate about whether abnormalities on different measures may in fact represent different aspects of hemodynamic dysfunction(1). In order to address the relationship between measures, we assessed cerebral hemodynamics in a group of patients with asymptomatic high grade carotid occlusive disease using four different measures of hemodynamics, each of which has been used to characterize carotid artery disease. Our first measure -- resting mean flow velocity (MFV) by transcranial Doppler (TCD) -- has been shown to be reduced in severe carotid stenosis(2), and to predict stroke risk(3). Our second -- resting cortical cerebral blood flow (CBF) using arterial spin labeling (ASL) MRI -- has been shown to be altered ipsilaterally in patients with unilateral carotid artery stenosis, and to correlate with PET CBF, long considered the gold standard for cerebral hemodynamics. (4) Our third measure -- vasomotor reactivity (VMR) using TCD with hypercapnia -- has been used to predict risk of subsequent ischemia in high grade carotid artery disease(5-7). And our fourth measure -- dynamic cerebral autoregulation (DCA) -- has been offered as an alternative to VMR, measuring the counter-regulation of blood flow to induced or spontaneous changes in blood pressure with TCD(8-11). Whereas each of these measures has been used to assess cerebral hemodynamics in carotid disease, it is unlikely that they are all measuring the same hemodynamic property. We hypothesized that each measure would show hemispherical asymmetry because of the presence of the unilateral severe carotid disease, but the measures would show low correlation with each other to indicate that the measures represent independent aspects of cerebral hemodynamics. Such a result would suggest that the measures are not interchangeable, but may provide unique information about hemodynamic function, either for prediction of stroke risk or for characterizing the functional consequences of hemodynamic failure.(5, 12-15).

2. Materials and Methods

2.1 Subjects

Thirty-three patients, age 50-93, 19 male, with unilateral 80-100% ICA occlusion but no stroke were enrolled in the study. Inclusion criteria were: 80% carotid stenosis or complete occlusion by carotid Doppler, MRA, or CTA, with <40% stenosis in the contralateral ICA. Other inclusion criteria were: asymptomatic status or TIA-only referable to the ICA stenosis, fluent in English, and able to give informed consent. Exclusion criteria were prior clinical stroke (defined as a clinical event with MRI correlate), diagnosis of dementia, history of

head trauma, current substance abuse, major psychiatric disease, NYHA Stage 3/4 congestive heart disease, or contraindication to MRI. Clinically silent small subcortical infarcts ≤ 3 mm in diameter were allowed, as well as leukoariosis, defined as confluent white matter hyperintensity abutting any portion of the lateral ventricles. The study was approved by the Institutional Review Board of Columbia University and all patients signed informed consent.

2.2. Measures of blood flow

2.2.1 MCA mean flow velocity—Hemispherical resting flow was estimated with transcranial Doppler (DWL-Multidop-X, Sipplingen, Germany). MFV in each MCA was measured with a 2 MHz probe at a depth of 50 to 56 mm on the occluded and unoccluded sides using the temporal window.

2.2.2 Resting Cortical Blood Flow (CBF)—Tissue-specific pseudo-Continuous Arterial Spin Labeling (ts-pCASL) fMRI(16, 17) was used to acquire CBF images with the following parameters: labeling duration = 2 s; post-labeling delay (PLD) adjusted to account for the inter-slice acquisition time as $PLD = (acquisition\ slice - 1) \times (60\ ms) + 1900\ ms$; number of slices = 12, slice thickness = 8 mm/1 mm gap. ASL images were processed using a partial volume correction method that yields tissue-specific flow density values in gray and white matter tissues independently. We used gray matter only in our analysis. This method has been shown to have lower intersubject variability, thus higher (~ 2.9 times) SNR at the group level analysis(18). CBF images were computed using a two-compartment formula(16).

2.2.3. Vasomotor reactivity—VMR was determined using TCD monitoring with the standard head frame and 2 MHz probes on each temporal window. We measured MFV at baseline and in response to 2 minutes of 5% CO₂ inhalation delivered by non-rebreathing face mask, using a Doppler-integrated inline capnometer (Spencer Technologies). Magnitude of response was calculated as the percent rise in MCA MFV per mmHg increase in PCO₂. A total PCO₂ rise of at least 10 mmHg was required for a valid measurement. The VMR CO₂ inhalation challenge was performed in each patient after the 10-minute monitoring period for the DCA.

2.2.4. Dynamic Cerebral Autoregulation—DCA measurements were performed in supine position with slight elevation of the upper body while the subjects were breathing spontaneously. The proximal MCA was insonated through the temporal window with a 2 MHz probe attached to a standard head frame at an insonation depth of 50-56 mm. Blood pressure was recorded simultaneously using servo-controlled finger plethysmography (Finometer Pro, Amsterdam, Netherlands). The appropriate finger cuff (Size: small, medium or large) was placed on the middle phalanx of the left or right middle finger. After establishing a stable recording, the intermittently occurring calibration procedure was turned off. Measurements were recorded for 10 minutes. All analog signals were digitized and stored for editing and offline analysis. Data sampling frequency was 100 Hz.

DCA Data analysis: The editing process included temporal synchronization of the blood pressure and blood flow velocity wave forms using ICUpilot software (Dipylon Medical, Solna, Sweden), followed by visual inspection and removal of all major artifacts. The data were then analyzed using Matlab (MathWorks, Natick, USA) with an in-house written program. The relationship between changes in oscillatory arterial pressure and CBFV was assessed with transfer function analysis, which quantifies the extent to which the input signal (ABP) is reflected in the output signal (CBFV) in a given oscillatory frequency range.⁽¹⁹⁾ The result was a characterization of the efficacy of the autoregulatory system. The primary outcome measure was phase shift (PS), the relative separation of signals in a frequency range in which auto regulation is known to occur. The more efficient the counter-regulation of flow, the more CBFV “leads” the fluctuating pressure wave (Figure 1). Lower degree of PS indicated worse autoregulation.

2.3. Statistical analysis

A two-tailed paired t-test was used to compare mean values in the occluded versus unoccluded hemisphere for each of the 4 blood flow measures. The Pearson correlation test was used to look for correlations among the 4 measures, controlling for age and circle of Willis collateral cross-filling (a dichotomous variable determined by reversed flow direction in the anterior circle of Willis on the side of the occluded carotid). All calculations were done using SPSS v.22.

3. Results

Among the 33 patients in this cohort, 4 had insufficient temporal windows to obtain mean flow velocities on one or both sides and 5 were unable to complete the CO₂ inhalation testing. An additional 4 had poor Finapres signal and so could not provide DCA data. Ten either could not complete the MRI, had a contraindication for MRI, or the ASL signal was not adequate for analysis. For the 23 with adequate MRI data 11 had leukoariorosis and 16 had small silent subcortical infarcts. Taking all patient data for those who completed each test, all 4 tests showed a statistically significant asymmetry by hemisphere, with the lower value on the occluded side (see Table 1). An illustration of the pCASL asymmetry is illustrated in Figure 2. None of the measures showed a statistical difference in side-to-side asymmetry between those with high-grade stenosis versus those with complete occlusion, nor between those with left versus right-sided occlusion.

On correlation analysis, there was no evidence that the four blood flow differences were correlated, controlling for age and anterior circle of Willis collateral (see Table 2).

4. Discussion

Among a cohort of patients with asymptomatic high grade carotid occlusive disease we showed that four commonly used measures of cerebral hemodynamics -- resting mean flow velocity, cortical CBF, vasomotor reactivity, and dynamic cerebral autoregulation -- all showed significantly lower values in the hemisphere supplied by the affected carotid artery. The asymmetry was not unexpected. Many studies of carotid disease have used the same or similar tests and have reported asymmetries related to the stenosis.^(2, 5-8, 20-23) Yet when

we assessed the four tests for concordance with each other, there was a very low correlation. Previous studies have addressed the multifaceted biology of cerebral blood flow regulation(1, 11) and differences have been shown to exist even within specific aspects of autoregulation(24). What makes our study unique is the concurrent examination of four commonly used measures of cerebral hemodynamics in a homogeneous population of patients who were likely to have hemodynamic abnormalities. Assuming that the low correlation represents true biological divergence rather than measurement or statistical variability, this finding has important implications for our understanding of cerebral hemodynamics. Our findings suggest that these tests are not interchangeable, but rather, provide unique information about different mechanisms controlling blood flow in the brain.

The brain is one of the only organs in the body to regulate its own blood flow, and the only organ whose function is critically dependent on this capacity. Loss of blood flow regulation occurs in a variety of cerebrovascular conditions, both in acute stroke(25-27), and in chronic cerebrovascular conditions such as small vessel disease(28, 29), metabolic syndrome(30, 31), and high grade carotid artery stenosis(32-34). Poor blood flow is an important predictor of stroke risk. The mechanisms, time course and additional variables that create abnormal blood flow remain crucial questions, both for an understanding of cerebrovascular physiology, and for the clinical management of cerebrovascular patients.

Each of the hemodynamic measurements examined in this study has a known association with carotid artery stenosis. Of the two measures of resting flow, MCA mean flow velocity by TCD may be considered the most direct measure. A blunted waveform in the MCA is common in high grade carotid stenosis(2), and the reduced flow velocity occurs as a direct result of the proximal ICA constriction. MFV may therefore be a sensitive but non-specific indicator of hemodynamic impairment. Our pCASL measurement specifically assesses cortical blood flow(35). Although CASL depends for its calculation on “arterial transit time” (36, 37) -- a variable related mathematically to MFV -- its final output of cortical blood flow is influenced by distinct physiological variables such as cortical blood volume,(16) collateral patterns,(38) cortical network connectivity,(39) and local neurotransmitter effects(40, 41). Impaired cortical flow may thus have functional implications for the cortex that are distinct from the non-specific reduced flow velocity identified by TCD. Cognitive function is dependent on cortical function, and can be influenced by alterations of blood flow, either directly(42) or as a marker of underlying metabolic dysfunction.(43)

The two measures of cerebral autoregulation – VMR and DCA – can also be considered distinct from one another.(44) Vasomotor reactivity is commonly tested in carotid disease with a vasodilatory challenge using CO₂ inhalation, acetazolamide, or breath holding. Vasoconstriction can also be assessed with hyperventilation to lower pCO₂. The vasoconstrictive or vasodilatory response is thought to be due to decrease or increase in pH, respectively, and is also modulated by adrenergic factors.(45) VMR assesses how much vasodilatory and vasoconstrictive reserve is available to protect the brain from extremes of hypo- and hypertension. In a state of chronic low perfusion pressure such as high grade carotid stenosis, the VMR with CO₂ inhalation demonstrates whether the system is close to maximum vasodilation and therefore to stroke risk. A recent data pooling analysis included 754 carotid stenosis patients from 9 studies who underwent CO₂ vasoreactivity as a

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predictor of stroke risk.(7) This study showed a hazard ratio = 3.69 for stroke for both symptomatic and asymptomatic patients for those with low VMR. VMR may thus be considered a measure of “static” autoregulation. DCA on the other hand, although influenced by pCO₂(46, 47), assesses the counterregulation of blood flow to spontaneous or induced changes of intracranial perfusion pressure. Although a variety of procedures and analytical approaches have been proposed for DCA,(24) we chose the transfer function analysis phase shift output because it has emerged recently as a metric to assess carotid disease.(10, 32) DCA is appropriately named “dynamic” cerebral autoregulation because it reflects real-time changes in flow. As measured in this study, it may be considered a reflection of homeostasis, as flow changes are assessed in an ongoing, short time frame, with low amplitude counter-regulatory responses. DCA has been shown to be abnormal for several days following acute embolic stroke.(25) It may be more useful in predicting stroke outcomes rather than stroke risk.

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Limitations of this study include the number of hemodynamic techniques we compared. Many others are available, but were beyond the scope of this study. We also had a relatively small numbers of subjects, which could have contributed to the low inter-test correlation. This outcome seems unlikely, however, since each of the measures had sufficient sensitivity to show a statistically significant difference by hemisphere. Another possible reason for the low correlation is that the four measures have different sensitivities to a common cerebral hemodynamic factor.. Another limitation is that not all subjects were able to complete all tests. Poor TCD bone windows are present in about 10-15% of older subjects in general, which was found in our cohort. The additional complexity of using the CO₂ inhalation and finger plethysmography equipment reduced the numbers who were able to complete the VMR and DCA tests, respectively, and there were several individuals who were unable to complete the MRIs.

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5. Conclusions. Toward a multidimensional model of cerebral blood flow regulation.

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The consistent hemispherical asymmetry across our four measures of cerebral blood flow supports their sensitivity to unilateral carotid occlusive disease, yet the dissociation among them suggests that each needs to be considered for its unique contribution to the patient’s hemodynamic state. Reduced MFV is rarely seen in carotid stenosis less than 80%, and therefore may be used as a screening tool for consideration of more specific hemodynamic testing. VMR appears to be a good test for assessing stroke risk among those who have some hemodynamic compromise as might be demonstrated by low MFV. Whereas MFV and VMR may both be relevant to stroke risk stratification, they may not be sufficiently sensitive or specific as biomarkers for brain function such as cognition. Although VMR has been shown by some investigators to correlate with cognitive impairment in carotid stenosis, other methods such as pCASL can have specificity for cortical blood flow and therefore may be more useful for assessing hemodynamic impact on cortical brain function. Finally, DCA addresses integrity of the real-time autoregulatory system in the normal perfusion range, and may be most useful as marker of autoregulation in a pathologically changing setting such as acute stroke. Our findings suggest that additional research is needed to explore cerebral

blood flow measurements as distinct entities, with unique information to elucidate cerebrovascular pathophysiology and guide clinical management.

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Highlights

- Cerebral hemodynamics can be measured in several ways in unilateral high-grade carotid stenosis
- Each measure showed significant asymmetry, but there was low correlation among them
- Low correlation among hemodynamic measures suggests unique physiological contributions
- Choice of hemodynamic measurement techniques depends on the outcome of interest

Figure 1.

Dynamic Cerebral Autoregulation (DCA) curves showing counterregulatory cerebral blood flow velocity (CBFV) curve “leading” the blood pressure (BP) curve with low phase shift (left) indicating abnormal autoregulation, and normal phase shift (right), indicating normal autoregulation.

Figure 2.
pCASL output showing cortical resting cerebral blood flow asymmetry due to carotid occlusion. Red color indicates higher CBF.

Table 1

Hemispherical asymmetry by blood flow test.

Test (units)	N	Mean ($\pm$ SD)		P
		UNOCCL	OCCL	
MFV (cm/sec)	29	55.0 (13.7)	39.1 (11.1)	<.001
CBF (mL/100g*min)	23	97.6 (24.8)	87.8 (25.6)	0.001
VMR (% increase)	24	2.5 (0.7)	1.9(1.2)	0.008
DCA (deg of PS)	19	45.7(21.5)	32.0(25.9)	0.047

MFV=mean flow velocity, CBF= Gray Matter Cerebral Blood Flow extracted from PVEc ASL, VMR=vasomotor reactivity, DCA=dynamic cerebral autoregulation, OCCL=measurement on the side of the occluded carotid artery, UNOCCL= measurement on the side of the unoccluded carotid artery, PS=phase shift

Table 2

Correlation among blood flow measures.

		VMR_DIFF	DCA_DIFF	CBF_DIFF
MFV_DIFF	Corr	0.120	0.000	0.112
	P	0.610	0.999	0.669
VMR_DIFF	Corr		0.085	0.149
	P		0.764	0.596
DCA_DIFF	Corr			0.233
	P			0.468

MFV=mean flow velocity, VMR=vasomotor reactivity, DCA=dynamic cerebral autoregulation, CBF= gray matter cerebral blood flow, DIFF=difference between measurement on hemisphere of the unoccluded –occluded carotid artery, Corr=correlation coefficient. P-values in boldface.