Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Editorial

Transcranial dopplers after cardiac arrest: Should we ride this wave?

Development of tools that allow assessment of individual physiology as it evolves over time is a prerequisite for precision medicine in the intensive care unit (ICU). Although non-invasive bedside measurement of many parameters including oxygen saturation, arterial blood pressure and cardiac output bedside monitors has existed for many years, strategies for brain monitoring have lagged behind. This limits clinicians' ability to minimize secondary brain damage among patients admitted to the ICU after cardiac arrest, brain trauma, stroke, and a myriad of other acute neurological injuries. Transcranial doppler sonography (TCD) has been used in neurocritical care for decades, but research exploring its ability to interrogate the integrity of cerebrovascular autoregulation or optimize individual cerebral perfusion is comparatively recent. TCDs can be performed at the bedside with little to no risk to patients and have a temporal resolution of ~5 ms. Important to titration of care, TCDs allow measurement of key parameters (cerebral blood flow velocity, pulsatility index [PI]) that allow ongoing real-time assessments of patients' autoregulatory indices, intracranial pressure, compliance and cerebral blood flow (CBF).[1] Prior studies of TCDs after cardiac arrest has been largely limited to small cohorts with conflicting results.[2–7] Given the potentially transformative therapeutic implications of successfully harnessing this tool, studies evaluating TCDs for predictive and prognostic enrichment are urgently needed.

In this issue of *Resuscitation*, Rafi et al., explore the prognostic value of TCD parameters to predict functional recovery after out-of-hospital cardiac arrest (OHCA).[8] The work builds on a longstanding and growing body of literature indicating cerebrovascular autoregulation is variably right-shifted or absent for several days following return of spontaneous circulation (ROSC).[9–13] The authors hypothesized that the magnitude of this pathology, quantified using TCD-derived estimates of cerebral vascular resistance, would reflect injury severity and therefore influence outcome at hospital discharge. The authors measured systolic and diastolic flow velocities (SFV and DFV) within 12 h of intensive care unit admission, and calculated mean flow velocity (MFV) and PI. They did not assesse autoregulatory index. Their main finding was that a higher PI resulting from reduced DFV predicted unfavorable outcome. This observation is consistent with findings from previous TCD-based studies.[12,14] A strength of this work is the timeframe in which TCD values were obtained (26–464 min after ROSC); it is the first report to identify the potential prognostic utility of PI and DFV this early post-arrest. If validated in larger studies, prompt recognition of patients at risk for unfavorable outcome based on these parameters may provide an opportunity for early intervention.

The interpretation of an elevated PI is complex, yet crucial to identifying future management strategies designed to improve outcome. PI values >1.19 are typically associated with increased downstream cerebrovascular resistance (CVR), identifying potential treatment targets that might attenuate this pathology directly, such as nitric oxide or endothelin, or a potential need for blood pressure augmentation to preserve CBF in the face of increased CVR.[15] PI not always inversely proportional to CVR — indeed, there are clinical situations where PI increases in the context of decreasing CVR and a vasodilatory cascade e.g. during an intracranial hypertensive crisis represented by an intracranial pressure plateau wave.[16] This situation would warrant a different management strategy than patients with high flow velocities and low CVR (as observed in early post-arrest hyperemia[17]), or those with global cerebral hypoperfusion where velocities may be driven primarily by low flow rather than primary changes in resistance.

While these nuances may contribute to different strategies in optimizing management *between* patients, they are also important considerations *within* an individual post-arrest patient based upon the timing at which the measurements are obtained. Compounding differences in age, mechanism of cardiac arrest, insult duration, and brain-region specificity (cortical, subcortical, thalamic), classic preclinical cardiac arrest models and subsequent clinical data suggest temporal variability in CBF: in most patients, there is an immediate period of hyperemia, followed by a hypoperfusion stage with low CBF, likely uncoupled from metabolic demand.[10,12,14,15,18–28] This underscores the need for future research to evaluate the prognostic value of serial TCD measurements and their potential to inform targeted management at different temporal stages.

TCD-parameters may complement other available neuromonitoring tools such as intracranial pressure monitors and near-infrared spectroscopy, both of which have also been used to successfully interrogate CVR and autoregulation.[29,30] Unlike magnetic resonance imaging, xenon/computerized tomographic imaging or other advanced radiographic studies of CBF, TCDs are portable and easily performed in serial measurements at the bedside. Unlike pressure monitoring, TCDs are also non-invasive and their validity may be superior to near-infrared spectroscopy.[31] Unlike ultrasonographic measurement of optic nerve sheath diameter or quantitative pupillometry,[32,33] both of which may predict outcome after cardiac arrest, TCDs may reveal not only prognostic data but also identify potentially treatable derangements in CBF or CVR. Despite these advantages, translation to routine clinical practice may be challenging. TCD interpretation and acquisition are

operator dependent and require acoustic windows amenable to insonation. The technique is further limited by its focality (TCDs are typically acquired from the middle cerebral artery), which may not adequately reflect heterogeneous regional variability in CBF and CVR observed after cardiac arrest[15,28]. Serial measurements are resource intensive and can currently be obtained only intermittently. Real-time data interpretation requires substantial bioinformatic infrastructure and clinician expertise.

The complexity of cerebrovascular hemodynamics is humbling. Even under normal conditions in a single patient, cerebrovascular autoregulation and hemodynamics are spatiotemporally variable, influenced by a network of neurogenic, myogenic, metabolic and endothelial pathways, and modulated by an interplay between genetics and environmental influences. This complexity is amplified after devastating injuries like cardiac arrest. Development and validation of accurate, non-invasive proxies for CBF, resistance, and autoregulation such as the TCD parameters identified by this study, are incremental but essential foundational steps towards understanding underlying pathophysiology and targeting management to improve patient-outcomes.

Disclosures

Dr. Elmer's research time is supported by the NIH through grant 5K23NS097629. Dr. Jha's research time is supported by the NIH through grant 5K23NS101036.

Conflicts of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Castro P, Azevedo E, Sorond F. Cerebral autoregulation in stroke. Curr Atheroscler Rep 2018;20:37, doi:http://dx.doi.org/10.1007/s11883-018-0739-5.
2. Cardim D, Griesdale DE, Ainslie PN, Robba C, Calviello L, Czosnyka M, et al. A comparison of non-invasive versus invasive measures of intracranial pressure in hypoxic ischaemic brain injury after cardiac arrest. Resuscitation 2019;137:221–8, doi:http://dx.doi.org/10.1016/j.resuscitation.2019.01.002.
3. Lin J-J, Hsia S-H, Wang H-S, Chiang M-C, Lin K-L. Transcranial Doppler ultrasound in therapeutic hypothermia for children after resuscitation. Resuscitation 2015;89:182–7, doi:http://dx.doi.org/10.1016/j.resuscitation.2015.01.029.
4. Heimburger D, Durand M, Gaide-Chevronnay L, Dessertaine G, Moury P-H, Bouzat P, et al. Quantitative pupillometry and transcranial Doppler measurements in patients treated with hypothermia after cardiac arrest. Resuscitation 2016;103:88–93, doi:http://dx.doi.org/10.1016/j.resuscitation.2016.02.026.
5. Blumenstein J, Kempfert J, Walther T, Van Linden A, Fassl J, Borger M, et al. Cerebral flow pattern monitoring by transcranial Doppler during cardiopulmonary resuscitation. Anaesth Intensive Care 2010;38:376–80, doi:http://dx.doi.org/10.1177/0310057X1003800223.
6. Belohlavek J, Skalicka H, Boucek T, Kovarnik T, Fichtl J, Smid O, et al. Feasibility of cerebral blood flow and oxygenation monitoring by continuous transcranial Doppler combined with cerebral oximetry in a patient with refractory cardiac arrest treated by extracorporeal life support. Perfusion 2014;29:534–8, doi:http://dx.doi.org/10.1177/0267659114529322.
7. Doepp Connolly F, Reitemeier J, Storm C, Hasper D, Schreiber SJ. Duplex sonography of cerebral blood flow after cardiac arrest–a prospective observational study. Resuscitation 2014;85:516–21, doi:http://dx.doi.org/10.1016/j.resuscitation.2013.12.021.
8. Rafi S, Tadie J-M, Gagouin A, Leurent G, Bedossa M, Le Tulzo Y, et al. Doppler sonography of cerebral blood flow for early prognostication after out-of-hospital cardiac arrest: DOTAC study. Resuscitation 2019;141:188–94, doi:http://dx.doi.org/10.1016/j.resuscitation.2019.05.024.
9. Oku K, Kuboyama K, Safar P, Obrist W, Sterz F, Leonov Y, et al. Cerebral and systemic arteriovenous oxygen monitoring after cardiac arrest. Inadequate cerebral oxygen delivery. Resuscitation 1994;27:141–52.
10. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128–32.
11. Wolfson SK, Safar P, Reich H, Clark JM, Gur D, Stezoski W, et al. Dynamic heterogeneity of cerebral hypoperfusion after prolonged cardiac arrest in dogs measured by the stable xenon/CT technique: a preliminary study. Resuscitation 1992;23:1–20.
12. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke 1997;28:1569–73.
13. van den Brule JMD, Vinke E, van Loon LM, van der Hoeven JG, Hoedemaekers CWE. Middle cerebral artery flow, the critical closing pressure, and the optimal mean arterial pressure in comatose cardiac arrest survivors-An observational study. Resuscitation 2017;110:85–9, doi:http://dx.doi.org/10.1016/j.resuscitation.2016.10.022.
14. Lemiale V, Huet O, Vigué B, Mathonnet A, Spaulding C, Mira J-P, et al. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. Resuscitation 2008;76:17–24, doi:http://dx.doi.org/10.1016/j.resuscitation.2007.06.028.
15. Iordanova B, Li L, Clark RSB, Manole MD. Alterations in Cerebral Blood Flow after Resuscitation from Cardiac Arrest. Front Pediatr 2017;5:174, doi:http://dx.doi.org/10.3389/fped.2017.00174.
16. de Riva N, Budohoski KP, Smielewski P, Kasprowicz M, Zweifel C, Steiner LA, et al. Transcranial Doppler pulsatility index: what it is and what it isn't. Neurocrit Care 2012;17:58–66, doi:http://dx.doi.org/10.1007/s12028-012-9672-6.
17. Wessels T, Harrer JU, Jacke C, Janssens U, Klötzsch C. The prognostic value of early transcranial Doppler ultrasound following cardiopulmonary resuscitation. Ultrasound Med Biol 2006;32:1845–51, doi:http://dx.doi.org/10.1016/j.ultrasmedbio.2006.06.023.
18. Blomqvist P, Wieloch T. Ischemic brain damage in rats following cardiac arrest using a long-term recovery model. J Cereb Blood Flow Metab 1985;5:420–31, doi:http://dx.doi.org/10.1038/jcbfm.1985.57.
19. Lee SK, Vaagenes P, Safar P, Stezoski SW, Scanlon M. Effect of cardiac arrest time on cortical cerebral blood flow during subsequent standard external cardiopulmonary resuscitation in rabbits. Resuscitation 1989;17:105–17.
20. Liachenko S, Tang P, Hamilton RL, Xu Y. Regional dependence of cerebral reperfusion after circulatory arrest in rats. J Cereb Blood Flow Metab 2001;21:1320–9, doi:http://dx.doi.org/10.1097/00004647-200111000-00008.
21. Sterz F, Leonov Y, Safar P, Johnson D, Oku K, Tisherman SA, et al. Multifocal cerebral blood flow by Xe-CT and global cerebral metabolism after prolonged cardiac arrest in dogs. Reperfusion with open-chest CPR or cardiopulmonary bypass. Resuscitation 1992;24:27–47.
22. Snyder JV, Nemoto EM, Carroll RG, Safar P. Global ischemia in dogs: intracranial pressures, brain blood flow and metabolism. Stroke 1975;6:21–7.
23. Kågström E, Smith ML, Siesjö BK. Local cerebral blood flow in the recovery period following complete cerebral ischemia in the rat. J Cereb Blood Flow Metab 1983;3:170–82, doi:http://dx.doi.org/10.1038/jcbfm.1983.24.
24. Iida K, Satoh H, Arita K, Nakahara T, Kurisu K, Ohtani M. Delayed hyperemia causing intracranial hypertension after cardiopulmonary resuscitation. Crit Care Med 1997;25:971–6.

25. Manchester LC, Lee V, Schmithorst V, Kochanek PM, Panigrahy A, Fink EL. Global and Regional Derangements of Cerebral Blood Flow and Diffusion Magnetic Resonance Imaging after Pediatric Cardiac Arrest. J Pediatr 2016;35:e1, doi:http://dx.doi.org/10.1016/j.jpeds.2015.10.003.
26. Pollock JM, Whitlow CT, Deibler AR, Tan H, Burdette JH, Kraft RA, et al. noxic injury-associated cerebral hyperperfusion identified with arterial spin-labeled MR imaging. AJNR Am J Neuroradiol 2008;29:1302–7, doi:http://dx.doi.org/10.3174/ajnr.A1095.
27. Brodersen P. Cerebral blood flow and metabolism in coma following cardiac arrest. Rev Electroencephalogr Neurophysiol Clin 1974;4:329–33, doi:http://dx.doi.org/10.1016/S0370-4475(74)80019-5.
28. Foley LM, Clark RSB, Vazquez AL, Hitchens TK, Alexander H, Ho C, et al. Enduring disturbances in regional cerebral blood flow and brain oxygenation at 24 h after asphyxial cardiac arrest in developing rats. Pediatr Res 2017;81:94–8, doi:http://dx.doi.org/10.1038/pr.2016.175.
29. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop "one-size-fits-all" hemodynamic targets? Resuscitation 2015;90:121–6, doi:http://dx.doi.org/10.1016/j.resuscitation.2015.03.001.
30. Balu R, Baghshomali S, Abella BS, Kofke WA. Abstract 12: Cerebrovascular Pressure Reactivity Predicts Outcome in Diffuse Hypoxic-Ischemic Brain Injury | Circulation. Circulation 2018;138:A12.
31. Caldwell M, Scholkmann F, Wolf U, Wolf M, Elwell C, Tachtsidis I. Modelling confounding effects from extracerebral contamination and systemic factors on functional near-infrared spectroscopy. Neuroimage 2016;143:91–105, doi:http://dx.doi.org/10.1016/j.neuroimage.2016.08.058.
32. Oddo M, Sandroni C, Citerio G, Miroz J-P, Horn J, Rundgren M, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med 2018;44:2102–11, doi:http://dx.doi.org/10.1007/s00134-018-5448-6.
33. Chelly J, Deye N, Guichard J-P, Vodovar D, Vong L, Jochmans S, et al. The optic nerve sheath diameter as a useful tool for early prediction of outcome after cardiac arrest: A prospective pilot study. Resuscitation 2016;103:7–13, doi:http://dx.doi.org/10.1016/j.resuscitation.2016.03.006.

Ruchira M. Jha
Departments of Critical Care Medicine, Neurology and Neurosurgery, University of Pittsburgh, Pittsburgh, USA

Jonathan Elmer*
Departments of Emergency Medicine, Critical Care Medicine and Neurology, University of Pittsburgh, Pittsburgh, USA

* Corresponding author at: Iroquois Building, Suite 400A, 3600 Forbes Avenue, Pittsburgh, PA 15213, USA.
E-mail address: elmerjp@upmc.edu (J. Elmer).

http://dx.doi.org/10.1016/j.resuscitation.2019.06.281