Brief Report

Detection of Anterior Circulation Large Artery Occlusion in Ischemic Stroke Using Noninvasive Cerebral Oximetry

Alexander C. Flint, MD, PhD; Shiv G. Bhandari; Sean P. Cullen, MD; Adhikari V. Reddy, MD; Daniel P. Hsu, MD; Vivek A. Rao, MD; Minal Patel, MD; Jasmeen Pombra, MD; Nancy J. Edwards, MD; Sheila L. Chan, MD

Background and Purpose—Large artery occlusion (LAO) in ischemic stroke requires recognition and triage to an endovascular stroke treatment center. Noninvasive LAO detection is needed to improve triage.

Methods—Prospective study to test whether noninvasive cerebral oximetry can detect anterior circulation LAO in acute stroke. Interhemispheric $\Delta BrSO_2$ in LAO was compared with controls.

Results—In LAO stroke, mean interhemispheric $\Delta BrSO_2$ was −8.3±5.8% (n=19), compared with 0.4±5.8% in small artery stroke (n=17), 0.4±6.0% in hemorrhagic stroke (n=14), and 0.2±7.5% in subjects without stroke (n=19) (P<0.001). Endovascular stroke treatment reduced the $\Delta BrSO_2$ in most LAO subjects (16/19). Discrimination of LAO at a −3% $\Delta BrSO_2$ cut had 84% sensitivity and 70% specificity. Addition of the G-FAST clinical score (gaze–face–arm–speech– time) to the $BrSO_2$ measure had 84% sensitivity and 90% specificity.

Conclusions—Noninvasive cerebral oximetry may help detect LAO in ischemic stroke, particularly when combined with a simple clinical scoring system. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020140.)**

Key Words: brain ischemia ■ oximetry ■ stroke ■ triage

Large artery occlusion (LAO) accounts for up to a third of ischemic strokes.[1] Endovascular stroke treatment (EST) trials show improved outcomes, with better outcomes at faster recanalization times.[2]

EST expertise is severely limited. Prehospital LAO detection is critical to accurate triage.[3,4] Scores such as the National Institutes of Health Stroke Scale (NIHSS) identify hemispheric signs, but these are too complicated for prehospital use. Simpler scoring systems such as G-FAST (gaze–face–arm–speech–time) have high specificity but lower sensitivity for LAO.[5]

Noninvasive cerebral oximetry by near-infrared spectroscopy identifies ischemia during cardiac surgery and carotid endarterectomy.[6] In this prospective study, we tested whether cerebral oximetry could detect LAO.

Patients and Methods

We conducted a prospective study of noninvasive cerebral oximetry in hospitalized subjects at a Joint Commission–certified Comprehensive Stroke Center.

Group 1 subjects (n=19) were referred for anterior circulation EST, with occlusion of the intracranial internal carotid artery or middle cerebral artery M1/M2 segments on computed tomographic angiography and catheter angiogram. Posterior circulation LAOs were excluded. Group 2 (n=17) was patients with small artery stroke, with no LAO on computed tomographic angiography. Group 3 (n=14) was supratentorial intraparenchymal hemorrhagic stroke subjects. Group 4 (n=19) was subjects with non-neurological medical diagnoses. Additional exclusions were age <18 and history of craniotomy or cranial access procedure.

Cerebral oximetry was performed with an INVOS monitor (Medtronic, Minneapolis, MN). Small adhesive sensors were placed on symmetrical forehead locations. Measurements were recorded after baseline signal stabilization of ≥30 s. Calculation of $\Delta BrSO_2$ was by the formula $((\%BrSO_{2[ipsilateral]} - \%BrSO_{2[contralateral]})/\%BrSO_{2[contralateral]})$, expressed as percentage difference. For group 4, ipsilateral side was randomly assigned.

G-FAST[5] was determined from the electronic medical record, blinded to the interhemispheric difference measurements.

Continuous data were compared with the nonparametric Kruskal–Wallis test for 2 groups and ANOVA with post-test Bonferroni correction for >2 groups. Receiver-operator characteristics analysis determined the optimum $BrSO_2$ difference cut.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Approvals

The Kaiser Permanente Northern California institutional review board approved this study. All subjects/surrogates gave written informed consent to participate in the study.

Results

Mean age was 66.7±15.5 years. In group 1 (LAO), median NIHSS was 18 (interquartile range, 17–21.5); in group 2 (small artery stroke), the median NIHSS was 2 (interquartile range, 1–3). In group 3, median ICH volume was 11 mL (interquartile range, 7–15 mL), and median Graeb IVH score

Received November 15, 2017; final revision received December 1, 2017; accepted December 11, 2017.

From the Division of Research, Kaiser Permanente, Oakland, CA (A.C.F.); and Neuroscience Department, Kaiser Permanente, Redwood City, CA (A.C.F., S.G.B., S.P.C., A.V.R., D.P.H., V.A.R., M.P., J.P., N.J.E., S.L.C.).

Correspondence to Alexander C. Flint, MD, PhD, Division of Research & Department of Neuroscience, Kaiser Permanente, 1150 Veterans Blvd, Redwood City, CA 94025. E-mail alexander.c.flint@kp.org

was 0 (interquartile range, 0–2). In group 3, ICH location was thalamic in 5, ganglionic in 4, and lobar in 5.

In LAO ischemic stroke, mean $\Delta BrSO_2$ was −8.3±5.8% (lower ipsilaterally), compared with 0.4±5.8% in group 2, 0.4±6.0% in group 3, and 0.2±7.5% in group 4 (P<0.001; Figure [A]).

Vessel recanalization by EST reduced or eliminated the interhemispheric difference in most LAO subjects (16/19), with a mean $\Delta BrSO_2$ of −8.3±5.8% before EST and a mean $\Delta BrSO_2$ of 1.6±9.6% after EST (Figure [B] and [C]). The change in $\Delta BrSO_2$ was associated with recanalization success (Figure [D]).

LAO discrimination at a $\Delta BrSO_2$ cut of −3% had 84.2% sensitivity and 70% specificity (73.9% correctly classified, receiver-operator characteristics area 0.77; 95% confidence interval, 0.67–0.88). Addition of G-FAST=3+ to $\Delta BrSO_2$ yielded 84.2% sensitivity and 92.0% specificity (89.9% correctly classified, receiver-operator characteristics area 0.88; 95% confidence interval, 0.79–0.97, significant increase in receiver-operator characteristics area by addition of G-FAST; P<0.001). As expected, adding a more stringent cut point for G-FAST of 4 versus 0 to 3 leads to lower sensitivity (68.4%) but higher specificity (96.0%).

Although calculation of positive and negative predictive values directly from our data would be spurious because LAO prevalence cannot be determined in this study design, if one assumes a prevalence of 15% to 30% for LAO in acute stroke,[1,7] the combination of G-FAST=3+ and $\Delta BrSO_2$ of −3% would have a positive predictive value of 65% to 82% and negative predictive value of 97% to 93%.

Discussion

In this pilot study, anterior circulation LAO caused a detectable $\Delta BrSO_2$ that was not seen in controls. EST reversed the $\Delta BrSO_2$ in most cases. Combination of $\Delta BrSO_2$ with G-FAST was found to yield high sensitivity and specificity for LAO.

Prehospital triage optimization in LAO stroke is critical to improve outcomes because most primary stroke centers cannot perform EST.[3,4] Primary diversion of all strokes to EST centers is infeasible and would delay tPA (tissue-type plasminogen activator) treatment by bypassing closer primary stroke centers.[4]

Prehospital identification of LAO has focused on clinical scores, largely derived from the NIHSS. Scores tested for this purpose include FAST, G-FAST (FAST+gaze abnormality), Los Angeles Prehospital Stroke Scale and the Cincinnati

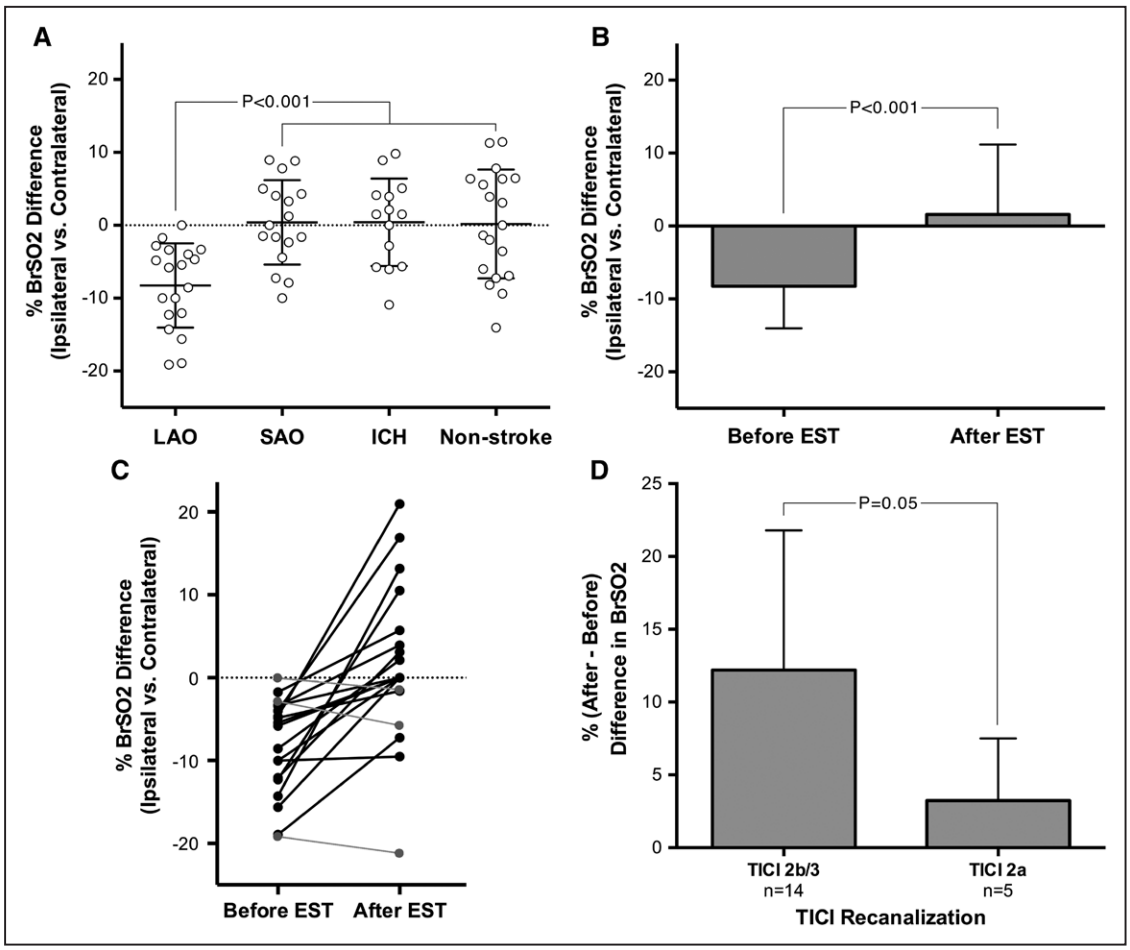

Figure. A, Interhemispheric %$BrSO_2$ difference in 4 groups: large artery occlusion (LAO), small artery occlusion (SAO), hemorrhagic stroke (ICH), and nonstroke, medical patients without stroke. Bars represent mean±SD. **B**, %$BrSO_2$ difference before and after endovascular stroke treatment (EST). **C**, Before–after plot of %$BrSO_2$ difference change with EST. For 16 of 19 subjects, the before EST difference in $BrSO_2$ was reduced (black symbols); for 3 of 19 subjects, the before EST difference in $BrSO_2$ was not reduced (gray symbols). **D**, Recanalization by EST and change in %$BrSO_2$ difference. Extent of recanalization shown by the Thrombolysis in Cerebral Infarction (TICI) score.

Prehospital Stroke Scale.[3] Simpler clinical scores have a sensitivity/specificity trade-off, depending on the cut.[5] G-FAST of 3+, as used here, has high specificity (89%) but low sensitivity (39%) for LAO.[5] Adding NIHSS hemispheric elements might improve the specificity for LAO detection, but the training required makes this impractical in the prehospital environment.

Given the need for accurate prehospital triage of LAO and non-LAO patients, an optimum screen should be both sensitive and specific. Here, cerebral oximetry alone demonstrated a balance between sensitivity (84%) and specificity (70%), and addition of G-FAST=3+ improved specificity to 92% without altering sensitivity.

Other noninvasive technologies are also of interest, including inductive phase shift spectroscopy[8] and electroencephalography. The relative performance, ease-of-use, and costs of noninvasive technologies will be important considerations for any attempt to deploy noninvasive LAO detection at scale. The approach tested here is clinically well established, with regulatory approval for many years. The monitor takes only 1 to 2 minutes to obtain measurements and is quite straightforward to deploy (in our experience, <10 minutes of in-service training was required for physicians, nursing staff, or technicians to learn to use the device).

Our study has limitations. This was a pilot study and was unblinded to patient diagnosis. Subjects were hospitalized and were not necessarily reflective of the prehospital triage population. Near-infrared spectroscopy has potential technical limitations, with heterogeneous field subject to potential variation in arterial flow. The device has to be applied to an area of skin without hair, which restricts use to the anterior circulation. The limited number of ICH subjects means that we cannot estimate any relative difference in $\Delta BrSO_2$ between deep and lobar hematoma or based on hematoma volume.

In conclusion, noninvasive cerebral oximetry may help detecting anterior circulation LAO in acute ischemic stroke, particularly when combined with a simple clinical scoring system. Next steps to further evaluate this approach will require assessment using unselected suspected stroke subjects in the emergency department and prehospital environments.

Sources of Funding

INVOS monitors provided without charge by Medtronic for the allowable period under the US Sunshine Act. Dr Flint provided conception and statistics and is responsibility for the article; Dr Flint, S.G. Bhandari, and Dr Chan are involved in article drafting; and all authors contributed substantially to revision.

Disclosures

None.

References

1. Beumer D, Mulder MJHL, Saiedie G, Fonville S, van Oostenbrugge RJ, van Zwam WH, et al. Occurrence of intracranial large vessel occlusion in consecutive, non-referred patients with acute ischemic stroke. *Neurovasc Imaging*. 2016;2:11.
2. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647.
3. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:3020–3035. doi: 10.1161/STR.0000000000000074.
4. Goyal M, Yu AYX, Menon BK, Dippel DWJ, Hacke W, Davis SM, et al. Endovascular therapy in acute ischemic stroke: challenges and transition from trials to bedside. *Stroke J Cereb Circ*. 2016;47:548–553.
5. Scheitz JF, Abdul-Rahim AH, MacIsaac RL, Cooray C, Sucharew H, Kleindorfer D, et al; SITS Scientific Committee. Clinical selection strategies to identify ischemic stroke patients with large anterior vessel occlusion: results from SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry). *Stroke*. 2017;48:290–297. doi: 10.1161/STROKEAHA.116.014431.
6. Edmonds HL Jr, Ganzel BL, Austin EH III. Cerebral oximetry for cardiac and vascular surgery. *Semin Cardiothorac Vasc Anesth*. 2004;8:147–166.
7. Zhao H, Coote S, Pesavento L, Churilov L, Dewey HM, Davis SM, et al. Large vessel occlusion scales increase delivery to endovascular centers without excessive harm from misclassifications. *Stroke*. 2017;48:568–573. doi: 10.1161/STROKEAHA.116.016056.
8. González CA, Villanueva C, Vera C, Flores O, Reyes RD, Rubinsky B. The detection of brain ischaemia in rats by inductive phase shift spectroscopy. *Physiol Meas*. 2009;30:809–819. doi: 10.1088/0967-3334/30/8/006.

Stroke
Journal of the American Heart Association

Detection of Anterior Circulation Large Artery Occlusion in Ischemic Stroke Using Noninvasive Cerebral Oximetry

Alexander C. Flint, Shiv G. Bhandari, Sean P. Cullen, Adhikari V. Reddy, Daniel P. Hsu, Vivek A. Rao, Minal Patel, Jasmeen Pombra, Nancy J. Edwards and Sheila L. Chan

Stroke. published online January 10, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628