A New Monitor of Pressure Autoregulation: What Does It Add?

Ken Brady, MD, Dean B. Andropoulos, MD, Kathleen Kibler, CCP, and R. Blaine Easley, MD

Cerebrovascular pressure autoregulation is a vital, protective mechanism that constrains cerebral blood flow during changes in arterial blood pressure. Pressure autoregulation is known to fail during profound hypotension, and the so-called lower limit of autoregulation (LLA) is diverse for different subjects.[1] The measurement and monitoring of pressure autoregulation is specifically useful to discriminate safe from harmful blood pressure: when arterial blood pressure is within range to render normal pressure autoregulation measurements, the brain is protected; when arterial blood pressure is too low and pressure autoregulation measurements show impairment, the brain is vulnerable.[2,3] In the present study, Hori et al.[4] present a novel method to measure pressure autoregulation using the Ornim UT-light technology (Ornim, Inc., Kfar Saba, Israel), rendered as a cerebral flow velocity index (CFVx). The UT-light method is proprietary and quantifies relative tissue blood movement from the Doppler shift of near-infrared light caused by red cells in motion. It is an uncalibrated, surrogate measure of cerebral blood flow. How does this measure autoregulation? How is this to be evaluated and validated? Not fewer than 15 metrics purported to measure autoregulation have infused the medical literature within hundreds of manuscripts in the past 2 decades.[5] It would be instructive to know how these metrics are related and to consider the evidentiary burden required to deploy them clinically.

Pressure autoregulation is distinct from, but often confused with, other servomechanisms that contribute to the homeostasis of cerebral blood flow. Examples include neurovascular coupling (or metabolic autoregulation), which rapidly matches cerebral blood flow to local metabolic demands[6]; the systemic vasoconstrictive response to shock, which diverts cardiac output from sympathetic, angiotensin, and vasopressin-reactive vascular beds to the brain and heart, which respond differently to these neurohormonal cues[7–9]; and cerebral vasodilatory and constrictive responses caused by changes in arterial carbon dioxide.[10] Each of these operates at the same point of action, that is to affect a change or to prevent a change in cerebral blood flow. The pressure autoregulation mechanism can be measured even when cerebral blood flow is influenced by the other mechanisms listed if the metric used is attuned to the proper frequency.

Three components are needed to construct a metric of autoregulation:

1. A change in arterial blood pressure must occur and must be measured.
2. A measure of cerebral blood flow, blood volume, or oxygenation is made synchronous to the blood pressure change.
3. A mathematical estimation of the relationship between the arterial blood pressure change and the intracerebral measurement is performed.

The myriad methods published to measure autoregulation are distinguished by the selection from each of these 3 components, and the combinations used affect the result and validity of any proposed metric. Each element is considered in turn.

ARTERIAL BLOOD PRESSURE CHANGE: THE PROBLEM OF PRECISION AND TIME

The change in arterial blood pressure can be categorized as either spontaneous or induced. Waves have been induced in the arterial blood pressure by slow breathing,[11] positive end-expiratory pressure valve oscillation in ventilated subjects,[12] postural changes with a tilt table,[13] thigh cuff deflation,[14] and vasoactive injections.[15] Obviously, the transition from measuring autoregulation to monitoring autoregulation requires repetitive changes in arterial blood pressure, and spontaneous, so-called slow waves have been used most commonly for this. Slow waves with a period between 20 and 200 seconds were first categorized in the intracranial pressure tracing by Lundberg, who categorized them as "B waves."[16] The low frequency of slow waves makes them appropriate for the measurement of autoregulation, a practice that was pioneered at Cambridge University by Czosnyka et al.[17] However, slow waves have a variable periodicity and amplitude, which can cause imprecision in the measurement of autoregulation. Imprecision from erratic slow-wave activity has been mitigated by filtering out epochs with inadequate slow-wave power and by averaging multiple measurements, which increases the time required to perform the monitoring.

In the present study by Hori et al.,[4] spontaneous slow-wave activity is used as the arterial blood pressure change

From the Department of Anesthesiology, Baylor College of Medicine, Houston, Texas.

Accepted for publication July 22, 2015.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Ken Brady, MD, Department of Anesthesiology, Baylor College of Medicine, 6621 Fannin St., WT 17-417A, Houston, TX 77030. Address e-mail to kmbrady@bcm.edu.

DOI: 10.1213/ANE.0000000000000952

to measure autoregulation. No filtering was applied to remove monitoring epochs with inadequate slow-wave power. These epochs are known to create signal noise and cause disagreement between modalities used to measure autoregulation.[18] One would expect, therefore, that such a filter would have improved the reported agreement between the "standard" mean velocity index (Mx) and the study index CFVx.

Improving the fidelity of autoregulation measurement is a key current obstacle in the development of autoregulation monitoring for cardiopulmonary bypass. Imprecision of autoregulation metrics prompted a neurosurgical practice of using 4-hour windows to monitor autoregulation, which is not practical for the cardiac operating room.[2] The shortest time to reliably monitor autoregulation with spontaneous slow waves is not known, but 20 to 30 minutes has been proposed.[5] The CFVx, as presented in this article, does not address this conundrum.

INTRACRANIAL MEASUREMENTS: FLOW, VOLUME, OR OXYGENATION?

Myriad intracranial measurements have been applied to the study of autoregulation, all categorized as surrogates of cerebral blood flow, cerebral blood volume, or cerebral oxygenation. Examples of flow surrogates include transcranial Doppler (Mx) and the UT-light method (CFVx) presented by Hori et al. These metrics of autoregulation are easiest to understand, but the Doppler is difficult to use continuously, especially in an environment of electrical noise such as the operating room. Because of difficulties acquiring and maintaining a stable transcranial Doppler signal, Mx is not the most widely studied monitor of autoregulation, although it was arguably the first. This practical problem is potentially solved by the introduction of the UT-light method shown here because it is easy to apply when compared with the transcranial Doppler, and this is possibly the most significant contribution of the CFVx.

When a surrogate of blood volume is applied instead of flow, the resultant metric is properly termed a measure of pressure reactivity, not pressure autoregulation, although the 2 are directly related. Autoregulation is the constraint of flow in response to a change in arterial blood pressure. Pressure reactivity is the constriction and dilation of the vascular bed in response to a change in arterial blood pressure. Pressure reactivity causes cerebral blood volume to be inversely related to the arterial blood pressure, and pressure passivity causes cerebral blood volume to be directly related to the arterial blood pressure. Blood volume in the brain is easily trended with an intracranial pressure monitor, reflectance near-infrared spectroscopy, or ultrasound time of flight.[11,19,20] Although less intuitive than metrics of autoregulation, measures of pressure reactivity have been much more widely studied. Optimal perfusion pressure identified with pressure reactivity is strongly associated with outcome in patients with traumatic brain injury.[2,3]

Finally, oxygenation measured in the brain with parenchymal probes or with reflectance near-infrared spectroscopy can be used to evaluate autoregulation. Passivity of brain oximetry to arterial blood pressure has been shown to be sensitive and specific for the loss of pressure autoregulation.[21]

Interestingly, all 3 types of autoregulation monitoring can be performed with the same device using the CerOx technology, which has UT-light to measure flow, a light wavelength isosbestic to the hemoglobin species to measure blood volume, and the ability to measure cerebral oximetry. The choice to focus on flow is possibly justified by conceptual convenience and a proprietary position to facilitate marketing. However, it is not clear that this is the most clinically useful pathway given the abundance of supportive data for pressure reactivity monitoring.

QUANTIFYING PASSIVITY: FREQUENCY, TIME, AND THE LACK OF A GOLD STANDARD

Quantification of the passivity of cerebral blood flow to arterial pressure has been reported using a variety of frequency domain cross-correlation functions and with the time-domain correlation function used by Hori et al.[4] Although all of these have been asserted to measure autoregulation, they do not measure the same thing, and most have not been tested against a "gold standard." This is largely because there is no true gold standard measurement of autoregulation. However, the time-domain correlation function used by Hori et al. has been validated in at least 2 ways: First, it has been shown to be sensitive and specific to the LLA, clearly demonstrated by static curves in lethal animal experiments.[20,21] More importantly, the optimal blood pressure identified by the linear correlation method is strongly associated with survival and neurologic recovery after traumatic brain injury (using pressure reactivity metrics).[2,3] Therefore, the development of a new monitor using the linear correlation construct is a logical choice.

Comparing CFVx with Mx is a straightforward way to pilot-test the validity of the new index. Both CFVx and Mx use surrogates of cerebral blood flow. Both are rendered by moving correlation coefficients. Both filter primary signals to remove high-frequency transients and oscillations, enhancing the effect of slow-wave activity on the measurement. The study construct places Mx in the role of standard, but given the similarities between Mx and CFVx, the study could also be characterized as a direct comparison between transcranial Doppler and UT-light after identical processing. Such a study design is reasonable given the lack of options for autoregulation standards in human subjects, but one predicts only modest agreement as a best result. The transcranial Doppler signal is noisy when used continuously in the cardiac operating room, and the relatively stable signal from UT-light may outperform the standard in this case, creating a falsely low performance. The demonstrated improvement in agreement when comparing Mx-derived LLA with CFVx-derived LLA is consistent with this interpretation. The signal noise causing divergence of the metrics is mitigated by the averaging process used to find LLA. Although these pilot data are an encouraging start, the true receiver operator characteristics are unknown for both the Mx and the CFVx.

The question of evidentiary burden is raised. What data are required to begin marketing the CFVx and to begin using it on patients? If Ornim can demonstrate adequate sensitivity and specificity for detecting LLA with UT-light, will it market the CFVx using predicate work from decades of autoregulation monitoring outcome research? Early adopters will be convinced by the logic of the monitor if

it can be shown that it is adequately sensitive and specific. Late adopters will wait for a randomized trial demonstrating improved patient outcome, but it will not likely be performed during our careers. No standard anesthesia monitor has been demonstrated to improve patient outcome in this way, so what company would put a monitoring device at such risk before marketing?[22]

DISCLOSURES

Name: Ken Brady, MD.
Contribution: This author helped write the manuscript.
Attestation: Ken Brady approved the final manuscript.
Name: Dean B. Andropoulos, MD.
Contribution: This author helped write the manuscript.
Attestation: Dean B. Andropoulos approved the final manuscript.
Name: Kathleen Kibler, CCP.
Contribution: This author helped write the manuscript.
Attestation: Kathleen Kibler approved the final manuscript.
Name: R. Blaine Easley, MD.
Contribution: This author helped write the manuscript.
Attestation: R. Blaine Easley approved the final manuscript.
This manuscript was handled by: Maxime Canneson, MD, PhD.

REFERENCES

1. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997;86:1431–3
2. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, Hutchinson PJ, Brady KM, Menon DK, Pickard JD, Smielewski P. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med 2012;40:2456–63
3. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med 2002;30:733–8
4. Hori D, Hogue CW Jr, Shah A, Brown C, Neufeld KJ, Conte JV, Price J, Sciortino C, Max L, Laflam A, Adachi H, Cameron DE, Mandal K. Cerebral autoregulation monitoring with ultrasound-tagged near-infrared spectroscopy in cardiac surgery patients. Anesth Analg 2015;121:1187–93
5. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. Neurocrit Care 2009;10:373–86
6. Roy CS, Sherrington CS. On the regulation of the blood-supply of the brain. J Physiol 1890;11:85–158.17
7. Hamner JW, Tan CO, Lee K, Cohen MA, Taylor JA. Sympathetic control of the cerebral vasculature in humans. Stroke 2010; 41:102–9
8. Saavedra JM, Nishimura Y. Angiotensin and cerebral blood flow. Cell Mol Neurobiol 1999;19:553–73
9. Katusic ZS, Shepherd JT, Vanhoutte PM. Vasopressin causes endothelium-dependent relaxations of the canine basilar artery. Circ Res 1984;55:575–9
10. Yang SP, Krasney JA. Cerebral blood flow and metabolic responses to sustained hypercapnia in awake sheep. J Cereb Blood Flow Metab 1995;15:115–23
11. Ragauskas A, Daubaris G, Petkus V, Ragaisis V, Ursino M. Clinical study of continuous non-invasive cerebrovascular autoregulation monitoring in neurosurgical ICU. Acta Neurochir Suppl 2005;95:367–70
12. Fraser CD III, Brady KM, Rhee CJ, Easley RB, Kibler K, Smielewski P, Czosnyka M, Kaczka DW, Andropoulos DB, Rusin C. The frequency response of cerebral autoregulation. J Appl Physiol (1985) 2013;115:52–6
13. Carey BJ, Manktelow BN, Panerai RB, Potter JF. Cerebral autoregulatory responses to head-up tilt in normal subjects and patients with recurrent vasovagal syncope. Circulation 2001;104:898–902
14. Mahony PJ, Panerai RB, Deverson ST, Hayes PD, Evans DH. Assessment of the thigh cuff technique for measurement of dynamic cerebral autoregulation. Stroke 2000;31:476–80
15. Vavilala MS, Lee LA, Boddu K, Visco E, Newell DW, Zimmerman JJ, Lam AM. Cerebral autoregulation in pediatric traumatic brain injury. Pediatr Crit Care Med 2004;5:257–63
16. Steinmeier R, Bauhuf C, Hübner U, Bauer RD, Fahlbusch R, Laumer R, Bondar I. Slow rhythmic oscillations of blood pressure, intracranial pressure, microcirculation, and cerebral oxygenation. Dynamic interrelation and time course in humans. Stroke 1996;27:2236–43
17. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. Stroke 1996;27:1829–34
18. Diedler J, Zweifel C, Budohoski KP, Kasprowicz M, Sorrentino E, Haubrich C, Brady KM, Czosnyka M, Pickard JD, Smielewski P. The limitations of near-infrared spectroscopy to assess cerebrovascular reactivity: the role of slow frequency oscillations. Anesth Analg 2011;113:849–57
19. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997;41:11–7
20. Lee JK, Kibler KK, Benni PB, Easley RB, Czosnyka M, Smielewski P, Koehler RC, Shaffner DH, Brady KM. Cerebrovascular reactivity measured by near-infrared spectroscopy. Stroke 2009;40:1820–6
21. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, Koehler RC, Shaffner DH. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. Stroke 2007;38:2818–25
22. Kasman N, Brady K. Cerebral oximetry for pediatric anesthesia: why do intelligent clinicians disagree? Paediatr Anaesth 2011;21:473–8