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"To measure is to know": no relationship between cerebrovascular and peripheral shear-mediated dilation in young adults

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Endothelial dysfunction is the first detectable manifestation of the atherosclerotic process, and its measurement is of both clinical and research importance. Vascular function in conduit arteries is promoted through shear-mediated dilation, where increases in shear-stress induce vasodilation through nitric oxide (NO) production. This is known as endothelium-dependent dilation, and is assessed in the peripheral vasculature through flow mediated dilation (FMD) of the brachial artery. This technique is associated with coronary artery endothelium-dependent vasodilation and is predictive of cardiovascular events. Endothelial dysfunction of the internal carotid artery (ICA) is a risk factor for cerebrovascular diseases (such as stroke, dementia and Alzheimer's disease), but whether brachial FMD is associated with cerebral endothelium-dependent vasodilation is unknown. Typically, cerebrovascular function is assessed by cerebrovascular reactivity (CVR) of middle cerebral artery blood velocity (MCAv) to carbon dioxide (CO_2). Although linked to FMD (Ainslie *et al.*, 2007), this approach has poor predictive value in healthy populations, measures only blood velocity (not vessel dilation) and does not isolate a shear-mediated response.

In a recent issue of *The Journal of Physiology*, Carr *et al.* (2020) explored the relationships between ICA and brachial artery shear-mediated dilation in 19 healthy adults (23±6 years). They also explored the endothelium-*independent* responses of these arteries, through glyceryl trinitrate (GTN) administration. Brachial artery shear-mediated dilation was assessed by FMD, and the authors utilised a cerebral-FMD protocol (cFMD) developed by Hoiland *et al.* (2017) for the ICA. In short, the cFMD test involved Duplex ultrasound imaging of the ICA during and following a rapid +9 mmHg increase in end-tidal CO_2 ($P_{ET}CO_2$) for 30 seconds. This test has been shown to be predominantly shear-stress mediated, with the subsequent ICA dilation significantly related to shear-rate area under the curve (SRAUC) (Hoiland *et al.*, 2017). This provides a suitable "FMD-equivalent" for the cerebrovasculature, where ischemia-induced hyperaemia is not possible. This is in contrast to "traditional" CVR tests involving sustained hypercapnia (typically 3–5 minutes), where the relationships between shear stress and ICA diameter can be secondary to other confounding factors (e.g. increases in blood pressure and cardiac output). Indeed, another strength of the study by Carr *et al.*, was the inclusion of a 5-minute hypercapnic CVR test to explore the relationships between ICA cFMD and commonly-used outcomes of MCAv- and ICA-CVR.

The primary finding was that ICA and brachial artery responses were not correlated in both the endothelium-dependent (FMD, $r^2 = 0.00$, $P = 0.93$) and independent (GTN, $r^2 = 0.12$, $P = 0.19$) tests, and this was maintained when data were allometrically scaled to account for between-artery differences in baseline diameter. Furthermore, ICA cFMD was not significantly related to MCAv or ICA blood flow CVR responses. These findings indicate that assessments of peripheral FMD and CVR cannot be used as surrogates of ICA endothelium-dependent function. These novel findings merit further discussion with respect to: (1) the lack of association between baseline cerebrovascular and peripheral artery shear-mediated function and (2) the lack of association between ICA endothelium-dependent function and traditional CVR outcomes.

Lack of association between baseline cerebrovascular and peripheral artery shear-mediated function

The absence of a significant correlation between peripheral and cerebral vascular function suggests that healthy adults with a greater FMD do not necessarily have a greater cFMD. Therefore, peripheral arterial function cannot be used to infer ICA function in this population, but rather a direct assessment of ICA shear-mediated dilation is required. Importantly, brachial FMD is typically used as a measurement of cardiovascular health in observational and interventional studies, but these data suggest that we cannot extrapolate previous observations from the peripheral vasculature to cerebrovascular function. However, these data are only available in healthy adults, and it remains to be explored whether populations with impaired FMD (such obesity, cardiometabolic disease) also present with impaired cerebral endothelium-dependent vasodilation, and importantly, whether chronic impairments in the two vascular beds are related. These data would be essential in exploring and discerning the effects of chronic conditions on both cardiovascular and cerebrovascular disease risk.

In addition, these findings can be developed in an acute setting. Initial evidence suggests that cerebrovascular and peripheral vascular function share the same NO-mediated pathway (Ainslie *et al.*, 2007). So, although unrelated at baseline, it remains to be determined whether acute alterations in FMD (for example following exercise, a postprandial or a stress challenge) are mirrored by a similar cFMD response. Importantly, the acute *changes* in shear-mediated function of the brachial artery and ICA within an individual may be significantly related, even though they share no association *between* individuals at baseline. This would provide support for a common NO-mediated pathway between vascular beds, which could be further explored in NO blockade studies. Previous evidence has demonstrated an association between the overnight fall in FMD and CVR (Ainslie *et al.*, 2007), but this warrants further investigation in different acute settings using new techniques of assessing cerebrovascular shear-mediated function. Furthermore,

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studying cerebrovascular and peripheral shear-mediated function following different interventions would provide valuable data on the vascular-specific benefits of interventions (such as exercise training) and how a stimulus could be optimised for peripheral and cerebrovascular health.

A strength of the paper by Carr *et al.*, is the use of allometric scaling of FMD to account for differences in baseline diameter between arteries. In terms of future research, this will become a particularly important consideration for studies where comparisons will be made between arteries, between populations and pre-post acute or chronic interventions, where differences and changes in artery diameter should be accounted for to avoid these confounding influences.

Lack of association between ICA endothelium-dependent function and traditional CVR outcomes

Another key finding from the study by Carr *et al.*, was the lack of a relationship between cFMD and the MCAv and ICA response to a "traditional" CVR test involving 5 minutes of hypercapnia. CVR tests are often considered to reflect cerebrovascular endothelial function, but these results indicate that "typical" CVR outcomes (ICA dilation, ICA-CVR and MCA-CVR expressed as %/mmHg) do not reflect shear-mediated ICA function. Indeed, there was no significant association between ICA dilation in the cFMD and CVR tests, and it is likely that CVR challenges cause ICA vasodilation through non-shear-mediated and endothelium independent mechanisms, as well as a shear-stress mediated endothelium-dependent mechanism.

In contrast to the cFMD test which provides a peak shear-stress challenge to the cerebrovasculature, CVR tests provide a steady-state hypercapnic challenge. CVR data is often reported as an average of "steady-state" blood flow (or velocity) change relative to the increase in $P_{ET}CO_2$. These data are typically taken from after the third minute of the response, and it is likely that these are influenced by confounding factors that occur with sustained hypercapnia (for example, significant elevations in blood pressure), likely contributing to the weak relationship between cFMD and CVR. A recent study utilised a kinetic modelling approach to MCAv data during a steady-state hypercapnic CVR test (Tallon *et al.*, 2020). It is possible that this onset, time-based response may have a better relationship with cFMD than commonly reported steady-state changes, as they may be less confounded by factors secondary to sustained hypercapnia. Future research exploring relationships between cFMD outcomes and alternative methods of CVR analysis would provide important data on the most appropriate handling of CVR data, for situations where Duplex ultrasound scanning is not possible, or end-tidal forcing may not be appropriate (for example, in children).

Given the above, the cerebral-FMD challenge used by Hoiland *et al.*, (2017) and Carr et al., (2020) appears to be a more appropriate test of cerebrovascular function that better measures predominantly shear-mediated dilation, compared to "traditional" CVR tests. However, Carr et al., (2020) did not report the relationship between SRAUC and dilation in neither the brachial nor internal carotid artery, though previous work has reported an $r^2 = 0.44$ for the cFMD test (Hoiland *et al.*, 2017). Continuing to report these relationships is an important consideration for future work studying shear-mediated responses of the cerebrovasculature, particularly when comparisons are being made between groups (for example, in the context of ageing). In the peripheral vasculature, SRAUC and brachial FMD dilation are significantly related in young adults, but are not associated in children or older adults (Thijssen *et al.*, 2009). It would be important to explore whether this extends to the cerebrovasculature, particularly for future work investigating cerebrovascular function and the role of shear-stress across the lifespan.

Brachial artery FMD is often considered the gold-standard, non-invasive assessment of peripheral vascular function as it is known to be endothelium and NO-dependent. Furthermore, FMD is reliable, related to coronary arterial function, associated with cardiovascular disease status and predictive of cardiac events. Before we can consider cFMD a true cerebral-equivalent of FMD, essential data on the underpinning mechanisms of this response, alongside its reliability, sensitivity to cerebrovascular disease risk, prognostic power and association with cerebral microvascular function is essential to determine. Overall, these novel findings from Carr *et al.* (2020) address an important research gap and demonstrate vessel-specific endothelium-dependent function in healthy young adults. This work is instrumental in informing valuable future research to better measure and understand both cerebrovascular function and dysfunction.

References

Ainslie PN, Murrell C, Peebles K, Swart M, Skinner MA, Williams MJ & Taylor RD. (2007). Early morning impairment in cerebral autoregulation and cerebrovascular CO2 reactivity in healthy humans: relation to endothelial function. *Exp Physiol* **92**, 769–777.

Carr JMJR, Hoiland RL, Caldwell HG, Coombs GB, Howe CA, Tremblay JC, Green DJ & Ainslie PN. (2020). Internal carotid and brachial artery shear-dependent vasodilator function in young healthy humans. *J Physiol*, https://doi.org/10.1113/JP280369.

Hoiland RL, Smith KJ, Carter HH, Lewis NCS, Tymko MM, Wildfong KW, Bain AR, Green DJ & Ainslie PN. (2017). Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia. *Am J Physiol Heart Circ Physiol* **313**, H24-H31.

Tallon CM, Barker AR, Nowak-Fluck D, Ainslie PN & McManus AM. (2020). The influence of age and sex on cerebrovascular reactivity and ventilatory response to hypercapnia in children and adults. *Exp Physiol* **105**, 1090–1101.

Thijssen DH, Bullens LM, van Bemmel MM, Dawson EA, Hopkins N, Tinken TM, Black MA, Hopman MT, Cable NT & Green DJ. (2009). Does arterial shear explain the magnitude of flow-mediated dilation?: a comparison between young and older humans. *Am J Physiol Heart Circ Physiol* **296**, H57–H64.

Additional information

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