CROSSTALK

CrossTalk opposing view: The middle cerebral artery diameter does not change during alterations in arterial blood gases and blood pressure

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The cerebral circulation is regulated by arterial carbon dioxide tension (P_{aCO_2}) with hypercapnia and hypocapnia increasing and decreasing cerebral blood flow (CBF), respectively (Serrador *et al.* 2000; Ide *et al.* 2003). This relationship between CBF and P_{aCO_2}, termed cerebral vasomotor reactivity, provides a measure of cerebral vascular function. Reduction of cerebral vasomotor reactivity is associated with carotid artery disease (Ringelstein *et al.* 1988), diabetes (Kadoi *et al.* 2003) and hypertension (Lavi *et al.* 2006), and is a predictor and contributor to stroke (Gur *et al.* 1996; Nur *et al.* 2009). Furthermore, cerebral vascular dysfunction has been implicated in other conditions including cognitive dysfunction and Alzheimer's disease (Silvestrini *et al.* 2006; Bar *et al.* 2007). A number of approaches are used to assess cerebral vascular function during perturbations of arterial blood gases or blood pressure. Transcranial Doppler (TCD) assessment of cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) is commonly used for measuring changes in CBF (Aaslid *et al.* 1989). Advantages of TCD include relative ease of use, being fairly inexpensive in comparison with other techniques, being non-invasive, and beat-to-beat data collection thus providing high temporal resolution. However, Doppler ultrasonography, and TCD in particular, cannot image the insonated intracranial blood vessels and thus relies solely on CBFV as an indirect measure of CBF assuming that the diameters of the insonated blood vessels do not change (Aaslid *et al.* 1989; Serrador *et al.* 2000; Claassen *et al.* 2007). Accordingly, any deviations from this assumption need to be considered carefully for TCD interpretation in that, based on the principle of the Hagen–Poiseuille law, a small change in the diameter of the insonated MCA would have an effect on CBF that is not reflected by CBFV.

Earlier work reported changes in diameter of smaller downstream cerebral resistance vessels during alterations in P_{aCO_2} (Huber & Handa, 1967; Giller *et al.* 1993). In the 1960s it was reported that the downstream cerebral arterioles dilated by ∼25% during hypercapnia (P_{aCO_2} of ∼58 Torr) whereas the larger cerebral arteries remained constant during relative eucapnia (Huber & Handa, 1967). These findings are supported by other angiographic studies (Djurberg *et al.* 1998). Additionally, Giller *et al.* (1993) reported an ∼25% dilatation in the anterior cerebral artery (ACA) and the M2 segment of the MCA during hypercapnia (ΔP_{aCO_2} of about +14 Torr); however, the diameter of the larger M1 segment of the MCA remained constant (< 4% change; Giller *et al.* 1993). More recently, Schreiber *et al.* (2000) imaged the M1 segment of the MCA, using magnetic resonance imaging (MRI; scans obtained at 1.5 T), before and during hypercapnia with a range of ΔP_{aCO_2} of +1.4 to 17.2 Torr. There was no effect of this stimulus on the diameter of the M1 segment of the MCA (Schreiber *et al.* 2000). These findings support the notion of a constant diameter of the larger cerebral arteries during changes in P_{aCO_2} and the validity of TCD assessment of CBF with CBFV since it is most commonly performed in the larger more proximal M1 segment of the MCA (Serrador *et al.* 2006; Coverdale *et al.* 2014; Yonan *et al.* 2014). However, the measures of Giller *et al.* (1993) were conducted during craniotomy under anaesthesized conditions while the individuals in the study by Schreiber *et al.* (2000) suffered from chronic internal carotid artery occlusion. It is unknown if these conditions would impact cerebral vascular function thereby masking potential effects of the perturbation. Serrador *et al.* assessed the diameter of the MCA during hypercapnia (ΔCO_2 ∼8 Torr) and hypocapnia (ΔCO_2 ∼12 Torr) using MRI scans at 1.5 T and reported no change in MCA diameter during either stimulus (Serrador *et al.* 2000). The findings in the hypocapnic range are in agreement with a previous study using MRI scans at 1.5 T that reported no change in MCA diameter during hypocapnia (ΔCO_2 ∼ 12 Torr; Valdueza *et al.* 1997). Importantly, these MRI studies were conducted in healthy individuals and thus lend support to the aforementioned findings of a constant MCA diameter of the M1 segment during alterations in blood gases (Huber & Handa, 1967; Giller *et al.* 1993; Djurberg *et al.* 1998; Schreiber *et al.* 2000).

In recent years, several studies have assessed blood flow in the extracranial arteries that feed the cerebral circulation including the internal carotid artery (ICA) and vertebral artery (VA). This approach combined with simultaneous measures of

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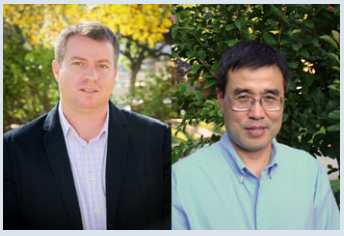

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CBFV in the MCA during changes in arterial blood pressure to assess cerebral autoregulation (Liu *et al.* 2013) and changes in arterial blood gases to assess extracranial and intracranial vascular reactivity has led to conclusions that there are some discrepancies between changes in blood flow in the ICA and CBFV assessed in the MCA by transcranial Doppler (Willie *et al.* 2012; Coverdale *et al.* 2014, 2015). Such findings may imply that the diameter of the MCA does in fact change during alterations in blood gases and/or arterial blood pressure. However, as of now there is no definitive evidence that changes in extracranial blood flow are linearly linked with changes in specific intracranial blood vessels (Thomas *et al.* 2015). This is particularly true of the ICA, which in addition to the MCA also delivers blood to the anterior cerebral artery (Willie *et al.* 2012; Liu *et al.* 2013). More direct measures are achievable using MRI. The aforementioned studies reporting no change in the M1 segment of the MCA were conducted using MRI scans at 1.5 T using imaging parameters that may have low spatial resolution (Serrador *et al.* 2000). Recent studies have been performed using high magnetic field strength of 3.0 T (Coverdale *et al.* 2014, 2015) and 7.0 T (Verbree *et al.* 2014) with high spatial resolutions (< 1mm). These studies reported a significant vasodilatation in the MCA of approximately 8% during higher degrees of hypercapnia (ΔCO_2 ~10–15 Torr; Coverdale *et al.* 2014, 2015; Verbree *et al.* 2014), while no changes in the MCA diameter during a less severe hypercapnia (ΔCO_2 about +7 Torr; Verbree *et al.* 2014). Thus, whether or not the diameter of the MCA changes is likely to be dependent on the magnitude of changes in P_{aCO_2} (Ainslie & Hoiland, 2014; Coverdale *et al.* 2014, 2015; Verbree *et al.* 2014). Hypercapnia results in increases in mean arterial pressure (MAP) and changes in cerebral autoregulation (Coverdale *et al.* 2014, 2015). Therefore, changes in MCA diameter during higher degrees of hypercapnia may be related to cerebral autoregulation in response to changes in blood pressure rather than hypercapnia *per se.* These studies also reported relatively small vasoconstriction in the MCA of ~1–4% during hypocapnia (ΔCO_2 about –7.5 (Verbree *et al.* 2014) and about −13 Torr (Coverdale *et al.* 2014, 2015)), interpreted as the cerebral circulation being in a tonic state of vasoconstriction resulting in a reduced effect of hypocapnia to induce further constriction (Coverdale *et al.* 2014, 2015; Verbree *et al.* 2014).

The effect of changes in blood pressure on the MCA diameter is even less understood than that of arterial blood gases. The ACA and M2 segment of the MCA dilated ~25% whereas the M1 segment of the MCA was unaffected during large alterations in blood pressure (Δ range of 30 mmHg during nitroprusside and phenylephrine infusion; Giller *et al.* 1993). Furthermore, the M1 segment of the MCA was unchanged during moderate hypotension in healthy humans as assessed using 1.5 T MRI (Serrador *et al.* 2000). Currently, there are few studies that have been designed to directly assess the relationship between changes in blood pressure and diameter of the MCA.

In conclusion, strong evidence indicates that the M1 segment of the MCA averaged over cardiac cycles under steady-state haemodynamic conditions remains relatively constant during moderate changes in arterial blood gases and blood pressure. However, we caution that the findings opposing this view, particularly during larger changes in blood gases and blood pressure, cannot be ignored. This degree of uncertainty combined with the physiological and clinical significance of regulation of the cerebral vasculature in health and disease highlights the importance of continued research in this area. With the advent of more innovative study designs and high temporal and spatial resolution neuroimaging methodologies it is likely that more definitive answers to this highly debated and relevant topic are to come.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.