Cerebral autoregulation: Making sense of the nonsensical

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Intact (A) and impaired (B) cerebral autoregulation.

Central Message

Optimization of cerebral autoregulation may allow better neuroprotection of neonates with congenital heart disease; however, there is still no consensus regarding how best to measure autoregulation.

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White matter injury is the most common brain injury in neonates with congenital heart disease^{1,2} because of their vulnerable, immature oligodendrocytes located in watershed areas.^{3,4} Cerebral autoregulation constrains cerebral blood flow (CBF) during fluctuations in arterial blood pressure (ABP). Impaired cerebral autoregulation, commonly seen during hypotension, increases vulnerability to both hypoperfusion and hyperperfusion injuries in the brain. It is therefore intuitively likely but unproven that measurement and optimization of cerebral autoregulation could be used to confer neuroprotection when there is risk of ischemic injury.

In this issue of the *Journal*, Votava-Smith and colleagues⁵ report their study of cerebral autoregulation in 24 neonates with congenital heart disease by determining coherence between ABP and cerebral oximetry from near-infrared spectroscopy. They concluded that neonates with severe forms of congenital heart disease show periodic impaired cerebral autoregulation, even when normotensive.

Every imaginable proxy of CBF has been used to measure cerebral autoregulation, including transcranial Doppler ultrasonography, cerebral oximetry, brain tissue oxygen tension, and intracranial pressure. Each of these suggested proxies has been quantitatively related to ABP both by time-domain metrics (analyzing signal associations in time with correlation) and by frequency-domain metrics (deconstructing the signal into components and applying cross-correlation functions, such as coherence and phase).

Complex, chaotic biologic signals such as ABP or cerebral oximetry can be expressed as a summation of sine wave components of different frequencies and amplitudes, which is known as a *Fourier transform*. When 2 signals share wave components at a given frequency with a constant phase relationship, they are *coherent* at that frequency. The use of coherence as a metric of autoregulation follows straightforward logic: Autoregulation is a mechanism that constrains CBF fluctuations, so CBF fluctuations coherent with ABP fluctuations are indicative of impaired autoregulation. This assertion is not

universally accepted, however, because high coherence does not specify a phase relationship. That is, two waves can be 180° phase shifted (inverted or negatively correlated) and have high coherence, or they can be 0° phase shifted (positively correlated) and again have high coherence.

Animal data suggest that negative correlation (high coherence with phase shift) between ABP and CBF represents a state of pressure *reactivity* (ie, intact autoregulation), rather than impaired autoregulation (Figure 1).⁶⁻⁸ On the basis of these studies, correlation and phase shift may be better suited to the analysis of autoregulation than is coherence, the method used in this study.⁹

There are competing models of cerebral autoregulation in the literature. According to one, autoregulation acts as a clamp on CBF, such that ABP coherence with CBF discriminates intact from impaired autoregulation. According to the other model, autoregulation causes CBF to fluctuate around a set value, such that dynamic vascular resistance causes a phase shift between ABP and CBF, which thus remain coherent even when autoregulation is intact.

Regardless of the chosen model, any clinical tool proposed to measure autoregulation will face a burden of proof that includes the following: (1) validation against a criterion standard (likely determined in animal models), (2) reproducible prospective evidence that the metric is associated with outcome, and (3) evidence that the metric can be acted on to optimize autoregulation and minimize morbidity. Pilot studies such as this study of Votava-Smith and colleagues⁵ are a first step.

FIGURE 1. Quantification of cerebral autoregulation from spontaneous blood pressure oscillations in a piglet with hemorrhagic hypotension induced for 4 hours. A, This graph displays changes in arterial blood pressure (ABP), intracranial pressure (ICP), and cerebral oximetry (rSO₂) during 30 minutes of normotension above the lower limit of autoregulation (intact cerebral autoregulation). Slow arterial blood pressure waves (changes across 2-5 minutes) are transmitted to the intracranial pressure and oximetry signals but with an inverted phase (negatively correlated). B, This graph demonstrates the same measurements during 30 minutes of hypotension, below the lower limit of autoregulation (impaired cerebral autoregulation). The slow arterial blood pressure waves are now transmitted without a phase shift (positively correlated). C, A criterion standard static autoregulation plot shows the cerebral blood flow (CBF) from the entire experiment, with arrows showing the position of intact autoregulation recording (A) and the impaired autoregulation recording (B). At steady state, cerebral blood flow is independent of arterial blood pressure above the lower limit of autoregulation and is correlated with arterial blood pressure below the lower limit of autoregulation. D, The table shows coherence (Coh.) and phase shift between arterial blood pressure and the output signals intracranial pressure and cerebral oximetry for panels (A) and (B). During both intact and impaired autoregulation, all signals are coherent. Above the lower limit of autoregulation (LLA), however, there is a phase shift between the arterial blood pressure and output signals. Below the lower limit of autoregulation, there is minimal phase shift between the arterial blood pressure and the output signals. Coherence was measured from the 30-minute segments shown, with a Hamming window that had 7 segments with 40% overlap in a frequency range of 0.003 Hz to 0.02 Hz. Phase was calculated with the same parameters.

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