Journal of the American Heart Association

EDITORIAL

The Quest of Characterizing Hemodynamic Failure in Patients With Cerebrovascular Disease

Alexander V. Khaw, MD; Jonathan D. Thiessen, PhD; Keith St. Lawrence, PhD; Sachin K. Pandey, MD

Health care providers today remain challenged by a remarkable lack of efficacious and specific secondary prevention options in many patients with symptomatic steno-occlusive disease of the extracranial brain-supplying arteries. This is particularly true in the large subgroup of atherosclerotic carotid artery occlusion or near occlusion, when surgical or endovascular revascularization is not recommended or has no supporting high-class evidence.[1] One of the lessons learned from the failed Extracranial–Intracranial (EC-IC) Bypass Study Group trial was that the risk of recurrent ischemic stroke among patients with carotid artery occlusion varies over a wide range.[2] Thus, identification and selection of high-risk patients is critical in designing trials for more precise risk estimates and their differences between intervention and control groups. Hemodynamic compromise has been established as a strong predictor of high recurrent stroke risk and is detected on the basis of the gold-standard of positron emission tomography (PET) imaging.[3] Despite implementation of $H_2{}^{15}O$ PET, which remains restricted to a small number of sites due to isotope availability and cost, the Carotid Occlusion Surgery Study failed to demonstrate a benefit in reducing the recurrent stroke risk in patients with hemodynamic compromise by undergoing EC-IC bypass surgery.[4] Most recently, a large randomized Chinese study of patients with atherosclerotic occlusion of the internal carotid or middle cerebral artery (CMOSS [Carotid and Middle Cerebral Artery Occlusion Surgery Study]) used a more pragmatic, less costly, and more globally accessible approach to detect hemodynamic compromise with computed tomography perfusion. Yet this trial also failed to show a benefit of EC-IC bypass surgery in the primary outcome event (stroke or death within 30 days or ischemic stroke in the qualifying arterial territory after 30 days), as well as in any one of the secondary outcomes.[5] These results highlight the need for imaging approaches that are safe, feasible, and well validated against gold-standard approaches for use in identification of patients for future phase II or possible phase III randomized clinical treatment trials. In this issue of the *Journal of the American Heart Association* (*JAHA*), Sebök et al[6] have taken up this challenge to validate a magnetic resonance imaging (MRI)-based method of identifying patients with incremental stages of hemodynamic failure (HF) by impaired cerebrovascular reactivity (CVR) against the clinically adapted gold standard of semiquantitative $H_2{}^{15}O$ PET (ie, without invasive arterial sampling).

See Article by Sebök et al.

Key Words: Editorials ■ cerebral hemodynamics ■ cerebrovascular reactivity ■ magnetic resonance imaging/MRI ■ positron emission tomography/PET

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Alexander V. Khaw, MD, Department of Clinical Neurosciences, University Hospital, 339 Windermere Road, London, Ontario N6A 5A5, Canada. Email: akhaw@uwo.ca

This manuscript was sent to Luciano A. Sposato, MD, MBA, FRCPC, Associate Editor, for editorial decision and final disposition.

For Disclosures, see page 3.

© 2023 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

The authors compared ^{15}O-water PET before and after acetazolamide to an MRI method to classify HF stages using blood–oxygen level–dependent cerebrovascular reactivity (BOLD-CVR) in 53 patients with symptomatic unilateral cerebrovascular steno-occlusive disease of various causes. BOLD-CVR was determined using a standardized CO_2 challenge and defined as percentage BOLD signal change/mm Hg CO_2. With reference to HF staging using ^{15}O-water PET, they established BOLD-CVR cutoff points for different vascular territories. Notably, BOLD-CVR applied to the middle cerebral artery territory demonstrated the highest consistency, with a sensitivity of 0.85, specificity of 0.81, and accuracy of 0.83 when classifying HF stage 2 versus HF stages 0 to 1. Conversely, the anterior and posterior watershed areas had lower accuracy, likely due to variations in anatomy, vascular distribution, and collateralization between patients, and all accuracy measures degraded substantially, when tested for each HF stage individually, as compared with dichotomized HF staging.

Accurate MRI-based measurements of CVR would have several advantages over PET and single photon emission computed tomography measurements of CVR. MRI would not require patient exposure to ionizing radiation. Further, MRI has far greater worldwide accessibility than PET imaging. This disparity is further exaggerated when compared only to sites with on-site cyclotrons needed for ^{15}O-PET imaging. Nevertheless, there are still challenges establishing standardized and quantitative MRI methods for measuring CVR. By establishing BOLD-CVR cutoff points with reference to a gold standard ^{15}O-water PET measurements, Sebök et al have made an important contribution toward demonstrating the clinical utility of BOLD-CVR.

CHALLENGES AND OPPORTUNITIES FOR STANDARDIZATION OF CVR MEASUREMENTS WITH MRI

There is a variety of physiological and technical factors that can affect the accuracy and repeatability of CVR measurements: physiological factors such as sex, age, weight, and use of caffeine or nicotine; methodological factors (eg, time of day, time between repeated studies, experience of reader[s], choice of vasodilator); and technological factors (eg, imaging modality and in the case of MRI, differences between pulse sequences, field strength, and image processing methods).[7]

Alternative MRI-based approaches for measuring CVR include phase-contrast MRI and arterial spin labeling (ASL) measurements of cerebral blood flow (CBF). Phase-contrast MRI can measure whole-brain CBF but lacks the voxel-wise localization of ASL and BOLD.[8] ASL measurements of CBF at rest and vasodilation are another compelling MRI-based approach for measuring CVR. Still, ASL remains challenged by low signal-to-noise ratio (which practically limits applications to 3T field strength or higher), and regional changes in arterial transit times.[9] In a recent publication from Stanford University, there was good consistency when comparing whole brain CVR measured with multipost-labeling delay pseudo-continuous ASL (multipost-labeling delay pCASL) MRI in healthy controls acquired simultaneously on a hybrid PET/MRI.[10] In a publication investigating moyamoya disease, there was high agreement between multi post-labeling delay pCASL and reference ^{15}O-water PET measurements of CVR.[11] A study comparing simultaneous pCASL and ^{15}O-water PET measurements of CBF in frontotemporal dementia revealed good concordance in different regions of the brain, supporting the use of MRI as an alternative to ^{15}O-water PET for measuring regional perfusion deficits across a spectrum of neurological disorders.[12]

The contribution of Dr. Sebök and colleagues continues a long tradition of validating MRI methods against gold-standard PET measurements. Given the potential for different physiological states when comparing PET and MRI measurements of CVR, as well as the convenience of acquiring all data in a single imaging session, simultaneous PET/MRI could play an important role in the development and validation of MRI-based measurements of CVR.

Another challenge when acquiring dynamic ^{15}O-water PET is related to quantification of CBF, with quantitative measurements historically requiring an invasive and technically challenging measurement of the arterial input function during a dynamic PET experiment. Image-derived input functions can be used to derive pharmacokinetic parameters.[13] Image-derived input functions are typically estimated from dynamic PET signal measured in the carotid artery and suffer from partial volume errors due to the relatively low intrinsic spatial resolution of ^{15}O-PET. One solution is to incorporate simultaneous phase-contrast MRI measurements of whole-brain blood flow into the model, allowing for a noninvasive PET/MRI measurement of CBF that approaches the accuracy of gold standard ^{15}O-water PET with invasive arterial input function measurements.[14] Similarly, MRI-based measurements of whole-brain cerebral metabolic rate of oxygen and CBF can be used to generate noninvasive cerebral metabolic rate of oxygen and oxygen extraction fraction maps with ^{15}O–O_2 PET/MRI, significantly simplifying a procedure that historically required three different PET tracers (^{15}O–O_2, ^{15}O–H_2O, ^{15}O–CO) along with arterial blood sampling for each tracer.[15,16] Simultaneous PET/MRI could both enhance the accessibility and repeatability of gold-standard quantitative PET measurements of CVR and provide a platform to validate

magnetic resonance–based measurements of CVR with BOLD-CVR or ASL.

Beyond the imaging technique, there is promise for better cerebral vasodilation techniques. Computer-controlled gas blenders such as the RespirAct enable precise delivery of CO_2 to induce a predictable and reproducible vasodilatory effect. Nonpharmacological vasodilation is desirable due to faster action and the option to end the challenge early if necessary. Interestingly, there have been parallel developments using precise CO_2 delivery with BOLD cardiac MRI detecting changes in myocardial oxygenation that are visually concordant with simultaneous measurements of ^{13}N-ammonia PET myocardial perfusion reserve in healthy canines and a canine model of coronary stenosis.[17] Inhalation of hypercapnic gas has several advantages as a vasodilator, with fewer side effects, improved compliance, and increased reproducibility relative to an infusion of acetazolamide or breath-hold methods.[7]

FUTURE DIRECTIONS AND CONCLUSION

As stated in their artibcle, a prospective multicenter trial will be needed to demonstrate the validity of the proposed quantitative BOLD-CVR thresholds, not only against the declared gold standard method but also against clinical end points.[18] These would have to be developed and validated for disease subgroups, which, as in this study, most often and debatably have been combined. Questions remain whether, even among a syndromal subgroup such as moyamoya disease, HF stages will have similar thresholds for those patients with idiopathic versus secondary disease or those presenting in childhood versus adulthood. Although outside the scope of this article, it would be interesting to see a direct comparison of BOLD-CVR to ^{15}O-water PET where hypercapnia is induced with the same CO_2 challenge paradigm for both modalities, ideally within the same session using simultaneous PET/MRI.Standardization of MRI-based CVR measurements will be another major challenge that would benefit from a common vasodilator, MRI methodology (currently either BOLD or ASL), and standardization of acquisition parameters. Of course, MRI's great benefit is also one of its greatest challenges: the multitude of acquisition parameters and quantitative approaches makes standardization challenging, geographically and over time. A significant effort will be needed to ensure quantitative MRI-based CVR measurements are widely adopted and replicable.

As shown in this study, BOLD-CVR is a promising approach to assess hemodynamic failure in various vascular territories. This technique may have clinical implications for diagnosing and managing cerebrovascular conditions in the future, with the potential to improve patient care and outcomes. While the hope for EC-IC bypass surgery as an effective treatment in a select patient subgroup has been attenuated from clinical trial to trial, the need for accessible and affordable selection tools to test new therapeutic agents and strategies has increased, especially in the light of incremental molecular targeting.

ARTICLE INFORMATION

Affiliations

Department of Clinical Neurosciences, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (A.V.K.); Lawson Health Research Institute, London, Ontario, Canada (A.V.K., J.D.T., K.S.L.); Department of Medical Biophysics (A.V.K., J.D.T., K.S.L.) and Department of Medical Imaging (J.D.T., K.S.L., S.K.P.), Schulich School of Medicine and Dentistry (J.D.T., K.S.L., S.K.P.), Western University, London, Ontario, Canada.

Disclosures

None.

REFERENCES

1. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2019;52:e364–e467. doi: 10.1161/STR.0000000000000375
2. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. *N Engl J Med*. 1985;313:1191–1200. doi: 10.1056/NEJM198511073131904
3. Derdeyn CP, Videen TO, Simmons NR, Yundt KD, Fritsch SM, Grubb RL Jr, Powers WJ. Count-based PET method for predicting ischemic stroke in patients with symptomatic carotid arterial occlusion. *Radiology*. 1999;212:499–506. doi: 10.1148/radiology.212.2.r99au27499
4. Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP Jr, Derdeyn CP; COSS Investigators. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the carotid occlusion surgery study randomized trial. *JAMA*. 2011;306:1983–1992. doi: 10.1001/jama.2011.1610
5. Ma Y, Wang T, Wang H, Amin-Hanjani S, Tong X, Wang J, Tong Z, Kuai D, Cai Y, Ren J, et al. Extracranial-intracranial bypass and risk of stroke and death in patients with symptomatic artery occlusion: the CMOSS randomized clinical trial. *JAMA*. 2023;330:704–714. doi: 10.1001/jama.2023.13390
6. Sebök M, van der Wouden F, Mader C, Pangalu A, Treyer V, Fisher JA, Mikulis DJ, Hüllner M, Regli L, Fierstra J, et al. Hemodynamic failure staging with blood oxygenation-level dependent cerebrovascular reactivity and acetazolamide challenged (^{15}O-)H_2O-positron emission tomography across individual cerebrovascular territories. *J Am Heart Assoc*. 2023;12:e029491. doi: 10.1161/JAHA.123.029491
7. Zhao MY, Woodward A, Fan AP, Chen KT, Yu Y, Chen DY, Moseley ME, Zaharchuk G. Reproducibility of cerebrovascular reactivity measurements: a systematic review of neuroimaging techniques. *J Cereb Blood Flow Metab*. 2022;42:700–717. doi: 10.1177/0271678X211056702
8. de Boorder MJ, Hendrikse J, van der Grond J. Phase-contrast magnetic resonance imaging measurements of cerebral autoregulation with a breath-hold challenge: a feasibility study. *Stroke*. 2004;35:1350–1354. doi: 10.1161/01.STR.0000128530.75424.63
9. Zhou Y, Rodgers ZB, Kuo AH. Cerebrovascular reactivity measured with arterial spin labeling and blood oxygen level dependent techniques. *Magn Reson Imaging*. 2015;33:566–576. doi: 10.1016/j.mri.2015.02.018
10. Zhao MY, Fan AP, Chen DY-T, Sokolska MJ, Guo J, Ishii Y, Shin DD, Khalighi MM, Holley D, Halbert K, et al. Cerebrovascular reactivity measurements using simultaneous 15O-water PET and ASL MRI: impacts

of arterial transit time, labeling efficiency, and hematocrit. *Neuroimage*. 2021;233:117955. doi: 10.1016/j.neuroimage.2021.117955
11. Zhao MY, Fan AP, Chen DY-T, Ishii Y, Khalighi MM, Moseley M, Steinberg GK, Zaharchuk G. Using arterial spin labeling to measure cerebrovascular reactivity in Moyamoya disease: insights from simultaneous PET/MRI. *J Cereb Blood Flow Metab*. 2022;42:1493–1506. doi: 10.1177/0271678X221083471
12. Ssali T, Narciso L, Hicks J, Liu L, Jesso S. Concordance of regional hypoperfusion by pCASL MRI and 15O-water PET in frontotemporal dementia: is pCASL an efficacious alternative? *NeuroImage Clin*. 2022;33:102950. doi: 10.1016/j.nicl.2022.102950
13. Su Y, Vlassenko AG, Couture LE, Benzinger TLS, Snyder AZ, Derdeyn CP, Raichle ME. Quantitative hemodynamic PET imaging using image-derived arterial input function and a PET/MR hybrid scanner. *J Cereb Blood Flow Metab*. 2017;37:1435–1446. doi: 10.1177/0271678X16656200
14. Narciso L, Ssali T, Liu L, Jesso S, Hicks JW, Anazodo U, Finger E, St Lawrence K. Noninvasive quantification of cerebral blood flow using hybrid PET/MR imaging to extract the [15 O]H2 O image-derived input function free of partial volume errors. *J Magn Reson Imaging*. 2022;56:1243–1255. doi: 10.1002/jmri.28134
15. Narciso L, Ssali T, Iida H, St Lawrence K. A non-invasive reference-based method for imaging the cerebral metabolic rate of oxygen by PET/MR: theory and error analysis. *Phys Med Biol*. 2021;66:065009. doi: 10.1088/1361-6560/abe737
16. Narciso L, Ssali T, Liu L, Biernaski H, Butler J, Morrison L, Hadway J, Corsaut J, Hicks JW, Langham MC, et al. A noninvasive method for quantifying cerebral metabolic rate of oxygen by hybrid PET/MRI: validation in a porcine model. *J Nucl Med*. 2021;62:1789–1796. doi: 10.2967/jnumed.120.260521
17. Yang H-J, Oksuz I, Dey D, Sykes J, Klein M, Butler J, Kovacs MS, Sobczyk O, Cokic I, Slomka PJ, et al. Accurate needle-free assessment of myocardial oxygenation for ischemic heart disease in canines using magnetic resonance imaging. *Sci Transl Med*. 2019;11:eaat4407. doi: 10.1126/scitranslmed.aat4407
18. Carlson AP, Yonas H, Chang Y-F, Nemoto EM. Failure of cerebral hemodynamic selection in general or of specific positron emission tomography methodology? Carotid occlusion surgery study (COSS). *Stroke*. 2011;42:3637–3639. doi: 10.1161/STROKEAHA.111.627745