CROSSTALK

Rebuttal from Y. C. Tzeng and R. B. Panerai

Y. C. Tzeng[1] and R. B. Panerai[2]
[1]*Wellington Medical Technology Group, Centre for Translational Physiology, University of Otago, Wellington, New Zealand*
[2]*Department of Cardiovascular Sciences, University of Leicester, Leicester, UK*
Email: shieak.tzeng@otago.ac.nz

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The central question of this debate is whether dynamic cerebral autoregulation (dCA) should be quantified using spontaneous or induced blood pressure fluctuations. Simpson & Claassen (2018) have argued in favour of the latter based on the analogy that induced blood pressure fluctuations would provide 'cobblestones, potholes and speed bumps' that engages a car's suspension system to give insight into its properties. At first blush their argument appears to be a clincher, but the analogy is misleading because a car's suspension system scarcely resembles the cardiovascular system. Several points warrant specific mention.

First, we agree that testing the response characteristics of a system does require an input, but it is remiss to assume that spontaneous blood pressure (BP) fluctuations are not inputs. Spontaneous BP fluctuations are associated with poor neurological outcomes in patients with acute stroke (Manning *et al.* 2014; Lattanzi *et al.* 2015) suggesting they are physiologically significant inputs. Also, when dealing with the concept of BP variability, time scale matters as the physiological factors that dominate cerebral haemodynamics are frequency dependent (Kontos, 1989; Zhang *et al.* 2009; Tzeng & Ainslie, 2014). This means that the haemodynamic response to rapid blood pressure transients may not reflect mechanisms buffering against low or very low (i.e. slower) BP changes.

Consistent with this notion, cerebral blood flow variance associated with external perturbation manoeuvres, such as those during oscillatory lower-body negative pressure (LBNP) (Tzeng *et al.* 2011), thigh cuff deflation (Tzeng *et al.* 2014) and other orthostatic manoeuvres (Tzeng *et al.* 2014) might also be affected by compliance properties of cerebrovasculature (Olufsen *et al.* 2002). So testing the system with large and abrupt stimuli (i.e. cobblestones, potholes and speed bumps) that are associated with a greater rate of change in BP (i.e. $\Delta BP/dt$) might tell you more about the visco-elastic properties of the cerebrovascular system than the capacity of cerebral arteries to actively dilate and constrict in response to changes in BP (Tzeng *et al.* 2011).

As mentioned in our initial statement, a major problem with inducing BP changes is that other physiological control mechanisms will also be stimulated, thus producing alterations in respiration (and therefore P_{aCO_2}), stroke volume, heart rate and sympathetic nervous system activity, all of which influence dCA (Willie *et al.* 2014). The corollary to this, and the observation above that spontaneous fluctuations also generate a BP 'input', is that perhaps the discussion should not focus only on 'spontaneous *versus* induced'. Perhaps spontaneous fluctuations are simply one of many BP input modalities that have their own specific physiological context (Tzeng *et al.* 2012).

An alternative view on this key methodological aspect of dCA assessment is the need to clarify what is meant by better 'signal-to-noise ratio' associated with induced changes in BP. Here it is important to clarify what we designate as 'noise'. One general type of noise affecting all physiological measurements could be described as 'physical noise', involving electrical interference,-distortions resulting from non-invasive measurements (transcranial doppler and finger BP), or artefacts caused by subject movement, etc. This kind of noise can often be spotted at the data editing stages and in some cases minimised by filtering or spike removal.

A much more serious (but more interesting) kind of noise is what could be termed 'physiological noise' introduced by complex physiological interactions. These would involve mental activation, temperature changes, baroreceptor reflex activation, or autonomic nervous system effects (Willie *et al.* 2014). Our contention is that in dCA assessment, 'physiological noise' is more problematic than 'physical' noise, tilting the balance towards the use of spontaneous fluctuations as a more physiologically stable condition for dCA assessment.

Notwithstanding the above, we agree that consensus is required around what is meant by 'best' method for assessing dCA. The key priority should be on establishing *construct validity*, defined as 'the degree to which a test measures what it claims, or purports, to be measuring'. The evaluation of construct validity can be achieved through, for example, iterative assessment of convergent validity (the extent to which two measures of constructs that are theoretically related are in fact related) and discriminant validity (whether two theoretically unrelated measures are indeed unrelated). Currently none of the dCA measures that are in popular use (spontaneous or induced) exhibit convergent validity (Tzeng *et al.* 2012) so we clearly have a construct problem. For all the reasons raised in our original and current submission, we maintain that the resolution is unlikely to come from simply forcing the cerebrovascular system with induced BP fluctuations.

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Additional information

Competing interests

None declared.

Author contributions

Both authors contributed equally to the conception, writing and editing of this article. 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.

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