Intracranial and extracranial CO_2 vasomotor reactivity: assessment, approaches and clinical applications

Cerebral blood flow (CBF) describes the volume of blood flowing through the blood vessels that supply the brain. The ability to regulate CBF can have profound effects on important cognitive processes and loss of such regulation can lead to serious consequences to brain homeostasis due to susceptibility to harmful systemic blood pressure changes. Partial pressure of carbon dioxide ($PaCO_2$) is a key mediator of CBF, causing decreased CBF in low $PaCO_2$ and increased CBF in high $PaCO_2$, facilitated through changes in the vasculature known as cerebrovascular reactivity (CVR). CVR is able to regulate CBF by dilating or constricting blood vessels in response to $PaCO_2$. Extensive research has been published investigating CVR, identifying that lower CVR, is associated with an increased risk of mortality and reflects an impaired vascular system.[1]

Positron emission tomography has been termed a reference standard of measuring CVR.[2] Single photon emission computed tomography and functional magnetic resonance imaging have been used, but limitations such as unavailability and high costs make it difficult to be used as a method. Transcranial Doppler ultrasound (TCD) is well-established as a technique, using velocity measurement (CBv) from the middle cerebral artery (MCA) as an estimate of changes in CBF, following a vasodilatory stimulus.

Acetazolamide infusions have been used, though this may induce hyperventilation which opposes its desired vasodilatory effect. CBv sensitivity to end-tidal carbon dioxide change is well documented.[2] Hence recently, studies on CVR mainly use end-tidal carbon dioxide change either through administered inhaled CO_2 or through breathing manoeuvres to create hyper- and hypocapnic states through which blood flow changes can be observed.[3]

Overall, research looking at CVR is heterogenous due to the use of different vasoactive stimuli, measured parameters, processing methods and populations studied. Therefore, the diversity of protocols makes it difficult to draw conclusions and have comparable results. This perspective will focus on identifying gaps in research on CVR, different approaches and their clinical applications.

Classic approaches to MCA assessment of CVR: $PaCO_2$ challenge is found to be the most appropriate stimulus[3] and as such utilising $PaCO_2$ change as a vasodilatory stimulus in measuring CVR has many features, such as non-invasiveness, easy termination, practicality, and ability to standardise. Hypercapnia can be achieved by the breath-holding test, administering inhaled CO_2 (with medical air) and re-breathing. Hyperventilation, used for hypocapnic responses, causes vasoconstriction.

A great proportion of studies utilise TCD as an efficient, non-invasive, portable and real-time measure of CBv. Changes in MCA velocity (MCAv) as a reflection of CVR must be continuously recorded simultaneously with arterial blood pressure (ABP) and end-tidal carbon dioxide, as baseline measurements, and during manipulation of $PaCO_2$ for at least five minutes. CVR can then be expressed as many different parameters ranging from absolute velocity change, percentage change from baseline per unit of $PaCO_2$ concentration, to a derived breath hold index.

The development of improved functional magnetic resonance imaging, with higher spatial and temporal resolution has more recently led to increasing evidence of intracranial and extracranial artery dilation in response to vasodilatory stimulus. In particular, the observation of diameter changes in the MCA is important, since failing to account for diameter changes can result in an underestimation of MCAv changes during vasodilation. Al-Khazraji et al.[4] demonstrated that hypocapnia MCAv CVR was 70% lower when calculated from flow rather than velocity.

A general consensus exists that MCAv decreases with age. The CVR is contradictory in relation to aging, in a recent systematic review,[5] 11 studies demonstrated that age was associated with reduced CVR, while three studies did not find any correlation between age and CVR.

Classic approaches to internal carotid artery (ICA) assessment of CVR: Reactivity of the ICA is also evident in hypercapnia and typically measured using duplex ultrasound.[6] In this way, alterations in both diameter and velocity can be observed, allowing calculation of changes in flow, shear stress (a tangential force on the endothelium) and resistance parameters.[7] Inherent difficulties exist in measuring velocity and diameter simultaneously, notwithstanding recording concurrent intracranial assessments while manipulating a vasoactive stimulus.[6] Inadequate ICA ultrasound images have led to up to 20% of patients being excluded from studies.[7,8]

Almost all studies observe increases in ICA velocity, shear stress and diameter in response to CO_2 breathing paradigms.[7,9] Over relatively long (15 minutes) acquisition times, and a broad range (50–65 mmHg) of $PaCO_2$, Willie et al.[8] found the ICA to dilate up to 25%; smaller changes were seen with hypocapnia.

Extracranial hypercapnic dilation through the flow-mediated mechanism of shear stress appears evident, as in the peripheral arteries.[9] Although shear stress did not always correlate with ICA diameter changes or ABP.[7] Carter et al.[9] saw strong association between shear stress and diameter in the ICA, but not in the ipsilateral common carotid artery. Koep et al.[7] conjectured that in older age, there may be a greater reliance on increasing perfusion pressure to produce CBF increases in response to hypercapnia, as accounting for ABP explained some of the age differences seen in the MCAv during hypercapnia. There is also some evidence to suggest the speed of response as opposed to amplitude may separate different groups.[7-9]

Similar to MCA reactivity, there are some disparities in studies examining whether reactivity of the extracranial arteries deteriorate with ageing. Miller et al.[10] only observed deterioration with age in males and Koep et al.[7] although saw no discernible differences with age, saw a blunted ICA shear stress response in females.

Combined MCA and ICA studies and challenges: Few studies have monitored both intracranial and extracranial parameters, and even fewer have compared their relative responses.[4,8] Al-Khazraji et al.[4] using magnetic resonance imaging to observe diameter changes found intracranial arteries exhibited greater reactivity in cross-sectional area than extracranial arteries. Although flow changes may be broadly similar, as Carter et al.[9] found, maximal increases occurred at different time points. Indeed, Carter et al.[9] provided evidence that hypercapnic responses in velocity and shear rate occurred firstly in the MCA, followed by the ICA then common carotid artery.

Comparing intracranial velocities with extracranial flow, Willie et al.[8] observed smaller responses in the intra compared with

extracranial vessels. This was statistically different in both the MCA and posterior cerebral artery when compared with the ICA or vertebral artery. However, MCA or posterior cerebral artery diameter changes were not accounted for.

Using high resolution magnetic resonance imaging and different breathing conditions, Al-Khazraji et al.[4] observed cross-sectional area reactivity across nine intra and extracranial arteries; the basilar and anterior cerebral arteries eliciting the most response, the right ICA demonstrating the least. Hypocapnic effects were most marked in the posterior cerebral artery. Changes in ABP correlated with ICA cross-sectional area, but not generally with the intracranial vasculature. Interestingly, Willie et al.[8] observed a marked 50% increase in vertebral artery flow under hypoxia.

Two factors are broadly agreed upon; CVR is not solely modulated by arteriole/pial vessels and is heterogeneous across hyper and hypocapnia states.[4,8]

Cerebrovascular disease state studies and assessments (small vessel disease (SVD), carotid stenosis, ischemic stroke): CVR has been studied in multiple disease populations; however varied methods and assessments mean it is difficult to conclude any possible associations. In patients with cerebrovascular disease, CVR has been adopted as a measure of haemodynamic reserve which can be used to indicate a patient's risk of further complications.[11] Numerous studies have investigated CVR in patients with varying patterns of carotid artery disease. One study performed a review of CVR measurements in stroke risk patients with high-grade stenosis (> 70%) or occlusion in the ICA or MCA. The studies included used either Acetazolamide or inspired CO_2 to produce a vasodilatory response and then used either positron emission tomography, TCD or single photon emission computed tomography to measure CVR. They found a positive relationship between reduced CVR and future ischemic events, suggesting patients with impaired CVR were four times more likely to have a stroke or transient ischemic attack.[11] For patients with asymptomatic (70–99%) carotid stenosis, impaired CVR, derived from breath hold index is one of several clinical and imaging features used to indicate increased stroke risk and as such, form part of a decision tool recommended by European Guidelines in identifying patients for whom revascularisation should be considered.[12]

CVR has also been looked at in patients with SVD. One study carried out a breath-hold test with TCD in SVD patients and found a reduction in CVR compared to matched controls. It has been suggested that the breath-hold test is a good indicator of CVR in such patients and may even be able to predict cognitive impairment within this clinical subgroup.[11]

A recent study used inspired CO_2 and magnetic resonance imaging to measure CVR in mild stroke patients. They were followed up 1 year after their initial event and found that patients with lower CVR experienced more lacunae, microbleeds and white matter hyperintensities. Therefore, suggesting CVR to be a potential biomarker of SVD in mild stroke patients.[13]

Overall, these studies suggest a prognostic application of CVR whereby it acts as an indicator for further complications, particularly in those who have suffered a stroke or those showing characterizations of SVD. They also suggest a prognostic application, with reduced CVR generally leading to a poor prognosis and therefore identifying those of the highest risk, and those who may benefit from more rigorous treatment.

However, the application of CVR clinically is hindered by the heterogeneous techniques, making it difficult to compare results between studies and reach secure conclusions. Therefore, identifying optimal and accessible techniques is important to help reduce disparities between results.

Identified gaps in the literature and future research directions: Aided by technological improvements and advancing methods, our understanding of CBF and its sensitivities to the local environment continuously evolve. Standard procedure settings to observe physiological responses exist[6]; similar standards for vasoactive stimulation, how we measure and judge CVR have yet to be detailed.

Significant vasodilation of the MCA means reactivity may be stronger than first thought and an ability to account for this may aid differentiation amongst both healthy and patient groups.[4] MCA flow appears a promising parameter, through improved functional magnetic resonance imaging techniques, future projects have to overcome the obstacles involved in measuring diameter and velocity concurrently. The relative ease of measuring extracranial flow could invite potential. However, it is unclear to what degree extracranial arteries react to a vasodilatory stimulus. Possibly less amplitude than MCA and possibly more influenced by blood pressure changes, as seen by its greater correlation to ABP in comparison to intracranial arteries,[4] underpinning the importance of continuous ABP during hypercapnic observations.

Numerous protocols exist around vasoactive stimuli, from a time-dependent CO_2 step-wise approach stabilising MCA diameter changes, to breathing paradigms and the less practical achievement of steady state. Protocols for hypocapnic states are even less consistent. Evidence steers towards separating hyper and hypocapnia analysis and, though conflicting at times, suggests there are regional differences between posterior and anterior circulation reactivity.[4] Beyond developing standardised vasoactive stimuli to ease comparison, to produce robust data, optimisation also requires consideration of tolerance in patients, particularly those with cerebrovascular disease, as results among this group remain under-investigated.

Time frame is inextricably linked to stimulus paradigms. Recent data suggest the rate of response rather than amplitude differences may provide greater detectable variations between groups, in particular, with respect to aging.[7] Several studies focus on ageing, yet their cohorts were of above average fitness.[7] Emphasis could shift alternatively towards condition, for example, investigating associations of CVR to blood pressure variability, SVD or hypertension.

Whilst the evidence is demonstrated through a variety of measures, many studies indicate differences between sexes.[7,9] This is worthy of further investigation and future analysis should therefore separate groups. Very few studies have addressed intra-individual differences in CVR,[3] warranting further investigation of reproducibility. **Table 1** provides a summary of these future considerations.

Table 1: Identified gaps and future recommendations of cerebrovascular reactivity

Identified gaps
Hypocapnic effects
Acute and chronic cerebrovascular disease
Intra-subject reproducibility
Regional cerebral differences, including possible greater anterior as opposed to posterior circulatory sensitivity to hypocapnic and hypoxic effects
Future recommendations
Separate males/females
Observation of response rate
Extracranial parameters/reactivity
Standardisation of protocol, expression of cerebrovascular reactivity and nomenclature
Control for arterial blood pressure and other co-variates

Conclusion: Overall, heterogenous methods between studies means the effective use of CVR in a clinical setting remains challenging. Standardisation of such methods and how we express CVR will help reduce disparities. Ensuring these methods are tolerable across all participant populations will allow more meaningful comparisons and translation to clinical populations. Encouraging data is emerging on the potential prognostic ability – with low CVR associated with chronic cerebrovascular disease states. Further longitudinal studies in those with early SVD and/or at high risk of lacunar events is needed.

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