Published in final edited form as:

Eur J Appl Physiol. 2013 November ; 113(11): . doi:10.1007/s00421-013-2718-4.

On the Judicious Use of Metrics for Cerebral Autoregulation

Can Ozan Tan* and J. Andrew Taylor

Cardiovascular Research Laboratory, Spaulding Rehabilitation Hospital, Boston, MA

Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA

To the Editor

We read the review by Tzeng and Ainslie (2013) with great interest and appreciate their emphasis on limitations in current paradigms to explore cerebral autoregulation. Clearly, “many extant methods ... are based on simplistic assumptions that can give rise to misleading interpretations.” Indeed, though the ability to easily capture beat-by-beat data on a myriad of interacting variables has led to numerous unique insights, these same insights can often be limited by our ability to apply well-informed analyses. In fact, the same data may lead to different conclusions if the assumptions that underlie the analytic methods are violated. The authors highlight the inconsistency between different metrics, and underscore that only “few [metrics] exhibit statistical associations with each other.” Though lack of agreement may indicate flawed assumptions, it might also indicate that some metrics are unfit to study the phenomenon under investigation.

The lack of convergence between metrics may evidence “a lack of a common functional basis,” and hence the researcher might ask “which metric, or combination of metrics, one should use.” However, the construct validity of the proposed metrics may provide the answer. The hallmark of autoregulation is the ability to buffer against arterial pressure changes and is manifested as a lack of linear dependence between pressure and cerebral blood flow fluctuations (i.e., low cross-spectral coherence or poor correlation). Most metrics are, in fact predicated on this manifestation: pressure – flow fluctuations exhibit low coherence (or correlation) when autoregulation is intact, and a close linear relation indicates when autoregulation is impaired. But, the issue is that if the pressure – flow relation displays a low linear relation (e.g., coherence), it cannot be quantified reliably via linear analyses. Autoregulation by its very nature limits the utility of linear estimates. Therefore, while *all* linear metrics may indicate the ‘presence’ or ‘absence’ of cerebral autoregulation, *none* can reliably quantitate the pressure – flow relation when autoregulation is intact. Therefore, the search for “analytical innovations that enable multivariate quantification of ... linear ... properties of the cerebral circulation” will suffer from the exact same limitations. For example, approximation of a three-element Windkessel model to characterize autoregulation is simply a multiple *linear* regression, and thus, is vulnerable to this very limitation; although it may provide excellent fits at the population level, its utility for intra-individual relationships remains unclear.

As the authors state, “physiological inferences are only as valid as the assumptions inherent in our methodological approaches.” Our two recent studies, wherein we showed that alpha-adrenergic and muscarinic receptor blockade increases the coherence and gain relation between pressure and flow at frequencies less than 0.06 Hz (i.e., slower than 15 seconds)

*Correspondence: CVLab, Spaulding Hospital Cambridge, 1575 Cambridge Street, Cambridge, MA 02138. cotan@partners.org.

The article commented on: Y. C. Tzeng and P. N. Ainslie. 2013. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol.* (in press).

were cited as particularly representative of this issue. Pressure and flow were highly coherent in both studies due to the use of oscillatory lower body negative pressure, thus, the authors suggest that it remains unclear to what extent observed gain changes reflect altered dynamic autoregulation. Coherence in these studies was ~0.25 - 0.50 at baseline, however, there were significant increases with blockade, indicating that the pressure – flow relation was linearized. Though this result does not inform the extent to which dynamic autoregulation was altered, it does conclusively show an impairment after sympathetic and cholinergic blockades. That is, the increased coherence after blockade does not obscure, but rather affirms a clear involvement of neurogenic mechanisms in autoregulation. Additionally, the authors accurately note that alpha-adrenergic blockade altered end-tidal CO₂ which could introduce an important confounder. Yet, we clearly addressed the fact that “hypocapnia decreased coherence and gain, and thus, at worst, our results underestimate the sympathetic nervous system’s role.” (Hamner *et al.*, 2010)

Tzeng and Ainslie emphasize that approaches which can circumvent the limitations of current methodologies might provide more insight. One example is Tan (2012) whose alternative analytic approach showed that a pressure – flow relationship with an autoregulatory region shouldered by “pressure-passive” regions can be observed when the input pressure fluctuations are relatively slow (~30 s). However, since the shape appears to be like Lassen’s classic static autoregulation curve, the seemingly narrow plateau (i.e., autoregulatory) region was interpreted by Tzeng and Ainslie to suggest that the classic autoregulation curve is inadequate to the true physiology. Yet, this highlights the issue of discriminating between what we think we are observing from what actually explains the observations. The autoregulatory curves revealed by the analysis of Tan reflect the relation between pressure and flow fluctuations *at particular frequencies*. In contrast, Lassen’s curve represents the relation between *absolute* pressure and flow. Therefore, the axes of the Tan’s and Lassen’s autoregulatory curves are incompatible, and stylizing both curves as if they represent the same phenomenon is incorrect. One might use Tan’s autoregulatory curve to derive the rate of pressure changes and the corresponding rate of cerebral flow changes to derive a simple physiologic relation that describes the effectiveness of autoregulation across all frequencies. However, direct comparison of Lassen’s and Tan’s autoregulatory curves is not possible and does not inform the physiology of cerebral autoregulation.

The authors are correct that linear methods are insufficient to measure autoregulation. However, if they are used for intra-individual changes, linear approaches can provide information on whether autoregulation has been impaired. Moreover, non-linear approaches can be applied to provide insight to autoregulatory capacity, but only if one appreciates the specifics of the metric.

Reference List

- Hamner JW, Tan CO, Lee K, Cohen MA, Taylor JA. Sympathetic control of the cerebral vasculature in humans. *Stroke*. 2010; 41:102–109. [PubMed: 20007920]
- Tan CO. Defining the Characteristic Relationship between Arterial Pressure and Cerebral Flow. *J Appl Physiol*. 2012; 113:1194–1200. [PubMed: 22961266]
- Tzeng YC, Ainslie PN. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol*. 2013 in press.