Cerebrovascular Reserve Imaging
Problems and Solutions

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KEYWORDS

• Cerebrovascular disease • Cerebrovascular reactivity • Cerebral blood flow • MR perfusion imaging • CT perfusion imaging

KEY POINTS

- A major function of the cerebral vasculature is to increase blood flow in support of the increased energy demand associated with neuronal signaling.
- Cerebrovascular reactivity (CVR) can measure blood flow augmentation, a valuable predictor of effective collateral blood and stroke risk in patients with steno-occlusive disease (SOD).
- Resting perfusion methods, commonly applied in patients with (SOD), have a limited ability to distinguish effective from ineffective collateral blood flow.
- Despite the high clinical potential for assessing cerebrovascular diseases, CVR is not a current standard of practice primarily due to a lack of standardization.
- A solution for standardizing CVR for clinical use is presented.

INTRODUCTION

The human brain with an estimated 80 to 100 billion neurons and approximately 1000 synaptic connections per neuron represents the pinnacle of biological complexity. If the neuronal networks were not complex enough, there are supporting glial and vascular networks that somehow must weave through the spatial confines of the neural net to provide the metabolic needs of the entire cellular assembly. Indeed, there are complex interactions between neuronal and nonneuronal elements that contribute to management of the tissue environment enabling optimal brain performance while managing valuable energy resources. From a blood flow perspective, the most relevant interactions are between the neurons, glial cells, and vascular cells with the latter including endothelial, smooth muscle, and contractile pericytes. These cells form the neuro-glio-vascular unit (NGVU). The NGVU became a crucial element in conserving cardiac output due to its ability to spatially regulate blood flow, a capability shared only by the skin. NGVU modulation of blood flow is tightly linked to the metabolic demand tuned to the spatial distribution of neural network activity. This avoids the need to increase blood flow to the entire brain when only aspecific neural networks become more active. The importance of local flow modulation may seem insignificant until the magnitude of brain blood flow changes in neural networks is considered. Because signaling within neural networks is associated with a threefold increase in energy demand,[1,2] the vasculature responds with increases in blood flow on the order of 50% over a resting baseline.[3,4] Somewhat surprisingly this flow increase is three times greater than the increase in oxygen consumption associated the increase in signaling.[3] As a result, there is a somewhat paradoxic increase in venous oxygen despite the increase in metabolic activity. This circulatory response will become important

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later in the discussion of MR imaging mapping of blood flow changes following vasodilatory stimuli.

A common theme in the evolution of a species is conservation of energy. Along these lines, humans are a striking example of the "energy premium" associated with the evolution of an energy hungry brain. Energy requirements drove significant changes in the body and brain during the transition from apex primates to sapiens concerning cardiac output, blood flow, skeletal muscle mass, and brain size. The higher energy demands of the larger human brain meant more work for the heart via increased cardiac output directed to the brain away from the rest of the body. Although the brain represents only 2% of body weight, it consumes up to 20% of the cardiac output.[5] It has been hypothesized therefore that a diversion of the cardiac output was necessary to support the enlarging brain requiring a compromise between skeletal muscle mass and brain size. Skeletal muscle decreased as brain size increased. We became smarter but weaker.

Another adaptation made by the growing brain, possibly to conserve space in a dense cellular network, was to sacrifice intracellular energy storage. Although glycogen is abundant in skeletal muscle, decreasing amounts are seen in the heart and brain. Although glycogen occupies approximately 2% of the cell volume in adult human cardiomyocytes,[6] its cerebral concentrations are so low that it is unlikely to act as a conventional energy reserve.[7] Although skeletal muscle can survive ischemic conditions up to 2 hours or more, the absence of cerebral energy stores severely limits brain survivability during ischemia. The often quoted "time is brain" concept concerns cerebral survivability during ischemic conditions underscoring the fact that the brain needs a constant source of glucose and oxygen provided by a healthy cervico-cerebral vascular system. "Brain is energy" is actually the central foundation of the homeostatic equation. Because there are limited energy stores in the brain, constant delivery of energy substrates by the vasculature is critical. An efficient distribution system that matches the metabolic needs within spatially distinct neural networks, which have highly variable energy requirements over time, is a necessity. A system such as this is exactly what has evolved, thereby conserving cardiac work. The system has contractile properties that manage vascular resistance and therefore blood flow along the entire course of the vascular tree from the level of the aortic arch (that contracts after closure of the aortic valve acting as a propulsive "second heart"), to the pericytes along capillaries.

Because there are numerous diseases that can impair the ability of the vasculature to provide an adequate source of cerebral blood flow (CBF) in the setting of acute and chronic disease conditions, assessing the ability of the vascular system to carry out this primary role in regulating blood flow would seem desirable. At issue is whether resting perfusion metrics, including blood flow, cerebral blood volume (CBV), mean transit time (MTT), time between the site of the measured arterial input function (AIF) and the peak tissue signal collaterals (Tmax), time from the tissue arrival of the bolus to the peak of the bolus signal time to peak (TTP), and blood arrival time, are adequate for this purpose. Or is a test of the ability of the vasculature to increase blood flow to a vasodilatory stimulus a more accurate measure? Somewhat surprisingly, the two different medical services, cardiology and neurology responsible for assessing circulations controlling blood flow in the most highly energetic human organs, are seemingly at odds with each other. Cardiology considers a vasodilatory stressor (cardiovascular reactivity known as "the cardiac stress test") essential for assessing disease within the coronary circulation. Neurology applies resting perfusion measurements instead of using a vasodilatory stressor for measuring cerebrovascular reactivity (CVR). Subsequently, widespread clinical application of the cardiac stress test has been adopted, but there has not been adoption of a "brain stress test." Part of the reason for this may be that cardiac research has benefited from a large number of clinical trials typically recruiting thousands of patients. From the neurology perspective, there are far fewer clinical trials recruiting fewer subjects. In fact, two of the most important and influential, but also controversial studies, one examining CVR,[8,9] and the other using oxygen extraction fraction,[10] disagreed on the clinical value of vascular dynamics. Although CVR research is increasing, it has not kept pace with research related to the cardiac stress test. A 2023 PubMed search revealed that there has been a slower rise in CVR publications compared with the cardiac stress test or even to that of already well-established CT scanning of the abdomen used as a control (**Fig. 1**).

The major theme of this article therefore examines resting cerebral perfusion metrics and CVR primarily for assessing the efficacy of collateral blood flow. A case will be made that application of resting perfusion metrics is effective for determining the presence of collateral blood flow but struggles to determine the *efficacy* of these collateral pathways especially as the degree and extent of steno-occlusive disease (SOD) increases. The concept of "effective collaterals" is based on the fundamental role of the vasculature to increase

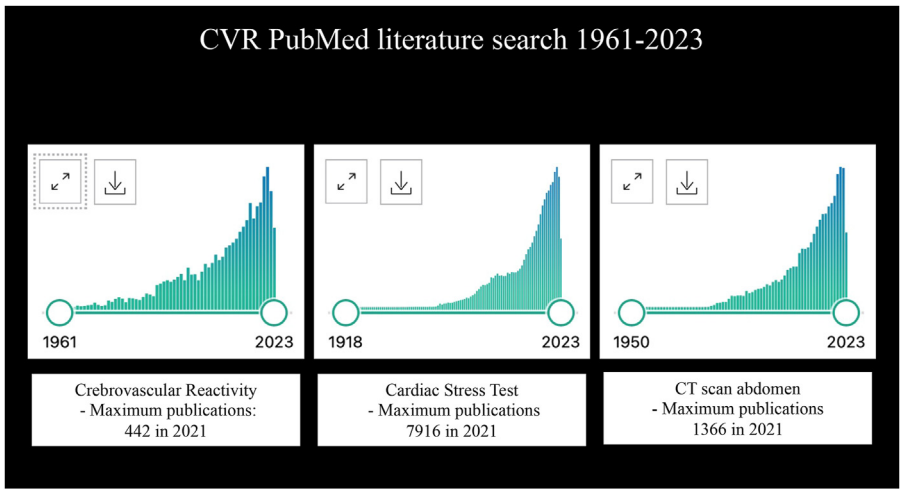

Fig. 1. PubMed literature search using search terms "Crebrovascular Reactivity," "Cardiac Stress Test," and "CT Acan Abdomen."

blood flow in response to increases in metabolic demand made possible by the ability of the cerebral vessels to dilate. CVR therefore is the critical element in the circulatory response for meeting increased metabolic demand.

CVR directly tests the ability of the vasculature to dilate but in doing so assumes that the average metabolic demand of the brain over time is relatively constant. Both CVR and resting perfusion metrics make this assumption. Issues concerning the major components of CVR testing including application of vasodilatory stimuli and mapping of associated blood flow changes will be thoroughly discussed. Ideally, the vasodilatory stimulus should only invoke action on the primary effector of the flow control system, which is vascular smooth muscle component of the NGVU, without influencing the other components. Finally, the potential value of CVR for assessing diseases other than stenoses of the major cerebral supply vessels will be discussed.

Regulation of Cerebral Blood Flow

CBF is regulated by altering the tone of vascular smooth muscle enabling control of vessel diameter and thereby flow resistance. There are, however, several incompletely understood mechanisms influencing arterial smooth muscle tone. The dominant mechanisms are blood pressure (BP), endogenous nitric oxide, glial cell modulators, and carbon dioxide (CO_2). Autoregulation relates to "reflex" changes in smooth muscle tone induced by mechanical stretching of smooth muscle as BP increases and modulates voltage-dependent Ca2+ channels.[11] Smooth muscle tone is also influenced by endothelial cells and neurons via release endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) vasodilators. Glial cells release arachidonic acid (vasoconstrictor) and prostaglandins (vasodilators) depending on tissue levels of neurotransmitters, oxygen, pH, and metabolites.[12] CO_2 influences smooth muscle tone through its effect on regulation of intracellular hydrogen ion concentration.[13]

Cerebrovascular Reactivity

CVR can be quantified as the ratio between the changes in blood flow per unit change in an applied vasodilatory stimulus. The relationship follows a sigmoidal curve (**Fig. 2**).[13] Cerebrovascular reserve is defined as the amount of vasodilatory capacity or increase in vessel diameter that remains for a given level of blood flow. The first CVR report in humans was published by Kety and Schmidt in 1948 using a nitrous oxide method for measuring total CBF and carbon dioxide as the stimulus.[14] Since that time, there has been an exponential growth in publications reaching an annual high of 442 in 2021. The main driver of this increase may be the perception in the ischemic stroke community that for a given stenosis of a large supply artery, patients with hemodynamic impairment, that is, reduced CVR, have a higher risk of ischemic stroke. This has been well documented in the older CVR literature in **Table 1**.[15–18] Why then has CVR testing not entered the mainstream of clinical practice? There are three main reasons. The first is the relative simplicity of obtaining resting cerebral perfusion metrics using dynamic susceptibility contrast-enhanced MR imaging or dynamic contrast-enhanced CT. Both require a bolus of contrast

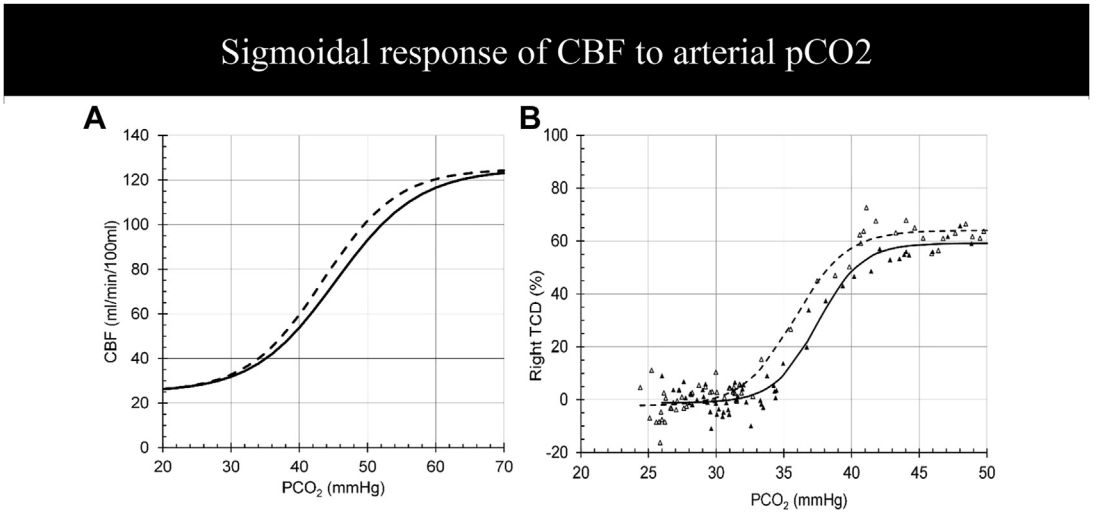

Fig. 2. CBF responses to P_{CO_2} to at P_{O_2} = 150 mm Hg (*solid line*) and P_{O_2} = 50 parentheses (*dashed line*). (*A*) Model response. (*B*) Example transcranial Doppler measurements of middle cerebral artery blood flow velocities.

with whole brain imaging with study durations of 90 seconds or less. The second reason is the lack of standardization of CVR testing. There are numerous ways to apply vasodilatory stimuli, and there are numerous ways to map blood flow changes. Unfortunately, the multiplicity of tools has resulted in inconsistency in CVR results. One of the more important inconsistencies is the fact that tissue blood flow responses in the setting of SOD will vary depending on the strength and/or duration of the stimulus yielding significant differences in the appearances of CVR maps (**Fig. 3**). The third reason is that CVR testing is more time-consuming compared with the time required to setup and then image a bolus of injected contrast. Finally, there is insufficient prospective clinical evidence supporting the added value of CVR over resting perfusion methods.

Cerebrovascular Reactivity Versus Resting Perfusion

Cerebral autoregulation can be global or local. The response to a drop in BP in a healthy individual is generalized relaxation of smooth muscle tone in all of the cerebral arteries that maintains resting

Table 1
The consequences of steal physiology

Author (journal)	CVR method	Subjects	Follow-up	Ischemic risk	Comment
Silvestrini (Jama 2000)	TCD breath-hold	94 prospective	28.5 mo	Annual risk TIA or stroke 3.4 higher	Asymptomatic carotid stenosis (≥70%)
Markus (Brain 2001)	TCD carbogen	107 prospective	21 mo	14.4 odds ratio TIA or stroke	Asymptomatic occlusion (3 mo) or ≥70% stenosis (2 y)
Blaser (Stroke 2002)	TCD carbogen	143 propsective	19 d	5.2 times higher risk of disabling stroke per month	Recent (0–92 d, median 10 d) ischemic event and 80–95% stenosis
Schoof (J of T&C Surgery 2007)	TCD carbogen	2797 prospective	Stroke post - cardiac surgery	28.3 odds ratio for stroke	If high grade stenosis ≥80%) or occlusion and decreased CVR present

See Reference section for complete documentation of listed studies

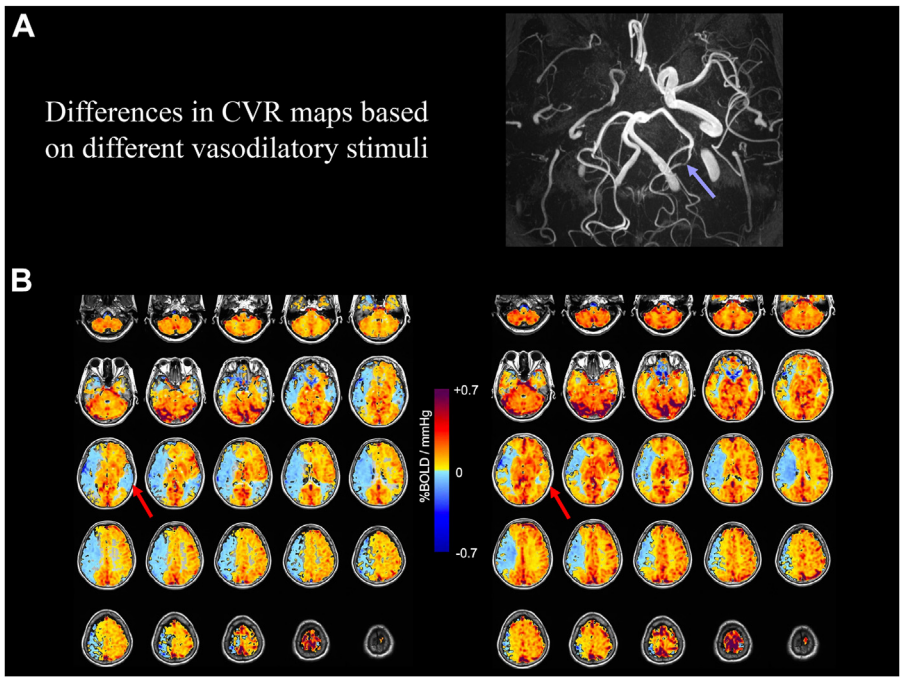

Fig. 3. CVR study with rapid (*left map*) and slow (*right*) map increases in CO2 each to 10 mmHg above resting baseline in 77 yo woman with atherosclerotic occlusion of the distal RICA and high-grade stenosis of left P2 branch (*blue arrow*). Yellow-red indicate increases in blood flow whereas blue indicates decrease in blood flow ("steal physiology"). Note differences in the left hemisphere (*red arrows*) depending on the nature of the stimulus.

perfusion. In an individual with SOD, there is a pressure drop across the lesion that invokes smooth muscle relaxation in the distal vasculature thus maintaining resting blood flow at normal or near normal levels. However, consumption of vasodilatory reserve has acute and chronic consequences. The acute consequence is that for a given stenosis, symptomatic patients with a significant loss of vascular reserve have a higher risk of permanent ischemic injury than those patients with a similar degree of stenosis who have retained vascular reserve—more commonly termed "hemodynamic" reserve (see **Table 1**). The chronic consequence is that normal augmentation of blood flow responses during neuronal activation are diminished to varying degrees depending on the degree to which vascular reserve has been consumed to maintain resting CBF. Under these circumstances, the blood flow increase in response to neural activity is reduced. The consequence of the reduced flow response in the absence of ictal events is the development cortical atrophy.[19,20] The adaptation of the cerebral circulation to SOD is variable. There is the ability to recruit collateral blood flow resources by amplification of existing collaterals or developing new vessels (angiogenesis). There is a substantial literature on collateral circulation; however, the major points relevant to this discussion are (1) the compensatory status of preexisting collateral pathways and (2) and the time frame over which SOD disease develops. The presence of an effective preexisting circle of Willis network and/or preexisting connections between vascular territories over the pial surface can fully compensate even for an acute vascular occlusion. Acute balloon occlusion of large cerebral supply arteries has been used in settings where sacrifice of the supply artery is a treatment necessity, for example, in patients with traumatic carotid cavernous fistulae. Slowly progressive stenosis eventually leading to occlusion of a large supply artery can provide the time needed for development of new collateral vessels (angiogenesis) or development of increased capacity in existing. **Fig. 4** is an example of a patient who developed transient ischemic attacks (TIAs) from a sudden thrombotic internal carotid occlusion secondary to a stenosing atherosclerotic plaque. TIAs were thought to be hemodynamic in nature based on increased mean transit time (MTT) on CT perfusion. However, the TIAs were subsequently proved to be embolic based on the following points (1) the CVR map showed near normal hemodynamics, (2) the symptoms were alleviated via medical management alone (anticoagulation), and (3) MR imaging showed tiny embolic infarcts. The CVR changed patient management

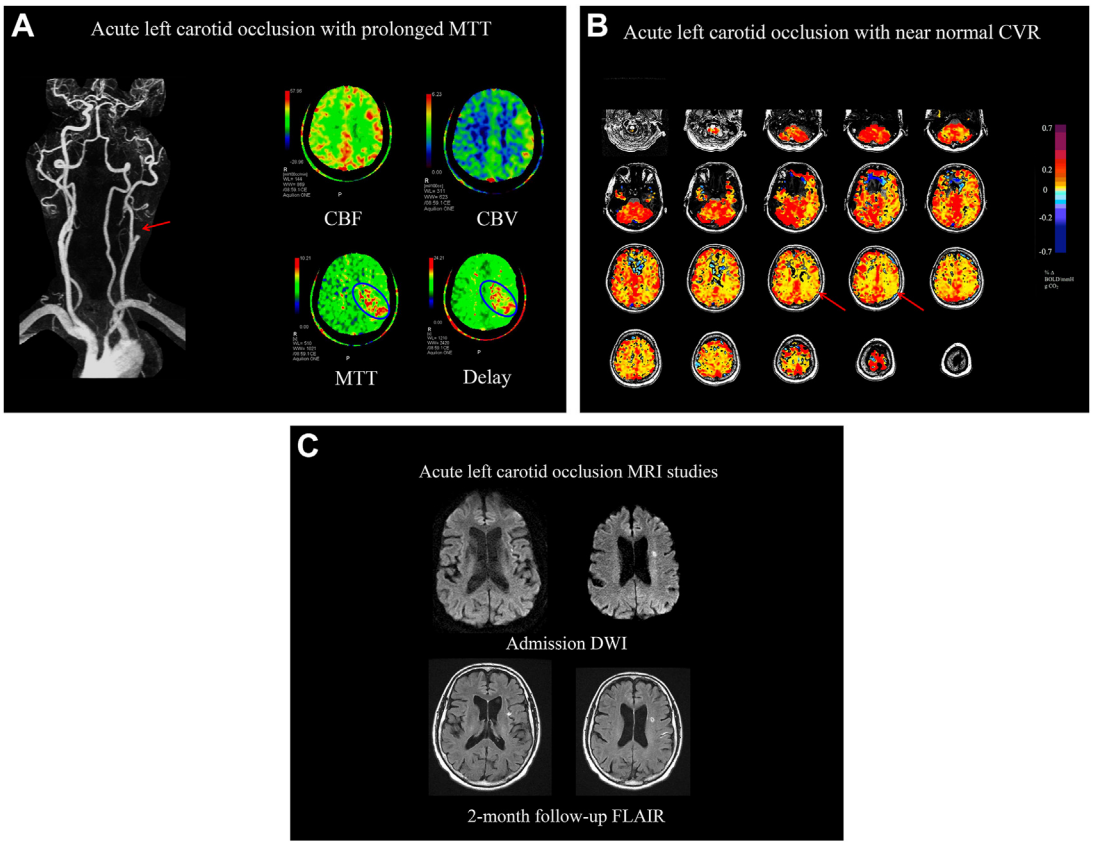

Fig. 4. (*A*) 76 yo patient seen in emergency room (ER) with regular episodes of right-sided facial droop, slurred speech, right sided arm and leg weakness, CTA indicated a left carotid occlusion (*red arrow*) with no string sign. CT perfusion map showed red areas involving left primary motor cortex indicating MTT > 4 sec compared to the remainder of the brain. Heparinization failed to control the TIAs and by-pass surgery was planned. (*B*) An urgent CVR study revealed near normal hemodynamic reserve (*red arrows*) indicating effective collaterals. The patient was managed conservatively. Symptoms persisted for 10 days and then stopped. The patient was subsequently discharged and continued asymptomatic at 2 month follow-up. Note the consistently higher CVR always seen in the cerebellum and brainstem. (*C*) MRI indicated only small areas of acute ischemic injury in the left hemisphere on admission with minimal progression on follow-up at 2 months.

(see **Fig. 4**). Importantly, MTT was not able to discern that the slow filling collaterals were actually effective.

Given sufficient time collateral circulation including neoangiogenesis can develop, however, the effectiveness of this collateralization can vary considerably. Resting perfusion imaging using boluses of intravenously administered contrast agents are the current standard of practice in symptomatic patients for testing the efficacy of collaterals in acute and chronic SOD.[21] However, an accurate measurement of blood flow metrics requires selection of an appropriate AIF for deconvolution with the tissue signal during bolus administration of a contrast agent. A significant problem with bolus perfusion methods is locating and measuring the AIF. Often the vessel with SOD is so narrowed or occluded that a reliable AIF cannot be generated on this vessel, thus requiring selection of a healthy vessel elsewhere. Selection of a vessel that is not directly involved in perfusing the tissue of interest violates the model on which the deconvolution is based. Nevertheless, resting perfusion methods have dominated assessment of collaterals despite the fact that the three primary blood flow metrics, CBF, CBV, and MTT, have shown limited utility. However, a shift toward measurement of *timing* metrics such as TTP and Tmax has evolved.[21] Unfortunately, studies have shown mixed results when comparing one resting blood flow method against another such as CT perfusion against multiphase computed tomographic angiography (CTA) (**Figs. 5** and **6**).[22–24] Furthermore, the gold standard digital subtraction angiography (DSA) grading scale, adopted for use in clinical trials, also uses timing metrics based on the

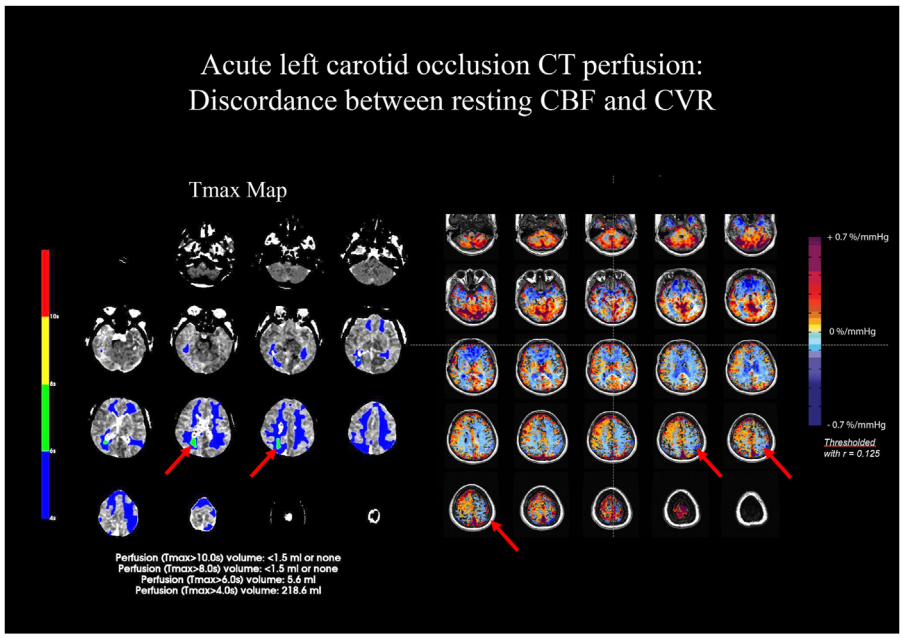

Fig. 5. Despite steal physiology in most of the left middle cerebral artery (MCA) territory (*red arrows right panel*), the longest Tmax values are in the right hemisphere (*red arrows left panel*).

subjective assessment of how quickly the cerebral vessels fill during direct arterial injection of contrast. A recent study assessing the performance of this scale was conducted using 30 pretreatment AP and lateral video loops chosen from the THRACE randomized controlled trial study in patients with proximal cerebral artery occlusion.[25] These video loops were sent to 19 readers for assessment of collateral efficacy. The conclusion from the study was that "Concordance

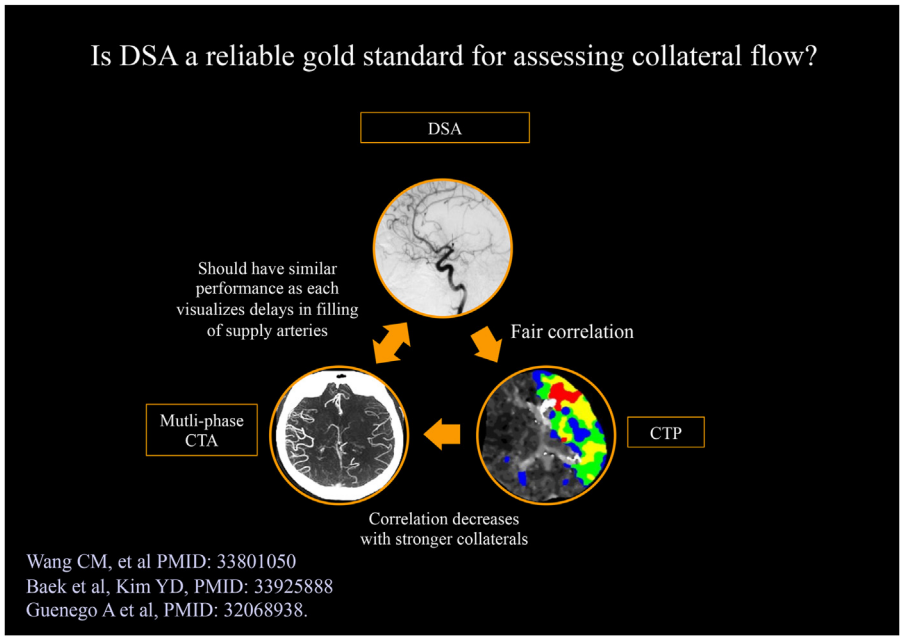

Fig. 6. DSA and CTA are subjective assessments prone to variance based on rater differences. CTP is objective and quantitative but has become dependent on timing metrics. By comparison, the fundamental flow metrics that compose the "Central Volume Principle" CBV = CBF × MTT have surprisingly shown limited clinical utility.

rates were poor among trained and experienced readers, and not improved by pre-test training or dichotomized grading." This research study revealed "*important limitations*" for collateral flow assessment within the definition of the American Society of Interventional and Therapeutic Radiology/Society of Interventional Radiology (ASITN/SIR) scale. In summary, it would seem that there are significant limitations in the use of timing metrics for the evaluation of collateral efficacy. It is sensible therefore, to consider that a better solution to this dilemma, is to show the ability of blood flow to increase when challenged by a vasodilatory stimulus as this is the normal vascular response to the metabolic requirement of highly energetic tissue. Increases in blood flow approaching 50% over baseline have been documented during activation of the cerebral cortex indicating the importance of flow augmentation in active neural networks.[3,4] From a metabolic perspective, it is interesting to note that not all of the blood flow increase is necessarily accounted for by increased oxygen utilization, which only increases by approximately 15% over baseline during neuronal activation.[3] Theories for this considerable increase in flow therefore include additional factors such as an increase in the surface area for oxygen transfer along the length of the microvasculature and removal of metabolic waste. Because blood flow increases are necessary for maintaining the health of cerebral tissue, it would seem that the most effective test of the circulatory system is not to assess the system at rest, but to challenge its capacity to increase flow through application of CVR methodology. However, the challenge of implementing CVR testing needs to overcome the existing disparity in available methods for administering the vasodilatory stimulus and for mapping tissue blood flow responses while doing so.

Cerebrovascular Reactivity Optimization and Standardization

Before beginning the discussion of CVR methodologies, an important aspect of the interpretation of CVR maps must be understood. The issue arises from the fact that interconnections exist throughout the vascular network brain that can result in a reverse "Robin Hood" phenomenon where vascular beds that have normal levels of vascular reserve can steal flow from those beds with reduced vascular reserve. This occurs because vascular beds distal to a stenosis consume vascular reserve through vasodilation to maintain resting blood flow at normal levels. As a result, these beds are unable to lower resistance to the same degree as healthy beds. When a global vasodilatory stimulus is applied, a steal phenomenon ensues where blood flow follows the path of least resistance. Flow is diverted away from beds with a limited ability to vasodilate. This has been termed vascular "steal." Some vascular beds are maximally vasodilated at rest and are therefore vulnerable to decreases in BP resulting in hemodynamic TIAs. Providing a global vascular stimulus can reveal and map the extent of these steal regions. However, the extent of steal physiology depends on the magnitude of the stimulus provided because a mild stimulus may not be sufficient to reveal the full extent of marginalized vascular beds. Two important issues are raised by this phenomenon. The first is what magnitude of vascular stimulus should be applied, and the second is how can the reproducibility within and across subjects be ensured for accurate clinical decision-making?

Control of the vasodilatory stimulus: The ideal CVR method would be to use the neuronal component of the NGVU to induce vasodilation. It is the most desirable but least achievable method. There is no conceivable way to activate each neuronal network within a vascular territory of interest because innumerable neuronal networks exist within a given vascular territory and no single task paradigm would be effective in activating these networks. Interestingly, recent work has shown that for a given vasodilatory stimulus that induces steal physiology in the primary motor cortex, different fMR imaging task responses can be observed from visible to no observable activation.[26,27] It is expected that further increases in arterial CO_2 with greater steal could eventually extinguish the ability of active neurons to increase CBF, but this would require further testing for confirmation.

With this background, the following is an example of our research effort over the last 20 years to optimize and standardize CVR methodology to meet the challenges of translating CVR from a research tool to full clinical standard of practice.[28] It is an example only and other investigators may find more optimal strategies, but is does highlight problems requiring a solution. The following details the current status of the approach addressing the two primary challenges derived from the definition of CVR itself, that is, the need to deliver a known stimulus and the ability to map whole brain blood flow changes.

There are numerous ways to provide a vasodilatory challenge. These include BP manipulation, pharmacologic challenges, and carbon dioxide inhalation. All of the methods can suffer from difficulty reproducing the stimulus and achieving a repeatable and quantifiable stimulus. CVR can be

obtained using manipulation of BP but reproducibly controlling BP to targeted levels is difficult and is associated with safety concerns. Pharmacologic manipulation for controlling blood flow is problematic as well. Acetazolamide is typically used for this purpose. However, it has unpredictable time courses and is considered to be a supramaximal stimulus that would induce vasodilation beyond the range of normal increases in CBF seen with neuronal activation.[3,4] A vasodilatory stimulus can be achieved using breath-holding techniques but the levels to which arterial CO_2 accumulates are unknown within and between individuals. Methods using simple inhalation of increased levels of inspired CO_2 induce unknown changes in arterial P_{CO_2} due to unpredictable respiratory responses in the form of increasing minute ventilation. The ability to control arterial CO_2 levels would be ideal as CO_2 is benign and can be rapidly absorbed and removed from the blood via the lungs. Fortunately, accurate control of CO_2 was made possible by advances in respiratory physiology that enabled targeting of selected arterial values of CO_2. This led to the development of two approaches: end-tidal forcing[29] and sequential gas delivery (SGD).[30] Arterial CO_2 levels targeted using SGD has been validated against arterial blood sampling and is the only method available having had this validation.[30–32] **Fig. 7** indicates the high degree of accuracy and reproducibility of the CO2 stimulus achieved with SGD over time benefitting assessment of interval changes in CVR critical for informing optimal patient management. Note that an increase in the CO_2 stimulus of 10 mm Hg over resting values was chosen. The reasoning behind this is that 6% to 8% increases in CBF per mm Hg increase in arterial P_{CO_2}.[33] Therefore, a 10 mm Hg in arterial P_{CO_2} would increase CBF by 60% to 80% covering the 50% increase in CBF seen with neuronal activation. The ramp increase in P_{CO_2} briefly exceeds this step increase in CBF but also includes a hypocapnic component that enables calculation of relative vascular resistance that may eventually be used to replace conventional CVR maps.[34] Details are beyond the scope of this document and the reader is referred to the cited reference for further information. Finally, there is an additional consideration regarding the application of CO_2 for selectively influencing vascular smooth muscle tone independent of the remaining elements of the NGVU. There is controversy in the literature, as to whether or not elevated CO_2 levels affect neuronal activity directly.[35] Because no consensus has been

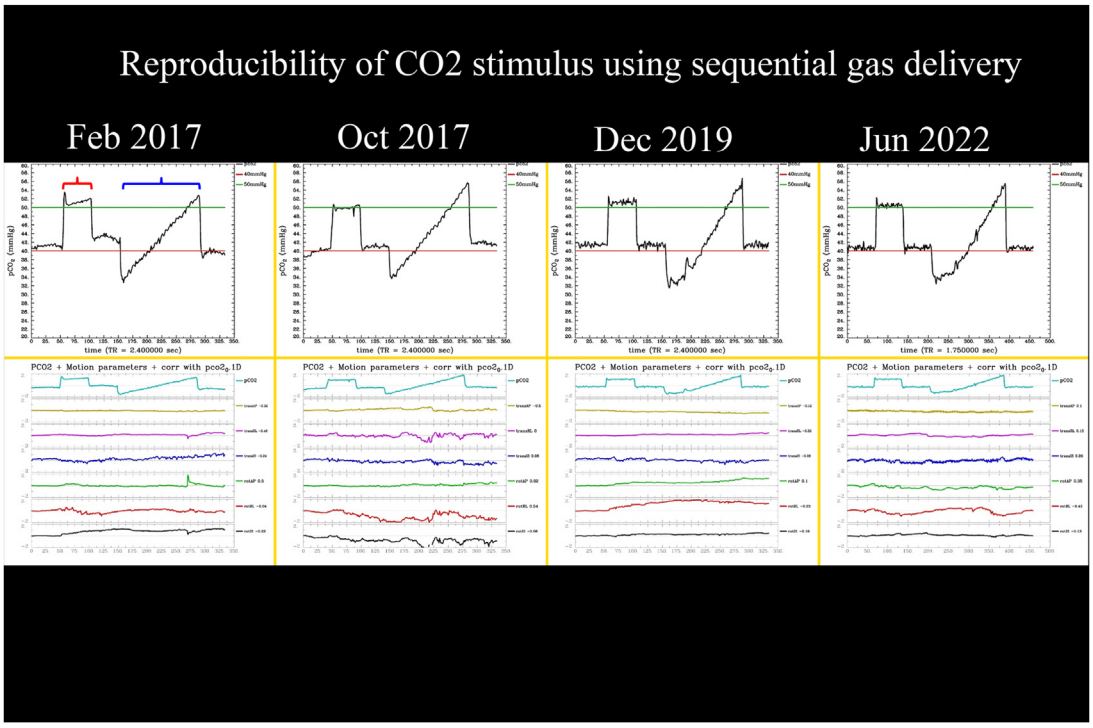

Fig. 7. Data in one patient scanned sequentially showing repeatability of the measured end-tidal (exhaled) CO_2 values to the preprogrammed end-tidal CO_2 targets used for each CVR session more than four different CVR sessions. Red bracket is the step stimulus and blue bracket is the ramp stimulus. Bottom graphs indicate head motion in six different axes during MR imaging data acquisition (in millimeters).

reached, it is assumed that the influence is insignificant for the purposes of measuring CVR. Nevertheless, continued monitoring of this issue in the research literature is warranted.

Mapping changes in CBF: The MR imaging pulse sequence used to map blood flow changes should be able to measure CBF accurately and quantitatively in the setting of advanced cerebrovascular disease with good signal to noise ratio (SNR), no signal drift, no required contrast administration, immunity to skull base susceptibility artifacts, and with very short scan times. Whole brain coverage is needed with good spatial resolution $\leq$ 3 mm isotropic voxels, and the sequence should be capable of mapping whole brain blood flow changes every 1.5 to 2 seconds in order to capture dynamic changes in the CO_2 vasodilatory protocol as seen in **Fig. 7**. As of this writing, there is no available MR imaging pulse sequence that fits all of these requirements. The only pulse sequence capable of meeting most of these needs is the blood oxygenation dependent (BOLD) sequence. It matches all the requirements except for: (1) its sensitivity to inhomogeneous magnetic fields at the skull base limiting assessment of cerebral tissues in this region, (2) nonlinearity of the signal with blood flow, and (3) signal drift. Fortunately, the extent of "invisible" brain secondary to susceptibility artifact is limited to small regions, and signal drift can be corrected using high band-pass filtering. The major issue is that the BOLD signal is nonlinear with blood flow and also depends on blood volume. The main nonlinearity assuming constant tissue metabolism is that increasing blood flow washes out deoxyhemoglobin approaching an asymptote at 100% oxygen saturation. Therefore, greater increases in CBF are associated with smaller increases in the BOLD signal. There is also the effect of the nonlinear relationship between CBF and CBV described the Grubb constant where CBV = 0.80 CBF 0. 38. The relationship indicates a rapid initial increase in CBV followed by a long shallow increase. Despite these issues, from a physiologic perspective and within the boundaries of Stage 1 and 2 ischemia where Stage 3 indicates ischemic tissue injury, the BOLD signal always increases with CBF. Furthermore, we are not aware of any publication where CBF and CBV behave inversely to each thus violating the Grubb relationship. BOLD is therefore a reasonable surrogate for measuring changes in blood flow. Measuring CBF with MR imaging arterial spin labeling (ASL) is an interesting alternative to BOLD especially because there is a linear relationship between CBF and ASL. However, the acquisition is plagued by poor temporal resolution, and significant loss of magnetization in labeled blood water protons due to T1 relaxation effects to the point where signal to noise is compromised. This is especially so in the setting of longer collateral pathways that develop in increasingly severe SOD. An additional problem seen in advanced SOD occurs when the labeled water remains in supply arteries including the pial

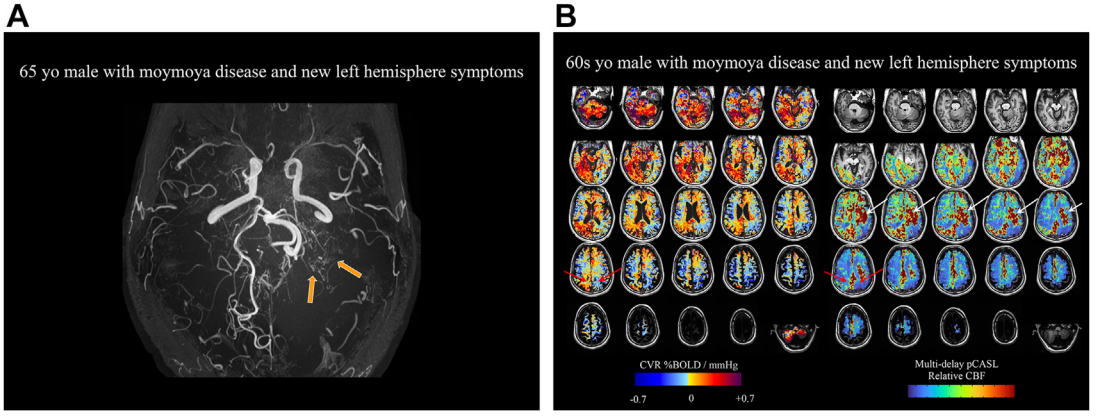

Fig. 8. (*A*) MRA shows bilateral ICA occlusions distal to the posterior communicating arteries and left PCA occlusion with moya collaterals (*arrows*). (*B*) CVR shows areas of steal physiology in both hemispheres. Compared with areas with CVR steal physiology, ASL in general shows somewhat larger regions with marked reduction in CBF. Note that the areas of concentrated spin label in the collateral moya vessels seen near the left PCA occlusion in (*A*) (*white arrows*). The tissue in the vicinity of this collateral site has mostly positive reactivity. The high signal intensity on the ASL images (ASL "artifact") in the midline (medial to *red arrows*) indicates the presence of collaterals with what seems to be a significant reduction in CBF in the adjacent frontal lobe gray matter bilaterally. The CVR map however indicates that most of the right anterior cerebral artery territory has positive CVR. The left ACA territory has steal physiology in the poster half of the left ACA territory. ICA, internal carotid artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery.

circulation. This labeled blood water may not reach the microcirculation. Because the spatial resolution of the scan cannot distinguish the small pial vessels on the brain surface from the microvasculature within the cerebral cortex, the cortex can appear to have a range of perfusion values from adequate to artifactually increased perfusion (**Fig. 8**) even when the most recent multi-delay ASL acquisitions are applied. In terms of ASL mapping, the true status of the vasodilatory capacity in the tissues is uncertain. The discordance between CVR and ASL in this case is concerning as surgical decisions can be influenced by the maps. In addition, ASL acquisitions do not have the less than 2 seconds whole brain temporal resolution for monitoring rapid changes in CBF that BOLD offers. We hope that continued ASL development would eventually offer a solution enabling replacement of BOLD for CVR studies.

CVR metrics speed and magnitude of response: The CO_2 stimulation paradigm seen in **Fig. 7** was developed after considerable debate over many years. The protocol begins with a baseline CO_2 level that is the individual subjects' resting level. The paradigm lasts 13.5 minutes and consists of an STEP and RAMP stimulus. Note that the speed in the rise and fall of the CO_2 change occurs in one breath. The response of the BOLD signal is slower and exponential in nature.[36] In healthy patients, the duration of the plateau is long and all vascular beds reach a maximum value before the fall in CO_2. This is not the case in patients with SOD. Some vascular beds continue to rise without plateauing before the drop in CO_2. Therefore, in order

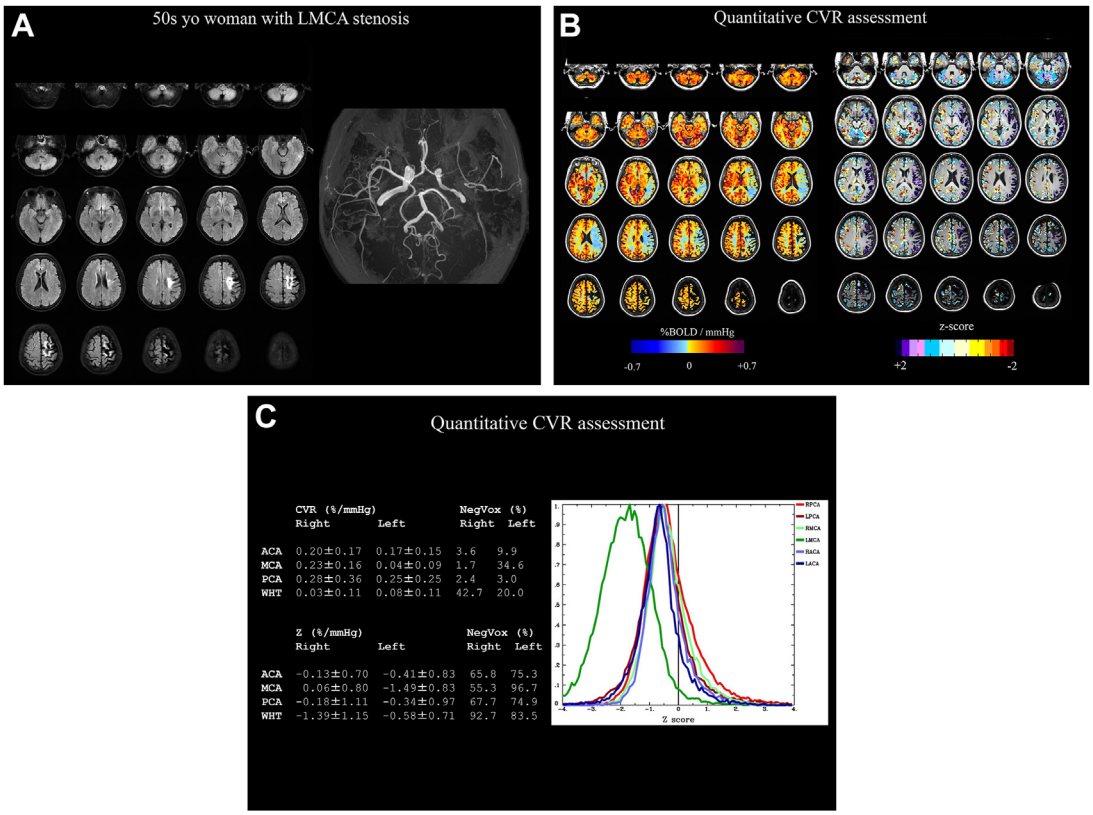

Fig. 9. (*A*) The FLAIR image indicates an old ischemic infarct in the left hemisphere. The MRA shows an occluded left MCA. (*B*) CVR indicates steal physiology persisting throughout the left MCA territory around the LMCA infarct. Z-score map indicates that the CVR in all other vascular territories is within normal limits (within two standard deviations) relative to a healthy control population. The left MCA territory is more than two standard deviations below the normal population as it should be since there is steal physiology in this territory. (*C*) Segmentation of patient gray matter into vascular territories from a standard vascular territory template enables quantification of CVR magnitude of response for each vascular territory. This provides a mean CVR magnitude and a total voxel count of negative responding voxels (steal) for each vascular territory. Rapid visualization of the distribution of the voxels is made possible by plotting the histograms of each vascular territory as shown in the graph. Note that the healthy territories have mean z-score distributions only minimally decreased (shifted to the left) compared with the healthy population.FLAIR, fluid attenuated inversion recovery; LMCA, left middle cerebral artery.

to accurately measure the magnitude of the flow response in patients, a longer slower RAMP increase in signal is required. Modeling the rise in the BOLD signal as a first order exponential enables measurement of the exponential constant representing the speed of response of a vascular bed.[36] The protocol therefore provides two CVR metrics representing biomarkers of vascular responses that have significant impact in measuring effectiveness of collateral circulations in patients with SOD, and the impact of non-SOD diseases on intraparenchymal vascular performance.[37,38]

CVR atlases: The design of functional neuroimaging studies that have examined disease states in patients depends on group data from healthy individuals. In conventional functional imaging studies, image data are typically merged from a group of healthy controls and compared against merged data from a patient population with a specific disease condition. This approach has proven effective in determining the effect of a disease condition on cerebral structure and function. The inherent problem with this approach is the inability to detect disease-related affects in patients. The reason for this is that signal-to-noise ratios in the acquired functional images of individual subjects are typically insufficient to detect disease-related effects. For example, fMR imaging techniques have been available for over 30 years, but no single diagnostic application of this tool has yet been developed. Although CVR uses the same BOLD image acquisitions used for fMR imaging studies on 3T systems (highly recommended field strength for CVR studies), the magnitude of the stimulus-induced signal changes is typically 50% to 100% stronger than those seen with fMR imaging activation of neural networks. Our approach to the diagnostic assessment of vascular disease in individual subjects takes advantage of the greater CVR signal changes and combines this advantage with the development of control atlases enabling voxel-wise z-scoring of individual patient responses.[39] These responses can be viewed as z-score maps and histograms enabling quantitative assessment

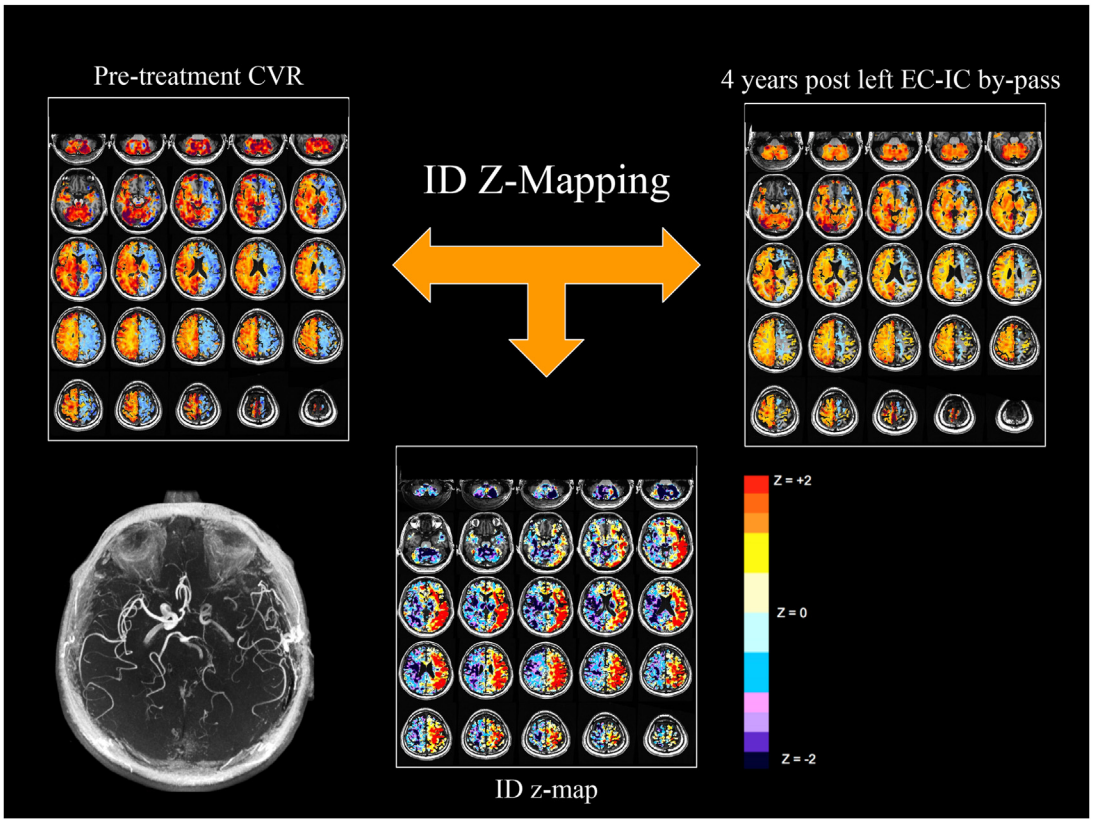

Fig. 10. Patient with distal left ICA occlusion treated with left EC-IC bypass. The "interval difference (ID) difference map" controls for differences in session-to-session variance caused by normal variations in physiology, magnet performance, and head positioning. The ID difference therefore grades the effects of management decisions in terms quantitative z-scores by comparing the patient's own ID difference map against a group ID difference atlas made from healthy controls. EC-IC, external carotid-internal carotid.

of the degree to which an individual patient differs from a healthy population (Fig. 9). The only drawback to this approach is that it requires building a healthy control atlas against which an individual patient can be assessed. In the ideal world, the atlases are generated on a single MR imaging platform used in scanning patients and controls. However, we have shown that the results are highly comparable on platforms from different vendors provided that the BOLD pulse sequence parameters are matched.[40] It has also been shown using a quantitative CO_2 stimulus that there is little age dependence on CVR between the third and seventh decades in disease-free controls. Areas of reduced CVR begin to develop after the seventh decade predominantly in the white matter of the frontal lobes.[41]

The control data collected for CVR atlas formation can be broken down into two separate atlases: one for the speed of response and one for the magnitude of response. From a clinical perspective, the assessment of large supply artery SOD has been the primary application of CVR testing. Under these circumstances, the relevant clinical information is primarily derived from the magnitude atlas. However, there are disease conditions where the disease itself has limited impact on large supply arteries but does have an impact on the brain parenchymal circulation. This is where the speed of response metric has shown considerable promise (see below).

We have also developed interval difference (ID) atlases. An ID image can be made from a healthy control scanned on two different days. The ID images from a group of controls are then merged into a common brain space creating an ID atlas. Comparing the patient ID map against the ID atlas can account for changes in the disease condition and the effects of management over time while controlling for differences in physiology, head positioning, and magnet performance.[42] Voxelwise interval difference z-score maps are then available for quantitative assessment of the temporal differences (Fig. 10).

Finally, during the acquisition of CVR data, it is recommended that BP and head movement are monitored. The effect of elevated BP often seen with induction of the CO_2 stimulus is believed to improve CVR, but the degree to which it influences CVR maps has not been formally studied. We have assumed that increases in BP greater than 10 mm Hg could significantly alter the results of CVR studies and as a result, monitoring of BP as frequently as possible before, during, and after the CO_2 stimuli is recommended. In our experience, translation or rotational head motion in excess of 3 mm should also raise concerns.

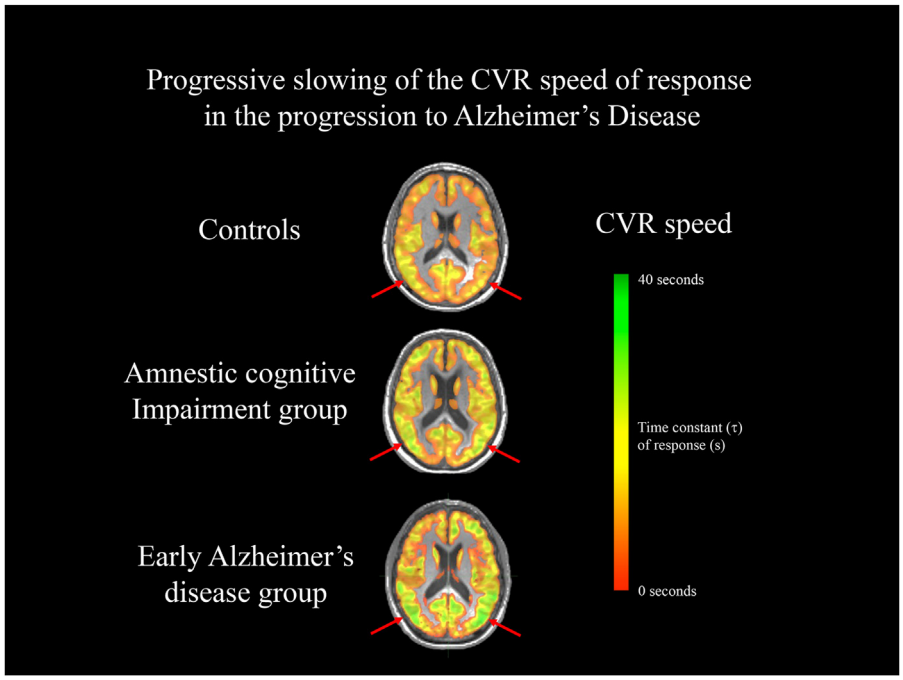

Fig. 11. Merged speed of response data from a healthy control group, amnestic cognitive impairment group, and early Alzheimer's disease group. Arrows indicate progressive slowing of the speed of response in temporoparietal regions of the brain associated with worsening cognitive impairment.

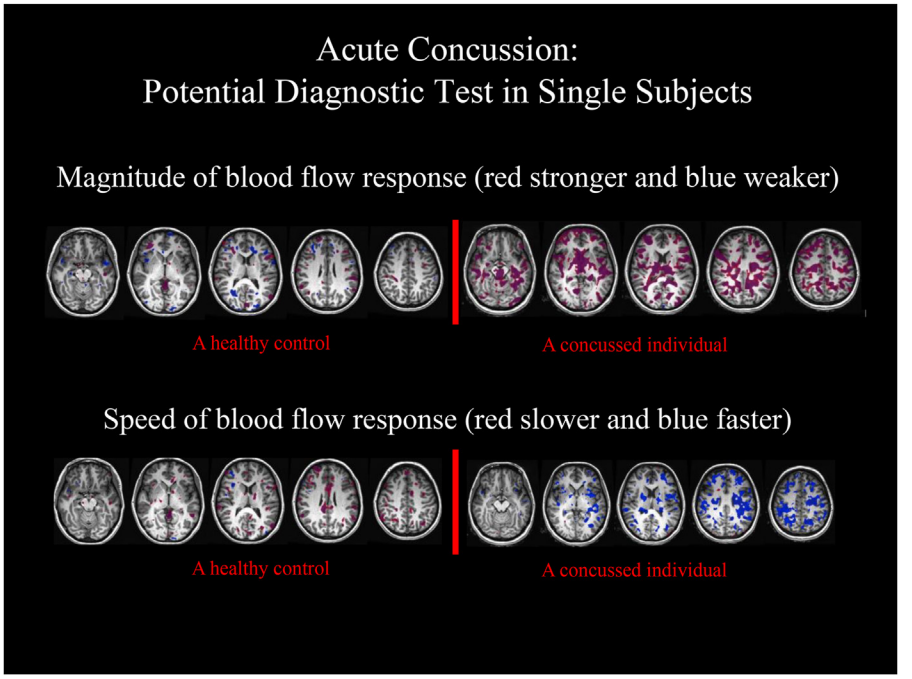

Fig. 12. Z-score maps thresholded at two standard deviations showing faster and stronger CVR responses in a patient scanned in the first week after concussion. There is a clear increase in the extent of abnormal CVR compared with the healthy control. Note that much of the change is in white matter the primary site of the concussive injury. The etiology of this "supernormal" CVR response remains unknown.

The speed of response CVR metric: The biological basis of the speed of response is not fully understood but multiple factors could be involved. If it can be assumed that the CO_2 stimulus used to increase blood flow only affects the vascular component of the NGVU, the speed of smooth muscle response may be the primary factor. Secondary factors may include vessel compliance, cerebral compliance, endothelial dysfunction, modulation of autonomic tone, mitochondrial disease, venous hypertension, trauma, migraine pathophysiology, drugs including ion channel blockers, sickle cell disease, infection (COVID), and subarachnoid hemorrhage to name a few. We have studied two diseases that have shown remarkable findings. The first is amnestic cognitive impairment (aMCI) the precursor of Alzheimer's disease (AD).[38] Compared with controls from a healthy control atlas, patients with aMCI demonstrated a significant slowing of the speed of response in temporoparietal cortex areas where amyloid deposition is prominent in AD. Furthermore, there was even greater slowing in the same regions in patients diagnosed with early AD (**Fig. 11**). A statistically significant correlation was also observed between a slower speed of response and decreased cognitive performance. Interestingly, a mouse model of AD showed concentric rings of amyloid deposition surrounding the microvasculature with much of the deposition between the glial foot processes of the NGVU. It would seem that encirclement of vessels by amyloid could decrease vascular compliance possibly made worse by glio-endothelial interference from amyloid deposition.[43] Because one of the earliest changes in the brain in patients who later develop AD is vascular in nature,[44] these studies justify further examination of CVR as a more available and potentially earliest marker for screening patients with amnestic MCI.

Another example of the value of the speed of response measurement is in concussed individuals. Concussion diagnosis has been elusive. CVR using quantitative stimuli has demonstrated high receiver operating characteristic (ROC) values between 0.90 and 0.95 based on both tails of the z-score distributions in the chronic stages of the injury when associated with persistence of symptoms. In the acute phase of the injury, the high z-scores were found in the tail of the distributions, indicating a faster speed and stronger magnitude of response specifically in the white matter (**Fig. 12**). This pattern of CVR metrics has not been reported in any other condition. Dysautonomia associated with the innervation of pial and parenchymal vessels has been suggested as a possible cause.

SUMMARY

The vasculature plays a vital role in meeting the metabolic demands of the tissues in any organ. Despite the similarity in high blood flow demand by the brain and heart, evaluation of the vasculature in these organs has taken very different paths. The difference is based on the established value of measuring cardiac blood flow augmentation. A cardiac stress test was developed for the heart, but resting perfusion metrics have become the mainstay in the brain. Because both organs depend on strong flow augmentation, it is somewhat perplexing that such a difference even exists. A simple reason may be that the heart feels pain when there is insufficient flow, but the brain does not. Perhaps a more significant reason is that there are myriad methods for measuring CVR, but standardization has never been achieved. This article has served to demonstrate advances that act as an example of how a "brain stress test" can be successfully standardized and implemented using a clinically tested method where most of the CVR studies were carried out in patients with the most severe SOD. The CVR protocol provides precise quantitative vasodilatory stimuli enabling acquisition of two CVR metrics: the speed and magnitude of the flow responses. They can be thought of biomarkers of vascular health and performance with acceptable image acquisition times at 13.5 minutes. These metrics have provided significant advantages in clinical and research settings.

With regard to patient research issues, current CVR methods apply nonquantifiable stimuli. CVR data generated from such stimuli will likely regress to the mean over a population thus providing reasonable hypothesis testing capability. However, an increased number of subjects needed to reach statistical significance are required. The consequences are increasing study costs and an increase in patient burden. Furthermore, the accuracy and reproducibility of studies using uncontrolled vasodilatory stimuli are uncertain.

Based on our clinical experience of more than 1200 patient CVR studies, we believe that the management of individual patients with cerebrovascular disease requires precisely controlled reproducible stimuli to optimize the diagnosis, appropriate treatment planning, and monitoring of treatment efficacy. Despite the fact that for a given stenosis, many studies have shown that the risk of permanent ischemic injury is up to five times higher in patients with hemodynamic impairment than without, there are no prospective outcome studies using a controlled vasodilatory stimulus. In a recent review of cerebral hemodynamics and oxygen extraction studies, it was stated that *"There is a great opportunity, and clinical need, to prove the therapeutic efficacy of hemodynamic assessment in patients with atherosclerotic asymptomatic extracranial carotid stenosis, and symptomatic internal carotid occlusion and intracranial stenosis. A better understanding of the long-term metabolic and physiologic impact of chronic regional hemodynamic impairment and the mechanism of hemodynamic stroke is needed."*[45] Moving forward, new approaches for assessing the ability of the vasculature to meet the metabolic needs of the brain including resting state BOLD techniques and artificial intelligence methods may eventually replace current CVR methods. This development would be most welcomed, but assessment of the need to move away from resting perfusion measures remains the same. The challenge for the future is therefore on the shoulders of the next generation of stroke neurology and vascular neuroradiology/neurosurgery to conduct the requisite clinical trials designed to compare CVR against resting perfusion metrics that are the current standard of practice. This represents an opportunity to improve patient care that is both compelling and long overdue.

CLINICS CARE POINTS

- The solution described for implementing cerebrovascular reactivity (CVR) was derived from testing in a clinical population based on more than 1200 patient examinations.
- The method has become a focal point in the clinical assessment of patients with advanced cerebrovascular disease who are now being seen in a newly formed "Revascualrization Clinic."
- Although standardized CVR methodology has shown defacto clinical utility, the need for randomized clinical trials comparing CVR metrics versus resting perfusion metrics is needed.

DISCLOSURE

D.J. Mikulis holds minor equity in Thornhill Medical Inc vendor of the Respiract enabling precise breath to breath control of arterial CO_2 for accurate delivery of vasoactive stimuli during CVR studies.

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