CROSSTALK

CrossTalk proposal: dynamic cerebral autoregulation should be quantified using spontaneous blood pressure fluctuations

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In healthy individuals, cerebral blood flow (CBF) is regulated by different mechanisms that maintain optimal blood supply to the brain, responding to changes in O_2 demand (neurovascular coupling, NVC), arterial partial pressure of CO_2 (P_{aCO_2}) (vasomotor reactivity, VMR) and arterial blood pressure (BP) (cerebral autoregulation, CA) (Willie *et al.* 2014). Whilst NVC and VMR are normally performed with some form of stimulation (e.g. sensorimotor protocols, CO_2 breathing or rebreathing), methods for CA assessment are still controversial, particularly regarding the decision to perturb changes in BP or not (Tzeng & Ainslie, 2014; Tzeng *et al.* 2014). On the one hand, the relationship between BP and CBF can be characterised at rest based on spontaneous fluctuations of these variables (Zhang *et al.* 1998). On the other hand, there is the argument that we can get more robust results using manoeuvres to induce larger changes in BP than normally observed at rest (Claassen *et al.* 2009; Tan, 2012). In this debate we argue that the former should be adopted whenever possible. But to understand how we arrived at these crossroads, it is important to review the recent conceptual and technological developments in this field.

Early studies of CA relied on measurements of CBF that required data acquisition times of the order of several minutes, usually involving pharmacological BP manipulations (Paulson *et al.* 1990). The introduction of transcranial Doppler ultrasound provided adequate temporal resolution to describe transient changes in CBF velocity (CBFV), lasting 2–10 s, thus allowing identification of the *dynamic* component of CA (Aaslid *et al.* 1989). This dynamic approach led to a paradigm shift and it overcame many limitations of the traditional *static* method (Tiecks *et al.* 1995; Panerai, 1998). In its original proposal (Aaslid *et al.* 1989) dynamic CA (dCA) was studied in response to the sudden release of compressed thigh cuffs. Two main indices derived from this approach – the rate of regulation (RoR) and the autoregulation index (ARI) – were shown to reflect dCA's dependence on P_{aCO_2} (Aaslid *et al.* 1989), good correlation with static CA (Tiecks *et al.* 1995), and to be sensitive to various pathological conditions (Panerai, 2008). Shortly after the formulation of the dCA concept (Aaslid *et al.* 1989), Giller proposed the coherence function, derived from transfer function analysis, as another dCA technique (Giller, 1990). The idea that dCA could be characterised as an input (BP)–output (CBF) linear system spurred two decades of research that showed the frequency response could express physiological and pathological correlates of dCA (Panerai *et al.* 1996; Panerai, 2008). The demonstration that the ARI index could also be derived from spontaneous fluctuations in BP and CBFV (Panerai *et al.* 1998) consolidated the use of spontaneous methods such as transfer function analysis (TFA) and the Mx index (Czosnyka *et al.* 1996) for dCA characterisation.

Returning to the induced-BP approach, with time, several alternatives were added to the original thigh cuff method, such as the Valsalva manoeuvre, leg raising, hand-grip, seat/squat-to-stand, tilting, cold stress test, controlled breathing and others. With this range of possibilities, the question of which protocol to adopt became even more pressing.

We favour the use of spontaneous BP fluctuations as the standard protocol for dCA assessment for several reasons. On a practical level, spontaneous fluctuations are present in all individuals throughout life and the technology needed for data acquisition is widely available. This means that the approach imposes a low burden for practical application with broad windows of opportunity for assessment and monitoring in conditions where knowledge of dCA are crucial, such as the critically ill patient. Similar flexibility is not always afforded by methods that require participant co-operation and fitness (e.g. sit-to-stand manoeuvres), use of invasive interventions (e.g. vasoactive drugs) or special equipment (e.g. lower body pressure chambers). Also, manoeuvres to induce changes in BP often provoke alterations in autonomic and breathing activity that will alter P_{aCO_2} levels. Due to these interferences, parameters reflecting dCA performance will be distorted and inter-subject as well as inter-institutional comparisons will be compromised. So, given these highly relevant advantages of spontaneous fluctuations for dCA assessment, why is the research community divided about which protocol(s) to adopt?

The specific reasons in favour of BP perturbation are addressed in the companion paper (Simpson & Claassen, 2018) but in general they reflect the view that BP challenges yield more accurate dCA measurements. Whilst we acknowledge that there are circumstances where resting recordings might provide insufficient BP variability (and therefore signal-to-noise ratio) to yield robust dCA estimates, this assumption is

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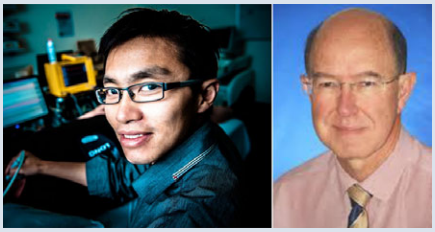

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context dependent. First, in many clinical conditions such as acute stroke, BP variability is elevated so accentuating BP variations may be unnecessary or even dangerous. Second, the idea that spontaneous conditions are associated with low signal-to-noise ratio depends on the analytical models you use. So-called 'noise' may be explainable variance that can be factored using more flexible models that can accommodate multiple system inputs (Peng *et al.* 2010) and account for system non-linearities (Mitsis *et al.* 2004). There is growing evidence that such methods have greater ability to discriminate intact from impaired dCA than conventional TFA (Saleem *et al.* 2016*a*,*b*). Finally, we must acknowledge that the definition of the 'cerebral autoregulation' remains debated. Are we referring only to active vasomotion in response to BP changes? Or do we include passive buffering secondary to other biophysical properties like vascular compliance in the definition? If it is the former then perturbing BP may yield inaccurate dCA estimates since passive processes can dominate pressure–flow dynamics in the presence of augmented BP fluctuations (Tzeng *et al.* 2011, 2014).

In our view the major benefit of a debate on topics surrounded by controversy is to identify priorities for research that will generate the knowledge needed to achieve consensus (Claassen *et al.* 2016). Related to this debate, further work is needed to understand the interdependence between levels of spontaneous BP variability and the reliability of derived dCA parameters, as well as their diagnostic and/or prognostic value. We must also tackle the white elephant in the room – how do we establish reference values for dCA indices that could guide the choice of protocols?

In relation to spontaneous BP oscillations two issues warrant special attention. First, extant models of dCA all differ in their underlying construct so derived metrics may not reflect the same physiological information. This is evident in the lack of convergent validity between most popular measures of spontaneous dCA (Tzeng *et al.* 2012). The lack of metric convergence is due partly to the use of arbitrary banding definitions in the frequency domain. We support calls for more rigorous validation of frequency bands to avoid artefactual truncation of spectral information (Tzeng *et al.* 2012; Saleem *et al.* 2016*a*). Second, most of the present discourse on dCA characterisation has referenced studies using transcranial Doppler ultrasound given its popularity for cerebral haemodynamic monitoring. However, transcranial Doppler measures blood velocity (not flow) and one cannot always assume the insonated vessel diameter remains constant (Hoiland & Ainslie, 2016). These technical factors introduce a great deal of additional complexity to the debate. In the absence of the knowledge needed to clearly answer these questions we hope this dialogue will stimulate new lines of inquiry and shed light on this complex vascular process.

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Additional information

Competing interests

None declared.

Author contributions

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