Unraveling the human cerebral circulation: insights from cerebral blood pressure and flow recordings

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A.C. BURTON ONCE COMMENTED that the relation of pressure to flow is the “central problem in hemodynamics” (2). This proposition remains true today, as it did more than 50 years ago when revolutionary concepts such as “vascular impedance” and “autoregulation” of regional organ perfusion were only emerging. What has changed over this period is that these concepts have gained acceptance, and their value is now widely acknowledged. However, progress has been staggered, with knowledge specific to the human cerebral circulation somewhat lagging behind other vascular beds because the validated means to record cerebral perfusion pressure and flow noninvasively has evolved only within about the last 20 years (1). Consequently, our understanding of the processes that influence cerebral hemodynamics is comparatively sparse. However, the gap is narrowed in this issue of the Journal of Applied Physiology by Zhu et al. (12), who present a novel approach to explore the impedance characteristics of the human cerebral circulation.

But first, what is vascular impedance? To help conceptualize the term, it may be helpful to begin with the more familiar concept of vascular resistance, which is a mathematical entity that relates the mean pressure at the entrance of a vascular bed to the mean blood flow through that vascular bed. This concept is often thought of as the hindrance or impediment that the pressure must overcome to drive blood flow. Impedance can be thought of in a similar way, except it is more comprehensive because it takes into consideration important physiological processes not accounted for by Poiseuille’s law, for example, the fact that arteries are distensible organs organized in a complex branching structure, that arterial pressure and flow are inherently pulsatile, and that pressure flow waves take time to propagate throughout the arterial tree and can reflect backward from downstream sites of impedance mismatch to alter proximal pressure flow waveforms, in accordance with physical laws governing wave summation and subtraction (8). Therefore, vascular impedance is a more complete but also more complex description of pressure-flow relations. To appreciate the concept of impedance, pressure and flow need to be viewed as compositions of sine waves at varying frequencies and the impedance as the linear flow to pressure transfer function defined in terms of modulus and phase at each frequency. In this context, 0-Hz impedance relating mean pressure and mean flow theoretically corresponds to resistance.

Vascular impedance patterns have been well documented for most major arteries in humans. Although our knowledge remains incomplete, we have a relatively firm understanding of what some key impedance features are and what underlying vascular properties they may inform. For example, one theoretical analysis (9) showed that the pattern of rising modulus seen in the lower frequencies of the vascular impedance spectrum is well modeled by the Windkessel, which indicates that at lower frequencies the arterial system behaves like a compliant chamber that is able to store blood. The impedance in the high frequency ranges resembles a plateau, which can be modeled by a uniform tube without reflection sites of infinite length. Therefore, high frequency impedance approximates the characteristic impedance, which is determined by entrance arterial compliance and vessel cross-sectional area, and refers to the impedance in the absence of wave reflection. Vascular impedance at intermediate frequencies (including the cardiac frequency) has been attributed to arterial topology that governs pulse wave reflections.

Given the potential to infer some vascular properties from pressure flow recordings, the means to study cerebrovascular impedance represents an important step toward further understanding age- and pathology-related changes in cerebrovascular function. Zhu et al. (12) makes a start by demonstrating that noninvasive measurements are feasible, using applanation tonometry and transcranial Doppler. They showed that cerebral impedance patterns exhibit some general features that are reassuringly similar to those seen in other vascular beds, indicative of shared mechanical properties. They also show that cerebrovascular impedance increases with age and is inversely proportional to cerebral blood flow (CBF), providing direct evidence that age-related reductions in CBF are associated not only with changes in vascular resistance but also to cerebrovascular stiffness properties. These observations concerning vascular “stiffness” deserve further consideration because they have important ramifications for our understanding of how CBF might be fundamentally regulated.

A major concept in vascular physiology is that cerebral vessels are stiffer compared with their systemic counterparts (7). This has led some investigators (ourselves included) to ignore stiffness-related properties when drawing inferences from cerebral pressure flow recordings. However, the findings of Zhu et al. (12) remind us that vascular stiffness is not a binary property that is completely absent in brain vessels. Rather, the similarities between cerebral and systemic arterial impedance and features such as flow leading pressure at low frequencies suggest that compliance likely exists within the cerebrovascular bed, which is consistent with anatomic studies showing that cerebral arteries exhibit circumferential distensibility (7). The findings also remind us that the very notion of stiffness is relative because it changes with age. Notwithstanding the fact that compliance is most widely considered in the
analysis of pulsatile arterial waveforms, research employing mathematical models of arterial segments has demonstrated that compliance also plays a crucial role in the relationship of beat-to-beat pressure and flow changes in the cerebral circulation. For example, using a Windkessel model simulation of the cerebral circulation, vascular compliance was implicated as an important determinant of dynamic cerebral pressure-flow relationships in the frequency domain (11). Using a data-driven approach, we have shown that the Windkessel accounts for ~80% of CBF variance under conditions where blood pressure is actively perturbed at low frequencies (3, 10). Collectively, these data indicate that compliance is a critical determinant of cerebral pressure-flow relations and that compliance may play a role in stabilizing beat-to-beat variations of blood flow into the downstream cerebral vasculature. Interestingly, these findings also match well with the postulate that Windkessel properties are most prominent within the lower frequency ranges of vascular impedance (i.e., below the cardiac frequency) (9).

Although an association between cerebrovascular events and aortic stiffness has been established (6), it is important to recognize that blood vessels exhibit significant regional differences in terms of morphology, neural innervation, receptor density, and overall functionality. Given such heterogeneity, it is worth emphasizing that the approach by Zhu et al. (12) potentially allows the specific interrogation of cerebrovascular impedance as opposed to impedance derived more proximally (e.g., aorta). Although unproven, the ability to characterize cerebrovascular impedance may offer new insights into the causation and treatment effects in disease processes associated with cerebral microvascular injury, such as transient or persistent white matter hyperintensities, lacunar infarcts, and vascular dementia (5).

Of course, no technique is perfect. Applanation tonometry is technically challenging and even with skilled operators may not be possible in some individuals due to anatomic variations. Vascular impedance should also ideally be determined from pressure flow waves recorded simultaneously at the same point in an artery. Although in practice small distances may be unavoidable, the distance between recording sites with this method means that phase relations will require correction using imperfect approximations. Furthermore, the assumption that pressure waveforms measured at the common or internal carotid is the same as those at the middle cerebral artery (or vice versa) deserves further scrutiny. Despite the relatively short distances between the sites, so-called conduit arteries, including the internal carotid, may impart significant resistance/impedance (4), whereas bifurcations and impedance mismatches can introduce wave reflection effects (8, 9), all of which can alter the pressure waveform. However, these potential limitations do not alter the fact that the technique is clearly a step in the right direction since it holds the prospect of generating new insights into the hemodynamics of the human cerebral circulation.

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REFERENCES