CROSSTALK

Comments on Crosstalk 30: The middle cerebral artery diameter does/does not change during alterations in arterial blood gases and blood pressure

Assessing the context and impact of potential changes in middle cerebral artery diameter

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The surrogate measurement of cerebral blood flow (CBF) in the middle cerebral artery (MCA) via transcranial Doppler ultrasound is a widely utilized technique in both clinical (Djurberg *et al.* 1998) and exercise (Périard & Racinais, 2015) settings. Whether changes in MCA diameter occur when arterial blood gases and blood pressure are altered has a significant impact on our understanding of cerebrovascular function within these settings. Based on the available evidence and this CrossTalk debate (Brothers & Zhang, 2016*a*; Hoiland & Ainslie, 2016*a*), it appears that uncertainty remains as to the extent and impact a change in MCA diameter might have on cerebrovascular function. For example, it has been suggested that an ∼2% change in MCA diameter (i.e. dilatation) can result in an ∼4% (Brothers & Zhang, 2016*b*) or even ∼8% (Hoiland & Ainslie, 2016*a*) change in volumetric CBF at a given MCA mean blood velocity. Accordingly, several context-specific (e.g. hyperthermic or hypoxic exercise) avenues of research remain to be explored with the use of high resolution technologies (e.g. magnetic resonance imaging; MRI) to determine whether the MCA diameter changes with alterations in arterial blood gases and blood pressure. The precise determination of the impact of these changes on cerebral metabolic and neural function also requires additional investigation. Perhaps the primary avenue of research remains in identifying the extent, if any, to which MCA diameter changes in specific settings (Hoiland & Ainslie, 2016*a*) and whether this change appreciably impacts upon the assessment of cerebrovascular function (Brothers & Zhang, 2016*b*).

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Additional information

Competing interests

None declared.

'The emperor has no clothes'– and probably never did

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Transcranial Doppler is a non-invasive technique we use clinically for cerebral microemboli detection, for middle cerebral artery (MCA) velocity determination during carotid cross-clamping and to assess MCA 'spasm' post sub-arachnoid haemorrhage. On 21 May 2007, during a 5 day sojourn at 7950 m on Everest, transcranial colour Doppler examinations were performed on profoundly hypoxic and hypocapnic mountaineers (Grocott *et al.* 2009). The MCA diameters (MCA_{Diam}) were almost twice those observed at sea level and were so remarkable they were re-measured with subjects on supplementary oxygen. MCA_{Diam} values rapidly reverted to sea level values. That the MCA_{Diam} could vary was confirmed in a study comparing 3T MRA and transcranial colour Doppler (Wilson *et al.* 2011). Others have demonstrated variability in both extracranial and intracranial arterial diameters during acute changes in arterial blood gases (ABGs) (Willie *et al.* 2012) and simultaneously investigated arterial and venous changes over 22 h (Sagoo *et al.* 2016).

The commonly used 'MCA flow velocity' reflects the widely held and convenient assumption that MCA velocity is a surrogate for flow. This is based upon the questionable premise that MCA_{Diam} does not vary. Quite why the cerebral arterial tree should, unlike all other medium sized arteries in the body, not vary when physiologically challenged is a major conceptual concern. Indeed, previous recognition that MCA_{Diam} does vary, appears to have been forgotten in the rush to endorse a simple non-invasive imaging modality. Mild aesthetic hyperventilation caused vasoconstriction whereas profound hypocarbia caused paradoxical MCA_{Diam} angiographic vasodilatation (du Boulay & Simon, 1971). Caution should be exercised when interpreting transcranial Doppler (TCD) 'flow velocity' when ABGs change.

It may be time for some to consider a visit to the optician (Giller, 2003).

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The Journal of Physiology

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Additional information

Competing interests

None declared.

Transcranial Doppler ultrasound still has a role in cerebrovascular research . . .

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Diameter changes in cerebral conduit vessels (middle and posterior cerebral arteries – MCA/PCA) has been a crux for transcranial Doppler (TCD) ultrasound research for decades (Aaslid *et al.* 1982). Hoiland & Ainslie (2016) present the argument that although MCA diameter remains unchanged with small (∼5 mmHg) CO_2 alterations, this notion doesn't hold true during large variations (> 10 mmHg). Brothers & Zhang (2016) agree that diameter changes are likely under these conditions; however, the actual change in cerebral blood flow (CBF) is minimal (∼4%). To counter the unknown diameter issues associated with TCD, Hoiland & Ainslie (2016) proposed the use of high resolution extracranial artery duplex ultrasound to quantify CBF. While this method does measure flow, as both diameter and velocity are recorded, it has the limitation of the subject being stationary while testing, precluding its use in situations including exercise and dynamic cerebral pressure flow (Smirl *et al.* 2015). Interestingly, the between-day reproducibility of MCA velocity measurements (∼2–3%) previously reported (Smirl *et al.* 2015; Smith *et al.* 2016) is comparable to CBF reproducibility in the extracranial vessels (∼4–5%) (Smith *et al.* 2016) and approximates the CO_2 induced changes in CBF proposed by Brothers and Zhang as a result of theoretical MCA diameter changes (Brothers & Zhang, 2016). Thus, while duplex ultrasound is a viable option for some CBF studies, for others such as those involving dynamic movements of the subjects, the functionality of TCD under these conditions cannot be discounted.

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Additional information

Competing interests

None declared.

Middle cerebral artery diameter changes during hypercapnia: impact on estimates of cerebrovascular reactivity

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Recent imaging data provide the first evidence of middle cerebral artery (MCA) dilatation in conscious humans with changes in end tidal carbon dioxide (CO_2). The debate now turns to details such as mechanism(s) of dilatation during hypercapnia and the role of blood pressure, and problems of the *extent* and *time course* of dilatation. Our data suggest that an increase in MCA diameter can occur after 1 min of 6% CO_2 while mean arterial pressure increased only from 82 ± 8 to 83 ± 9 mmHg (Coverdale *et al.* 2015), minimizing the passive dilatation hypothesis. In any case, future studies should verify this assessment by examining MCA diameter with higher resolution MRI at a low level of CO_2 to minimize blood pressure changes. Brothers and Zhang's rebuttal raises the issue of whether or not 'important' changes in diameter occur under physiological conditions in which MCA velocity measures are made. The time course of dilatation becomes an important element of this discussion. MRI-based measures currently suffer from poor temporal resolution, providing a single averaged measure of diameter over about 1 min. Within this limitation, MCA dilatation during a hypercapnic/hypocapnic test varies across individuals but can begin within the first minute, and peak after approximately 3 min, despite the consistent stimulus (Coverdale *et al.* 2015). Clinical applications often rely on the standardized 'cerebrovascular reactivity' to a 5–6% CO_2 gas mixture over 5 min. In this case, the reactivity increases from 3.13 ± 1.55% $mmHg^{-1}$ based on MCA velocity to 4.88 ± 2.46% $mmHg^{-1}$ based on MCA flow, a difference of 58 ± 25%

(Coverdale *et al.* 2015): this difference in estimates is not negligible.

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Additional information

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None declared.

Do you use transcranial Doppler-determined blood velocity in middle cerebral artery as an index of cerebral blood flow?

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Each side of this CrossTalk debate presents data from previous studies to support its claim. However, the most important question here is whether transcranial Doppler (TCD)-determined blood velocity can be used as an index of cerebral blood flow (CBF) changes under physiological conditions. Some previous studies (Coverdale *et al.* 2014; Verbree *et al.* 2014) demonstrated that hypercapnia increased the middle cerebral artery (MCA) diameter, but those studies employed severe physiological conditions (+10–15 mmHg). Verbree *et al.* (2014) in the same study reported that the MCA diameter was unchanged by +7.5 mmHg hypercapnia. Similarly, Wilson *et al.* (2011) reported that the MCA diameter was changed at extremely high altitudes (6400 m altitude, 9% O_2); however, they also indicted that large differences were not observed in blood velocity and flow in MCA (11.7% and 13.1%, respectively) at an altitude of 5300 m. However, with heavy exercise, blood velocity changes in the posterior cerebral artery (PCA) (Yamaguchi *et al.* 2015) were the opposite of blood flow changes in the vertebral artery, which is upstream of PCA (Sato *et al.* 2011). This indicates that compared with MCA, the diameter of the peripheral or small vessels in the cerebral vasculature, such as PCA, may be altered to a greater extent with heavy exercise, affecting flow responses. Although careful consideration regarding the physiological condition for TCD measurement is needed, I believe that TCD-determined cerebral blood velocity can be used to estimate CBF changes, at least in MCA, under physiological conditions.

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Additional information

Competing interests

None declared.

Phenylephrine-induced increases in arterial blood pressure and transcranial Doppler-determined middle cerebral artery mean flow velocity

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Authors from this debate (Brothers & Zhang, 2016; Hoiland & Ainslie, 2016*a*) highlight important issues about the constancy (or lack of) of the middle cerebral artery (MCA) diameter during alterations in blood pressure (BP). One matter related to this discussion is the utilization of transcranial Doppler (TCD) ultrasound to monitor changes in MCA velocity following vasopressor-induced increases in BP. Elevations in MCA velocity have been reported following steady-state (Lucas *et al.* 2010; Ogoh *et al.* 2011) and acute (i.e. following a bolus infusion) (Brassard *et al.* 2010) increases in BP with phenylephrine. One may interpret these findings as an increase in cerebral blood flow (CBF) if assuming a constant MCA diameter with phenylephrine. However, in the study by Ogoh *et al.* (2011) they also used Duplex ultrasound to monitor internal carotid artery (ICA) flow in addition to the TCD-determined MCA velocity, and demonstrated that infusion of phenylephrine was associated with vasoconstriction such that CBF was not significantly increased when measuring *flow* in the ICA (Ogoh *et al.* 2011).

For TCD to remain a valid modality for CBF monitoring, investigators need to consider what possible changes in the insonated vessel would mean for their findings (i.e. the underestimation/overestimation of CBF), particularly if their sole measure of CBF is estimated by MCA velocity. Consequently, and as highlighted by others (Hoiland & Ainslie, 2016*b*), a multimodal assessment approach should be strongly encouraged to ensure the appropriate physiological interpretation of changes in MCA velocity, and ultimately what effect an intervention is having on CBF.

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Additional information

Competing interests

None declared.

Cerebrovascular reactivity to carbon dioxide and the systemic pressure confound

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I read with interest the crosstalk articles by Brothers & Zhang (2016) and Hoiland & Ainslie (2016) discussing the effects of systemic pressure on the diameter of the middle cerebral artery. My concern is with the subsequent use made of such flow measurements to measure the responsiveness of the cerebrovasculature to vasodilatory stimuli such as carbon dioxide (CO_2). In these circumstances, changes in mean arterial blood pressure (MAP) with CO_2 become a major confound, and cerebrovascular reactivity (CVR), measured as the ratio change in blood flow to change in CO_2, does not estimate the vasoactive effect of CO_2 (Battisti-Charbonney *et al.* 2011; Fan *et al.* 2016). Attempts to account for the pressure confound by calculating the conductance as the ratio of change in blood flow to change in blood pressure do not account for the complicated interactions of CO_2-induced changes in MAP and CO_2-mediated vasodilatation. An increase in MAP has three effects on flow. First, the obvious hydraulic effect that increases flow even if vascular resistance is unchanged. Second, the autoregulatory effect of an increase in perfusion pressure to increase vascular resistance and thereby minimise the pressure-induced increase in flow. Third the hydraulic effect to increase the vessel diameter. Which of these factors play a role is currently indeterminate, and so measurements of the vasoactive effects of hypercapnia are uncertain and untrustworthy when MAP increases in hypercapnia (Regan *et al.* 2014), and comparisons of CVR between groups or subjects with different MAP responses to hypercapnia are problematic.

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Additional information

Competing interests

None declared.

The data must dictate our research practices

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Ever since the introduction of transcranial Doppler (TCD) ultrasound over 30 years ago, the assumption of constant vessel diameter has been challenged (Kontos, 1989; Giller, 2003). In fact, while Giller and colleagues were among the first investigators to report relatively small changes in the diameter of some major intracranial vessels with variations in arterial pressure and arterial CO_2 during craniotomy (Giller *et al.* 1993), 10 years later Giller cautioned the common practice of assuming constant vessel diameter under all physiological and pathological conditions, particularly if this assumption had not been experimentally verified (Giller, 2003). As a research community, we have enthusiastically welcomed the publication of evidence that supported this assumption, including the direct measurements during craniotomy (Giller *et al.* 1993), and magnetic resonance imaging (MRI) data from a number of investigators at the turn of the century (Valdueza *et al.* 1997; Serrador *et al.* 2000). Perhaps this is why the most recent reports that MCA diameter does change with physiologically relevant hypo- and hypercapnia from investigators employing much higher resolution MRI (Coverdale *et al.* 2014; Verbree *et al.* 2014) have been challenging to accept.

As a community, however, these findings should encourage us to continue developing and refining novel methodological approaches that do not rely on these assumptions, including transcranial colour-coded Doppler, near infrared spectroscopy for assessment of cerebral oxygenation, and others. Our data and our conclusions are only as definitive as the technology we employ to make the measurements; let's work together to close the gap between assumption and reality.

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Additional information

Competing interests

None declared.

To measure diameter or not: experimental design is key

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We commend the authors for their discussion. Emerging evidence suggests middle cerebral artery (MCA) diameter is dynamic, which may profoundly impact interpretation of cerebral blood flow (CBF) regulation.

Current data indicate MCA diameter changes depending on both stimulus strength and duration. For example, mild changes in arterial blood gases (P_{CO_2} < 7.5 mmHg, or P_{O_2} > 50 mmHg) appear not to change MCA diameter (Wilson *et al.* 2011; Verbree *et al.* 2014), providing many physiologically relevant study opportunities. Conditions such as sleep apnoea, or exposure to moderate altitude are often associated with similar mild alterations in arterial blood gases. Stimulus duration is also an important consideration. MCA diameter changes take 3 min during hypercapnia (Coverdale *et al.* 2015) and may take up to 45 min during hypoxia (Imray *et al.* 2014). Thus, experiments manipulating gases within moderate ranges and for a controlled duration might utilize MCA blood flow velocity to investigate CBF regulation.

Absolute CBF quantification during more severe alterations in arterial blood gases (and possibly blood pressure) require advanced imaging techniques, such as MRI (Wilson *et al.* 2011; Coverdale *et al.* 2015). The MCA is one of many vital arteries comprising the complex cerebral circulation. High-resolution imaging that can measure multiple arteries is needed to address this complexity and advance our *quantitative* understanding of CBF regulation. However, imaging is not without its practical limitations (temporal resolution, movement artifacts, cost, etc.). Ultimately, the validity of CBF measurements via ultrasound and/or advanced imaging is defined by the experimental context.

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Additional information

Competing interests

None declared.

Method to the madness – interpreting measures of cerebrovascular health

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This debate highlights recent technological advancements in Doppler ultrasound and functional magnetic resonance imaging (fMRI) that allow us to measure brain vessel function with higher spatial resolution (Brothers & Zhang, 2016; Hoiland & Ainslie, 2016). These different techniques have revealed conflicting findings for key markers of brain vascular health (e.g. resting 'flow' and/or cerebrovascular responsiveness to carbon dioxide ($CVR\text{-}CO_2$); (Bailey *et al.* 2013; Thomas *et al.* 2013); perhaps resulting from how such measures are derived (i.e. blood flow velocity, blood flow or changes in blood-oxygen level dependent (BOLD) signal), methodological variations between and within studies, and/or pertinent study population characteristics.

This issue is well illustrated in Braz and colleagues' recent study (2016), where age and fitness effects for baseline blood flow were different depending on the Doppler technique used (i.e. Duplex Doppler showed fitness but not age effects, whereas transcranial Doppler (TCD) showed age but not fitness effects). Given the potential for middle cerebral artery (MCA) diameter changes with ageing and to CO_2, perhaps lack of MCA diameter constancy accounts for their differential findings (including the trend for a differential effect with $CVR\text{-}CO_2$).

Considering the accessibility and functional testing advantages of TCD, researchers will continue to use this approach to assess brain vascular health and the effectiveness of interventions (e.g. exercise training). Therefore, further research is needed to validate and quantify

TCD measures against other brain perfusion measures (e.g. MRI, Duplex Doppler, near-infrared spectroscopy). Finally, like other dynamic non-invasive physiological measures, interpretation of TCD data must carefully consider measurement constraints.

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Additional information

Competing interests

None declared.

Transcranial Doppler remains a good tool for measuring cerebral blood flow: understanding vessel diameter/calibre and the limits of validity

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While a very informative and important CrossTalk, I believe we must ask why we are interested in middle cerebral artery (MCA) diameter changes. The impetus for this research was to determine if transcranial Doppler (TCD) could be used to represent cerebral blood flow changes. In fact, diameter changes were only detected with increases in end tidal CO_2 of greater than 7 mmHg (Coverdale *et al.* 2014, 2015; Verbree *et al.* 2014) and only after 3 min of extreme hypercapnia (> 50 mmHg) or 5 min of significant hypocapnia (< 25 mmHg) (Coverdale *et al.* 2015). The exact same was true when comparing percentage changes in internal carotid artery (ICA) flow to MCA flow (Coverdale *et al.* 2014).

Thus, these data suggest that during normal physiological changes in ET_{CO_2} seen in most laboratory conditions, MCA diameter remains stable and TCD is a valid estimate of cerebral blood flow (CBF). This is also true for conditions of greater hyper- or hypocapnia, if less than 3 min. Therefore, data testing cerebral blood flow response to CO_2 should be limited to 2 min exposures to ensure MCA dilatation does not occur. Since TCD allows the flexibility to obtain data in many unique paradigms (whole body exercise, artificial gravity, spaceflight, ICU, sleep, etc.), its use continues to provide a wealth of knowledge that we cannot yet obtain with other imaging paradigms. In summary, TCD remains a valid tool to assess CBF regulation and should be interpreted with the knowledge that large changes in ET_{CO_2} (> 7 mmHg) for several minutes (> 3 min) will affect its interpretation.

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Additional information

Competing interests

None declared.

Modality and methods impact the interpretation of cerebral blood flow

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Recent studies indicate substantial heterogeneity between different cerebral blood vessels, particularly the middle cerebral artery (MCA) and internal carotid artery (ICA), in response to arterial blood gas changes (Willie *et al.* 2012; Coverdale *et al.* 2015; Kellawan *et al.* 2016). Thus, inferring changes in MCA diameter based on other vessels is problematic. Additionally, the divergent responses are likely to be related to differences in (1) experimental controls, (2) duration of the stimulus, and (3) measurement technique.

Ultrasound and neuroimaging studies should be compared with caution. Each technique has inherent limitations based on temporal/spatial resolution and assumptions. Neuroimaging modalities quantify intracranial blood flow, cross-sectional area or blood flow velocity, which may not correspond to ultrasound-derived measurements. Comparisons of ICA and VA measurements with phase-contrast MRI and colour-coded duplex ultrasound were correlated, but with method-dependent variability between individuals. Ultrasound resulted in a 30% overestimation of flow velocity and 12% smaller ICA diameter compared with phase-contrast MRI (Khan *et al.* 2016).

A final consideration is elevated MAP during arterial blood gas changes, which may impact cerebral vessel diameter. Greater MAP, independent of P_{CO_2}, elevated ICA and VA resistance without corresponding changes in blood flow (Warnert *et al.* 2015), whilst no changes in resistance of smaller vessels above the circle of Willis, were observed. Thus, alterations in MAP can

influence diameters of a variety of cerebral vessels.

Our perspectives lead us to support the idea that arterial blood gases and/or MAP fluctuations are likely to change MCA diameter; however the magnitude of change and its effect on regional cerebral perfusion remain to be determined.

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Additional information

Competing interests

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Middle cerebral artery diameter: another difficult measurement

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Over 40 years ago McDonald (1974) analytically presented the complexities of blood flow in arteries. This dynamic convolution of pulsatile pressures, changing velocity profiles, and moving arterial walls challenges the accuracy and precision of all non-invasive measurements. All techniques have limitations with competing spatial, temporal and dynamic resolutions. Thus, reports should include measurement resolutions, uncertainties and quality control validations (Evans & McDicken, 2000).

Hoiland & Ainslie and Brother & Zhang present clear, concise, and complete evidence to support their conflicting diameter positions. Ultimately, the issue depends on the range of the measured variable, overall resolution of the transduction/signal, systematic errors/bandwidth of the device, skill of the operator and significance of the outcome. Obviously, the dynamic middle cerebral artery (MCA) diameter varies directly or indirectly with pressure and blood gases. Significance is determined by this question. How much does it change and how well can we measure it? MCA diameters of 2.0–3.0 mm with mean and phasic changes of 5–10% (0.1–0.3mm) under normal physiological conditions are currently very difficult to measure non-invasively. Given the significant composite assumptions, uncertainties, sources of errors, and the limited *in vitro* and *in vivo* validation reports, the 95% confidence levels for relative changes in MCA blood flow, as conveniently indexed by changes in MCA blood velocities/frequency shifts and assuming a constant diameter, are at best, within 10–20%. This range can clearly increase with more dramatic conditions, interventions and disease states. Nevertheless, a solid power analysis will allow many meaningful hypotheses to be tested even with the false, but reasonable and practical, assumption of a constant diameter.

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Middle cerebral artery diameter in varying age groups and breathing gas mixtures

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The CrossTalk debate on middle cerebral artery (MCA) diameter changes during alterations in arterial blood gases and blood pressure (BP) covers various aspects that have to be considered during research (Brothers & Zhang, 2016; Hoiland & Ainslie, 2016). There is change in MCA diameter during gas-mixture breathing (henceforth, changing arterial blood gas) (Wilson *et al.* 2011), but how much is too much? It is important that we consider the changes in diameter that lead to a statistically significant discrepancy during the flow measurements. To my knowledge, there are no studies in consideration of this and it has not been well addressed in the debate. Secondly, there have been studies across varying age groups to estimate cerebral blood flow responses (Barnes *et al.* 2012) using transcranial Doppler. Here, we have to take into consideration that the biology of arteries changes with ageing, and this is likely to reflect changes in their ability to dilate and constrict (due to differential production of nitric oxide, prostaglandins and other vaso-mediators). This might be pertinent in cases where the population varies with conditions such as metabolic syndromes (Tyndall *et al.* 2016). Most of the integrative studies that have used human subjects lack estimation of such vascular biomarkers. Future research needs to consider these aspects along with the possibility of MCA diameter estimation.

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Additional information

Competing interests

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