CROSSTALK

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Comments on CrossTalk 34: Dynamic cerebral autoregulation should be quantified using spontaneous/induced blood pressure fluctuationsOn the choice of optimal stimulus type for assessing dynamic cerebral autoregulation

To perturb or not to perturb: a novel physiological approach using closed-loop feedback to understand feedback systems

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Evaluating the interactions between cerebral blood flow and dynamically changing blood pressure can provide meaningful insight into cerebrovascular pressure–flow relationships, whether changes in blood pressure are driven by spontaneous fluctuations or by large intentional external perturbations (Phillips *et al.* 2014, 2017).

Using observational data to estimate physiological coupling during the regulation of cerebrovascular perfusion requires estimation of hidden variables underlying the feedback system, which are activated or inactivated by spontaneous fluctuations in the system. Large intentional perturbations may allow a clearer understanding, but to avoid potentially dangerous approaches in critically ill patients (Phillips *et al.* 2018), we propose closed-loop microperturbations as a balanced approach to both sufficiently influence the system inputs and estimate the feedback model/system-coupling safely (Hovorka *et al.* 2004). An example of how this could be accomplished is mechanical or pharmacological closed-loop control over venous capacitance or systemic vascular resistance. This approach has distinct advantages that extend into basic science and clinical research. For example, closed-loop microperturbations will not simply increase the amplitude of the physiological perturbations, which could bias detection towards effects occurring near the autoregulatory extremes instead of effects representative of more common regulatory processes. On the other hand, closed-loop microperturbations would also avoid the detection of false-positive coupling between slowly varying systems, which can occur from purely observational measures of interactions. Control paradigms combined with computational models also allow variation across multiple influential factors, and can accurately detect the relative influence of these factors within the system when sufficient variation is achieved.

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Additional information

Competing interests

None declared.

Quantification of dynamic cerebral autoregulation: the whole is more than the sum of the parts!

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This debate highlights critical issues concerning spontaneous compared to induced blood pressure (BP) fluctuations as the primary metric for the specific assessment of dynamic cerebral autoregulation (dCA) (Simpson & Claassen, 2017; Tzeng & Panerai, 2017). Previous research has demonstrated most dCA metrics have little direct relation to each other, or at the very best, weak to modest correlations. As such, it is quite possible each measure is revealing distinctive aspects of dCA (Tzeng *et al.* 2012). We suggest employing a composite multi-modal approach as it may help improve our physiological interpretation of this 'black-box' regulatory system.

The following point-in-principle justifies the suggested approach. We have recently highlighted that the cerebrovasculature effectively buffered spontaneous BP fluctuations yet was incapable of dampening rapid augmented BP oscillations in aerobically trained healthy individuals (Labrecque *et al.* 2017). The suppressed amplitude of spontaneous BP oscillations during transfer function analysis may fail to detect the subtle, albeit physiologically important, irregularities in dCA. It has been our experience that these dCA modifications may only become obvious when BP oscillations are 'forced' during sit-to-stand or repeated squat–stand manoeuvres which provide an ∼100-fold increase in BP spectral power at 0.10 Hz. The incorporation of induced combined with spontaneous

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BP oscillations remains feasible in a patient population (pulmonary arterial hypertension) (Malenfant *et al.* 2017). We therefore urge other investigators to strongly consider employing a multi-modal approach when quantifying dCA (and broader cerebrovascular functioning – cerebrovascular reactivity, neurovascular coupling) to enhance its interpretation and understanding, limiting the potential to overlook subtle differences.

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Additional information

Competing interests

None

Author contributions

P.B. drafted the comment. D.M.B. and J.D.S. critically revised the comment and all authors have approved the final version.

There is no silver bullet for a low signal-to-noise ratio

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Both opinions (Simpson & Claassen, 2018; Tzeng & Panerai, 2018) identify the main issue: we do not yet have a clear understanding of the relation between spontaneous fluctuations in pressure and flow. We completely agree that part of the problem is analysis methodology. However, the contention that the analytical models can overcome low signal-to-noise ratio is misleading: there is no silver bullet. In fact, as pointed out by Simpson and Claassen, low signal-to-noise ratio could easily explain why relations derived from spontaneous measures lack agreement and reproducibility. If so, standardizing analyses will not solve this problem. It is true that perturbing the system is not always practical, and any measure with predictive power has clinical utility. But a relation cannot be fully understood without first maximizing the signal-to-noise ratio, a feat that can be achieved by inducing changes in pressure. We do agree that manoeuvres to induce changes in pressure often alter other variables that can impact autoregulation independently. However, these variables, which fluctuate even at rest, are measurable. In fact, assessing responses to perturbations of multiple systems can afford unique insights into autoregulation (Jordan *et al.* 2000; Yoshida *et al.* 2018). Thus, perhaps the best way to understand autoregulation is to perturb the system while including complementary variables in analysis. With a high signal-to-noise ratio, one can obtain a robust characterization of the system while determining the role of other factors that impact it. Only then can one determine whether spontaneous fluctuations faithfully reflect autoregulation.

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Additional information

Competing interests

None.

Change in arterial pressure indirectly affects dynamic cerebral blood flow regulation

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The current CrossTalk debate is predicated on the assumption that changes in dynamic cerebral autoregulation derived from spontaneous or induced fluctuations in arterial blood pressure (ABP) mostly reflect the vascular consequences of altered cerebral perfusion pressure. However, changes in ABP can in and of themselves alter myriad 'extraneous' physical factors that can equally impact cerebral blood flow regulation, thereby precluding a truly 'direct' assessment of dynamic cerebral autoregulation (dCA).

In support, abrupt changes in ABP have been shown to stimulate the arterial baroreflex exerting both a direct and an indirect effect on the cerebral vasculature. Pharmacological blockade of sympathetic nerve activity (SNA) has been shown to impair dCA, and baroreflex-mediated tachycardia contributes to dynamic cerebral blood flow response to acute hypotension (Ogoh *et al.* 2010). Furthermore, acute hypotension results in a regional redistribution of blood flow in the external carotid artery that likely serves to preserve intracranial blood flow and ultimately defend cerebral oxygenation (Ogoh *et al.* 2014; Hirasawa *et al.* 2016; Ogoh *et al.* 2017). Additionally, acute

exercise reduces arterial baroreceptor reflex sensitivity at the operating point subsequent to a withdrawal of vagal tone (Ogoh *et al.* 2005). These findings highlight the interpretive complications associated with 'extraneous' changes in both heart rate and SNA that collectively impact on dCA. These physiological confounds need to be considered when attempting to select the appropriate methodology and ever elusive 'gold-standard' (dCA) metric. Its technical simplicity belies its underlying physiological complexity.

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Competing interests

None declared.

Autoregulation testing: one size will not fit all

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I read with great interest the contributions of both groups of experts and would like to thank them for the high quality of this discussion. Arriving late to the party and arguing with the hosts is rarely looked upon kindly. Being asked to comment on an ongoing debate, in only 250 words, feels very similar to that.

The optimal assessment of dynamic cerebral autoregulation (dCA) remains controversial. The debating experts pointed out that both spontaneous and induced variability methods have significant shortcomings (Simpson & Claassen, 2018*a*,*b*; Tzeng & Panerai, 2018*a*,*b*). To complicate matters, metrics of dCA also have inconsistent reproducibility. In this setting a debate predicated on a dichotomous view does little to advance things.

Autoregulatory testing may serve two purposes; in health to elucidate the physiology of the autoregulatory response. In disease, it may facilitate the personalized care of the critically ill.

In my view, if one is interested in understanding the physiology, the assessment protocol does not really matter so long as all confounders are controlled for. In fact I would argue that with a phenomenon as multifaceted as dCA, pluralism in assessment methods enriches our knowledge.

A dichotomous approach in testing dCA in disease is again likely to be erroneous. Clinical practice in other domains teaches us that frequently a combination of spontaneous and induced variability methods is required (e.g. NICE guidance on DM testing https://cks.nice.org.uk/diabetes-type-2). Moreover, dCA impairment is encountered in a varied disease spectrum and spans diverse age groups. To me, it is unlikely that a test fit for premature newborns will also be appropriate for an elderly patient with a disabling stroke.

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None declared.

On the choice of optimal stimulus type for assessing dynamic cerebral autoregulation

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The two recent CrossTalk articles present an excellent overview of the comparative advantages of using spontaneous arterial blood pressure (ABP) variability (Tzeng & Panerai, 2018) or larger, induced ABP changes (Simpson & Claassen, 2018) to quantify dynamic cerebral autoregulation (dCA). The choice of an 'optimal' stimulus depends on the *accuracy* of the obtained estimates as well as the *physiological relevance* and *interpretability* of the results. Importantly, the precise characteristics of dCA depend on both the underlying operating point (mean values of ABP and cerebral blood flow (CBF)) and the variability around that point (magnitude of ABP and CBF fluctuations around their mean values). Increased variability generally translates to a higher signal-to-noise ratio (SNR); also, broadband stimuli that excite many frequencies of interest are generally preferable. Spontaneous ABP variability yields sufficient SNR for obtaining reliable dCA estimates, comparable to induced ABP changes (Claassen *et al.* 2009), as well as a relatively uniform spectral distribution that reflects naturally occurring physiological oscillations and lends itself to interpretation. Larger, externally induced pressure changes yield a higher SNR but they typically do so within a narrow range of frequencies, which may tend to dominate the final result. On the other hand, extrapolating the results obtained from spontaneous fluctuations to a larger dynamic range warrants some caution as dCA may exhibit non-linearities when ABP variability becomes larger and/or at operating points that are closer to the limits of the static autoregulatory range. Importantly, resting protocols can be applied to any population (on a related note, fMRI-based resting-state networks have received tremendous interest (Damoiseaux *et al.* 2006), despite the low SNR of the fMRI signal) and they are amenable to continuous, real-time monitoring for predicting critical events. In conclusion, the above suggests that there is no perfect stimulus for assessing dCA and the choice depends also on the specific physiological question. However, using spontaneous variability presents an attractive alternative in most cases, given the accuracy of current experimental techniques (related to this, spontaneous protocols are less likely to be affected by changes in arterial diameter) and availability

of advanced modelling tools. As pointed out in both articles, I believe that future studies should address comparisons between different stimulus types as well as standardization methods (Claassen *et al.* 2016).

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None declared.

Cerebrovascular autoregulation: what is a sufficient amount of blood pressure variability?

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Central in this CrossTalk debate is whether the 'induced BP approach' (Tzeng & Panerai, 2017) facilitates the frequency domain assessment of dynamic cerebrovascular autoregulation (CA). Intuitively, as one side of the coin (Simpson & Claassen, 2017), augmenting blood pressure oscillations enhances accuracy of dCA determination (Hamner *et al.* 2004). This seems to be the case at least in anaesthetized humans with sympathetic outflow being suppressed, thus lacking BP oscillations with sufficient amplitude as input to the arterial pressure-to-cerebral blood flow velocity transfer function. Intraoperative CA efficacy determined from BP oscillations imposed by mechanical positive pressure ventilation at different frequencies corresponded to pre-operative values during paced breathing at identical frequencies (Sperna Weiland *et al.* 2017). On the other side of the coin (Tzeng & Panerai, 2017) there is the question: can BP variability in the resting state be designated as 'sufficient' to deliver a robust dCA estimate? The observation in type 2 diabetes patients that a seriously reduced BP variability down to 30% of the value in healthy subjects did not affect coherence does suggest so (Kim *et al.* 2008). Standardization is welcome, but assumes a much better understanding of the process of CA to provide a guideline on how much BP variability at the cost of minimal sympathetic activation is required with a focus on reproducibility of methods and conditions. Linking of dual time and frequency domain approaches in the same groups of healthy subjects (Lind-Holst *et al.* 2011) as well as in patients with cerebrovascular disease may be a start.

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Additional information

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None declared.

Dynamic cerebral autoregulation: to poke or not to poke, what ís the question?

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The problem presented in this CrossTalk debate is a futile one as long as the final objective is not made explicit. The position taken by Tzeng & Panerai (2018) is that of the careful doctor at the bedside: how is my patient doing and what can I say to the family in the waiting room about the to-be-expected outcome of their father's stroke? The one taken by Simpson & Claassen (2018) is the position of the investigator/diagnostic nurse–practioner: in this subject/case to be diagnosed, what can I tell about the condition of the cerebrovascular circulation if I poke it? In the end, both aim to quantify the same parameter: dynamic cerebrovascular autoregulation.

This is an elusive entity, or so it seems: in the same subject within one session, in response to both spontaneous and provoked (larger) blood pressure oscillations the numbers may vary considerably (Panerai *et al.* 2001), let alone between sessions (Nikolić *et al.* 2015). Both CrossTalk teams, in fact, agree on one crucial point: we don't know which physiological complex we are measuring or how we can improve the stability of the final result. That being the case, we have no alternative but to continue on both pathways: the careful doctor and the investigator. If this discussion makes one thing clear, it is that we are in desperate need for more basic physiological knowledge.

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Assessing dynamic cerebral autoregulation: do we know what we are assessing?

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While it is completely logical to argue that to assess the effectiveness of the system, you should perturb it (Simpson & Claassen, 2018), there are data that suggest this may not be required. Hamner *et al.* (2004) found transfer function values were unaffected by oscillatory lower body negative pressure despite a ∼10-fold increase in blood pressure variance, suggesting that inducing pressure oscillations did not improve assessment of autoregulation.

The lack of correlation between techniques (Tzeng *et al.* 2012) may represent the fact that each technique is measuring a different aspect. I have previously found that LF gain was correlated to the drop in cerebral flow velocity when standing (Serrador *et al.* 2005). Similarly in a study of over 400 elderly (Deegan *et al.* 2009) we found the same correlation (unpublished). R^2 values were ∼0.2 indicating only 20% of the variance could be attributed to estimates of autoregulation. This isn't surprising since cerebral flow when standing is affected by a number of other inputs (activation of the motor cortex, end tidal CO_2 changes, etc.). Another problem when comparing these techniques is the arbitrary frequency bands used. Could a higher frequency band (say 0.3–0.5 Hz) be related to dynamic changes and lower more related to static changes? Further work is needed to develop physiologically guided determinations of what each frequency represents.

In summary, spontaneous fluctuations appear to provide relevant information while minimizing inputs from other systems. We just need to better elucidate what aspects of autoregulation they are measuring.

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Additional information

Competing interests

None declared.

Magnetic resonance imaging to understand cerebral autoregulation

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Cerebral autoregulation (CA) is incompletely understood, and whether cerebral blood flow velocity (CBFV) responses to endogenous and induced blood pressure (BP) fluctuations are governed by the same processes is unclear. Transcranial Doppler (TCD) provides indirect measures of perfusion, and is only sensitive to intracranial arteries with an available acoustic window. We propose that MRI is a promising method for understanding CA, and believe insights gained with this modality will help validate more clinically applicable TCD methods. For example, MRI allows investigation of how different vascular segments alter their resistance during CA; we found evidence of differential arterial changes during lower body negative pressure (Whittaker *et al.* 2018), and using a similar MRI approach, Warnert *et al.* found arteries proximal to the Circle of Willis contribute to CA (Warnert *et al.* 2016).

Additionally, the ability to spatially map localised CA perfusion responses reveals MRI to be a clinical tool in its own right, as regional variations across the brain are likely to predict specific clinical outcomes (Juttukonda & Donahue, 2018). Currently, regional variations in CA have not been explored in detail, but we have used functional MRI to map blood pressure correlated perfusion fluctuations (Whittaker *et al.* 2016), and Wu *et al.* have mapped the response to the Valsalva manoeuvre (Wu *et al.* 2015). We advocate using MRI to better understand the potentially complex perfusion-supporting cerebrovascular changes that drive CBFV changes in major intracranial arteries. Both endogenous and induced experimental methods have been applied, but uniquely MRI offers multiple different methods providing complementary information at different vascular scales. This may shed light on the best experimental approach to characterise CA with TCD.

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Additional information

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None declared.

Spontaneous fluctuations are appropriate, more complex analysis is needed

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In Simpsom and Classen's analogy there are two different roads to choose from: a well-maintained highway and a worn-down road. In the case of cerebral autoregulation (CA) there is but one single individual. As noted by Tzeng & Panerai,

adding cobblestones, potholes and speed bumps (i.e. induced blood pressure perturbations) might damage the individual and/or the measurement. Thus, spontaneous fluctuations (SF), not just of arterial blood pressure (BP) but of all affecting variables, seem more convenient from both the clinical and measurement points of view.

In our experience, CA *is* working in SF, though the signal-to-noise ratio in these types of measurements hinders its evaluation. Therefore, the key challenge is to devise robust mechanisms to distinguish spontaneous variations from noise (i.e. filtering the signal).

The most widely used method for evaluating AC in SF is transfer function analysis (Claassen *et al.* 2016). But this method is linear, univariate and time-invariant. We have found that more elaborate descriptions are required to adequately represent such a complex mechanism as CA in SF.

In particular, we have seen that dynamic non-linear modelling does provide significant improvements in the robustness of CA assessment in SF: Chacón *et al.* (2011) found that different non-linear structures yielded less variability than linear models (Table 2); similarly, CA measures produced by dynamic non-linear models exhibited lower coefficients of variation than measures obtained with transfer function analysis in Chacón *et al.* (2018); moreover, these models showed a superior ability to distinguish normal from hypercapnia-induced impaired AC.

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Additional information

Competing interests

None declared.

The 'best' method for quantifying cerebral autoregulation simply depends on the question

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Thank you for the opportunity to comment on the elegant and important CrossTalk debate between Tzeng and Panerai (2018), and Simpson and Claassen (2018), on the 'best' method to quantify cerebral autoregulation (CA): spontaneous or induced changes in blood pressure. The former are typically indexed by more non-linear and non-stationary analyses (which reflect the typical behaviour of pressure–flow regulation in the brain) whereas the latter is normally determined under assumptions of linearity and stationary behaviour (i.e. transfer function analysis; TFA) (Tzeng and Ainslie, 2014). Using larger perturbations of blood pressure to challenge the cerebrovasculature helps validate the inherent assumptions of TFA, and may provide more of a 'physiological' stimulus. However, the clinical implications of 'impaired' or 'intact' CA in the healthy human model are still unknown (assuming that there is some). In contrast, CA quantified by relying on spontaneous oscillations in blood pressure (i.e. pressure-reactivity index) has been shown to correlate with better patient outcome (Czosnyka *et al.* 1997), making an exemplary argument for quantifying CA using small spontaneous changes in blood pressure. So, which approach is correct? The answer is simple, they both are, and the best method of quantifying CA solely relies on the circumstances and the fundamental question(s) that is being addressed.

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None declared.

MRI of induced blood pressure fluctuations can improve validity and extend clinical impact of CA measurements

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This debate highlights the challenges of using transcranial Doppler (TCD) to fully and consistently characterize cerebral autoregulation (CA), whether using spontaneous or induced changes in blood pressure. Tzeng and Panerai state the key priority is establishing *construct validity*, such that a test successfully measures the expected parameter. Emerging MRI techniques will improve the validity of CA measurements in two ways.

First, MRI techniques can provide more consistent measurements than TCD (Leung *et al.* 2013). Second, MRI sessions can incorporate multiple scans to improve the specificity of CA-related measurements. A single estimate of blood flow velocity in one large artery may be insufficient for characterizing the complex mechanisms underlying CA in patient cohorts. New 4D flow techniques capture velocity patterns throughout the Circle of Willis (Mikhail Kellawan *et al.* 2016). Arterial compliance imaging assesses the stiffness of smaller vessels throughout the brain (Yan *et al.* 2016). Downstream tissue perfusion can be quantified, and changes in arterial, venous, or total blood volume can be specifically measured (Jahng *et al.* 2014, Bright *et al.* 2018).

Simpson and Claassen assert the ability to predict patient outcome is another important criterion for CA measurements. MRI enables *regional* characterization, and spatial specificity is prognostically powerful: regional vaso-regulatory impairment predicts development of white matter hyperintensities (Sam *et al.* 2016). Combining multiple MRI images, tissue metabolism can also be modelled (Bright *et al.* 2018), thus linking CA dysfunction to what ultimately matters – neural health.

Many MRI methods achieve sufficiently fast sampling to characterize dynamic CA; however, most remain inherently low-signal-to-noise ratio techniques. As such, they necessitate larger, induced BP changes that can be repeated to facilitate signal averaging. However, MRI techniques will improve the validity of CA measurements while providing additional clinical insight.

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Additional information

Competing interests

None declared.

Assessing cerebral blood flow regulation in normobaric and hypobaric hypoxia: spontaneous *vs.* induced blood pressure changes

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Acute and chronic exposure to high altitude (5260 m) induces marginal changes in blood pressure (BP) and cerebral blood flow velocity (CBFv) at rest. S*pontaneous* changes in BP demonstrated an initial impairment of cerebral autoregulation (CA) upon acute exposure, which was invariant after a 16-day acclimatization (Subudhi *et al.* 2014). CO_2 rebreathing *induced* a rise in BP, which increased cerebrovascular CO_2 responsiveness upon arrival at altitude and even further after acclimatization (Fan *et al.* 2014). Both studies explored cerebral blood flow regulation in hypoxia, yet they suggested distinct regulatory mechanisms. While the pressure–flow relationship is a characteristic response to hypoxia, unaffected by acclimatization, the increased CO_2 responsiveness may be due to changes in acid–base balance in the blood and cerebrospinal fluid. Therefore, according to the authors of the CrossTalk debate, there is no clear advantage of one or the other protocol; both were necessary to obtain a more comprehensive understanding of various CBF regulatory mechanisms. Recent research further suggested differences between normobaric (NH) and hypobaric hypoxia (HH) for sleep disorder and breathing (Heinzer *et al.* 2016), but *not* baroreflex sensitivity (Bourdillon *et al.* 2017). The differences between NH and HH are subtle (Millet *et al.* 2012); research is needed to determine whether *spontaneous* changes in BP are a sufficient trigger to document any difference between NH and HH on CA, or if CO_2 responsiveness is necessary to *induce* a stronger stimulus.

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Additional information

Competing interests

None declared.

Dynamic cerebral autoregulation should be considered as a balance between myogenic and metabolic responses (and quantified accordingly)

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The choice of 'spontaneous' or 'induced' oscillations in blood pressure is clearly a fundamental assumption in dynamic cerebral autoregulation assessment. A definitive answer is hard to find in the absence of a gold standard and it would be hoped that both methods would yield much important information; what perhaps is lacking is a way to interpret the results. It might thus be worth considering an additional avenue for exploration, one that picks up on an important point made in the first rebuttal.

Fundamentally, arteriolar tone is set by a balance between vasoconstricting and vasodilating factors; autoregulation operates by adjusting this balance in response to changes in blood pressure. Surprisingly, there have been only a few attempts to separate out the myogenic and metabolic components, for example Panerai *et al.* (2012) and Salinet *et al.* (2013). Testing autoregulation with different stimuli over different time scales could well interrogate the two components in different ways, potentially leading to results that are hard to reconcile as a single response (see the rebuttal by Tzeng and Panerai).

Perhaps it is time to consider converting what we traditionally think of as a single autoregulation response into its two components, each of which will behave differently. Such an approach could help to determine whether the choice of stimulus is in fact less critical than is currently thought. Since this is likely to be challenging, due to the responses to different stimuli being non-linear and non-stationary, mathematical modelling of the underlying physiology is likely to be very important.

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Additional information

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None declared.

Spontaneous *vs.* induced blood pressure: it depends on your question

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Arterial blood pressure (BP) and, as a consequence, cerebral blood flow (CBF) fluctuate spontaneously with different amplitudes and at multiple time scales at rest, and may change dramatically during mental and physical activities in daily life (Zhang *et al.* 2000). Under these conditions, dynamic cerebral autoregulation (DCA) may operate differently, depending on the neural and/or vascular regulatory mechanisms (Zhang *et al.* 2002, 2009), the linear *vs.* non-linear relation between changes in BP and CBF (Marmarelis *et al.* 2016), or both. In clinical settings, the choice of whether to assess DCA during spontaneous or induced BP fluctuations may also depend on the biological factors or disease conditions being studied. For example, in patients with mild cognitive impairment, cerebral amyloid deposition was associated with a reduced transfer function (TF) gain only during repeated sit–stand manoeuvres, suggesting that the pathophysiological effect of brain amyloid deposition on DCA may be manifested only by large and induced BP changes (Tarumi *et al.* 2015). In contrast, it is also important to acknowledge that DCA assessed by both methods has substantially shared characteristics, as demonstrated by spontaneous TF estimates that closely predict the CBF response to a sudden change in BP (Zhang *et al.* 1998). Therefore, the answer(s) to this CrossTalk debate may not be a choice between spontaneous or induced BP changes, but rather to include both or either one depending on the particular study purpose and experimental conditions, and to understand the vascular regulatory mechanisms and their clinical significance revealed by DCA.

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Additional information

Competing interests

The authors do not have any competing interests.

Reducing the number of unknowns

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The 'bumpy road' ABP stimulus of Simpson and Claassen may provoke multiple physiological responses that complicate analysis of cerebral autoregulation. This is a valid criticism, but it does not convince me that we should use spontaneous ABP variations instead. Similar unwanted physiological activity may exist during spontaneous ABP fluctuations (Rickards & Tzeng, 2014). It is a reasonable assumption that a stimulus will evoke larger involvement from these confounding variables, but the ABP change will also be larger. Therefore our choice is between large evoked ABP changes with large confounding factors or smaller spontaneous ABP changes with smaller confounding factors. This looks well balanced, which is why this is such an excellent topic for debate.

Simpson and Claassen argue that the response to larger stimuli is more likely to be clinically relevant than the response to small stimuli, favouring evoked changes. However Tzeng and Panerai argue that passive processes can dominate the pressure flow dynamics in the presence of augmented ABP fluctuations, favouring small lower frequency changes in ABP. Small low frequency changes in ABP are delivered (sometimes) by spontaneous variations, but perhaps they could also be evoked. A gentle stimulus, perhaps a small bed angle change (Hughson *et al.* 2001), will not necessarily introduce larger confounding variables than exist spontaneously. I believe that evoked responses have another advantage over spontaneous changes: there are many different physiological reasons why blood pressure might change spontaneously (Langager *et al.* 2007; Rickards & Tzeng, 2014), whereas when we evoke a blood pressure change we know exactly what has happened to cause the change. This reduces the number of unknowns in the experiment and that can only improve our understanding and the consistency of analysis.

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Additional information

Competing interests

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