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Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients

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Object. Near-infrared spectroscopy (NIRS) offers noninvasive bedside measurement of direct regional cerebral arteriovenous (mixed) brain oxygenation. To validate the accuracy of this monitoring technique, the authors analyzed the statistical correlation of NIRS and CT perfusion with respect to regional cerebral blood flow (CBF) measurements.

Methods. The authors retrospectively reviewed all cases in which NIRS measurements were obtained at a single, academic neurointensive care unit from February 2008 to June 2011 in which CT perfusion was performed at the same time as NIRS data was collected. Regions of interest were obtained 2.5 cm below the NIRS bifrontal scalp probe on CT perfusion with an average volume between 2 and 4 ml, with mean CBF values used for purposes of analysis. Linear regression analysis was performed for NIRS and CBF values.

Results. The study included 8 patients (2 men, 6 women), 6 of whom suffered subarachnoid hemorrhage, 1 ischemic stroke, and 1 intracerebral hemorrhage and brain edema. Mean CBF measured by CT perfusion was 61 ml/100 g/min for the left side and 60 ml/100 g/min for the right side, while mean NIRS values were 75 on the right and 74 on the left. Linear regression analysis demonstrated a statistically significant probability value ($p < 0.0001$) comparing NIRS frontal oximetry and CT perfusion–obtained CBF values.

Conclusions. The authors demonstrated a linear correlation for frontal NIRS cerebral oxygenation measurements compared with regional CBF on CT perfusion imaging. Thus, frontal NIRS cerebral oxygenation measurement may serve as a useful, noninvasive, bedside intensive care unit monitoring tool to assess brain oxygenation in a direct manner.

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Key Words • near-infrared spectroscopy • cerebral oxygenation • computed tomography perfusion • cerebral blood flow

Early detection and correction of cerebral ischemia is an essential part of the ICU treatment of patients after traumatic brain injuries or hemorrhagic and ischemic stroke.[14,24] Current methods used to monitor cerebral hemodynamics have significant limitations. Stable xenon-enhanced CT, PET, SPECT, or perfusion-weighted MR imaging requires transportation of a critically ill patient, which is impractical for most ICU settings and carries the risk of clinical deterioration. Other bedside methods such as jugular bulb oximetry indicate changes in CBF without direct measurement of CBF.

Near-infrared spectroscopy offers the advantage of measuring brain tissue arteriovenous oxygenation via an emitted near-infrared light that penetrates the scalp and underlying brain tissue and detects the absorption of oxygenated hemoglobin compared with deoxygenated hemoglobin. As a result, NIRS provides a noninvasive, real-time, bedside monitoring tool of cerebral oximetry in critically ill brain-injured patients without exposing patients to radiation. The correlation of CBF as measured by NIRS and CT perfusion has not been studied previous-

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; ICH = intracerebral hemorrhage; MTT = mean transit time; NIRS = near-infrared spectroscopy; SAH = subarachnoid hemorrhage.

ly, and we hypothesized that there is a linear correlation between CBF as evaluated by NIRS and CT perfusion measurements, which would validate the use of NIRS as a noninvasive tool of direct CBF evaluation.

Methods

We retrospectively reviewed all patients admitted to the Mayo Clinic in Jacksonville, Florida, from February 2008 through June 2011 with SAH, ischemic stroke, or ICH who underwent CT perfusion studies. Computed tomography perfusion was performed at the same time as NIRS data were collected. The CT perfusion method uses an iodinated contrast agent administered intravenously with subsequent acquisition of repeated high temporal resolution images. An increase in Hounsefield units can be measured in the intravascular and tissue beds. The transient increase in radiation attenuation is proportional to the amount of contrast in a given region and the speed at which the agent passes from arterial to venous circuits through the tissue bed.[9] The CT perfusion technique is based on the central volume principle, which relates CBF, CBV, and MTT in the following equation: CBF = CBV/MTT. Contrast agent time-concentration curves are generated in arterial and venous regions of interest and in each pixel. Deconvolution of arterial and tissue enhancement curves provides the MTT. Cerebral blood volume is calculated as the area under the curve in a parenchymal pixel divided by the area under the curve in an arterial pixel. The central volume equation can then be solved for CBF.[9]

The CT perfusion images were analyzed on a Siemens Leonardo postprocessing workstation. The CT perfusion regions of interest were obtained 2.5 cm below the NIRS frontal scalp probes with an average region of interest volume of 2–4 ml. The CT perfusion data parameters reviewed included CBF, CBV, time to drain, and MTT. Mean values and average SD were established for all CT perfusion parameters.

Bifrontal NIRS optodes (Casmed) were placed on the scalp per the manufacturer's recommendations, separated by an interoptode distance of 4–5 cm. The NIRS retrieved cerebral oximetry values 2.5 cm from the level of the scalp for bifrontal hemispheres. The data received were compared with the CT perfusion data. Both CT perfusion and NIRS were used within as close a time frame as possible (≤ 2 hours apart or ideally ≤ 32 minutes) to ensure comparable study data. The NIRS cerebral oximetry data recorded closest in time to the complete CT perfusion examination were analyzed.

Comparative data analysis was performed using the GraphPad Prism statistics software. A linear regression analysis was performed for a "best fit" standard 95% CI analysis. Statistical significance was defined as $p < 0.05$.

Results

Of 1287 patients admitted to the neuroscience ICU or hospital during the study period with SAH, ICH, or stroke-related diagnosis, we identified 16 data sets from 8 paired examinations of CT perfusion versus NIRS cerebral oximetry that met study criteria. Patient demographic data included 2 men and 6 women with a mean age of 68.4 years (range 47–86 years). Six patients suffered SAH, 1 had ischemic stroke, and 1 had ICH and brain edema. Mean values established for CBF in the CT perfusion study were 61.2 ± 21.28 ml/100 g/min (range 43.6–76.4 ml/100 g/min) for the left hemisphere and 60.2 ± 21.21 ml/100 g/min (range 43.4–77.4 ml/100 g/min) for the right hemisphere. Mean CBVs were 3.25 ± 1.04 ml (range 2.34–3.93 ml) for the left and 3.27 ± 1.00 ml (range 2.29–4.48 ml) for the right. The mean of MTT was 3.32 ± 0.709 seconds (range 3.01–3.78 seconds) for the left and 3.45 ± 0.837 seconds (range 3.01–4.22 seconds) for the right. The mean time to drain was 3.96 ± 0.694 seconds (range 2.65–4.99 seconds) for the left and 4.07 ± 0.942 seconds (range 2.57–5.15 seconds) for the right. The data collected by the NIRS device were as follows: mean value for left frontal oximetry was 74.5 ± 9.02 oximetry units (range 60–87 oximetry units) and 75.2 ± 10.7 oximetry units (range 56–84 oximetry units) for the right. Analysis of the linear regression revealed a p value < 0.0001 comparing NIRS frontal oximetry and CT perfusion–obtained CBF values (Fig. 1).

Discussion

We found a linear correlation between the use of frontal NIRS cerebral oxygenation and frontal CBF as measured by the CT perfusion method. This association has not been reported in any prior human studies that we could find and validates the accuracy of CBF measurement by NIRS.

Near-infrared spectroscopy oximetry has been evaluated in the use of vasospasm,[10] but not directly with CT perfusion CBF. These previous evaluations were animal studies using NIRS with indocyanine green in piglets[2,16] and other experiments.[1,5,6,10,19] We believe that our data, although small in number, may validate the use of NIRS as an important noninvasive real-time bedside application for NIRS in critically ill brain-injured patients who are too unstable to transport to a CT scanner for the CT perfusion-derived method. Near-infrared spectroscopy has the additional advantage of not exposing patients to radiation, a concern that is significant in patients undergoing numerous CT perfusion scans during prolonged ICU stays.

Some inherent technical limitations of NIRS need to be addressed. Cerebral blood flow measurements are of a regional nature, in contrast to CT perfusion and xenon-enhanced CT, which allow a more global assessment of brain perfusion. Also, NIRS measured approximately 2.5 cm down from the skin level, which was directly compared with regions of interest on the CT perfusion-derived regional CBF.[3] This information must be regarded with caution by clinicians. Regional information such as invasive brain tissue oxygenation (for example), Licox probes, and cerebral microdialysis probes do not always correlate with global cerebral metabolic states or even hemispheric states and are sometimes very specific to the region of injured brain. In Fig. 2, for example, in the upper left image, the posterior right hemisphere shows a hemorrhage with surrounding edema and low CBF, which would be missed by a left frontal NIRS oxygenation measurement.

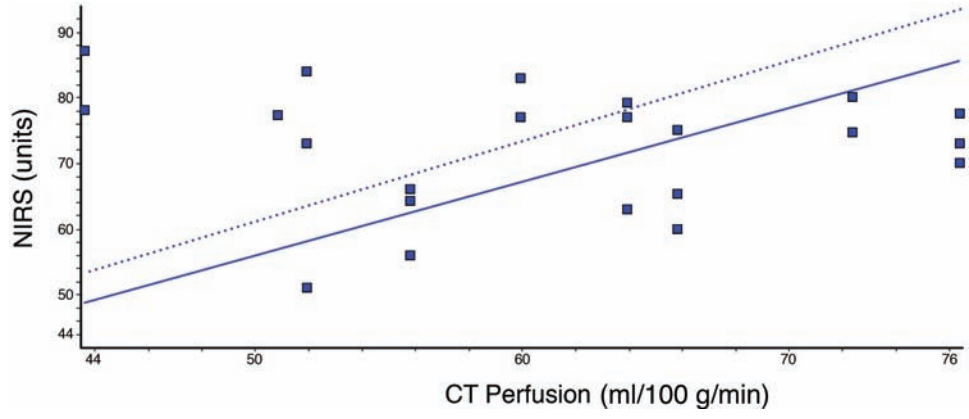

Fig. 1. Linear regression analysis comparing NIRS frontal oximetry and CT perfusion–obtained CBF values ($p < 0.0001$). The *solid line* represents the linear regression line and the *dashed line* represents the 95% CI. Twenty-two data points are shown because 3 patients underwent 2 CT perfusions with NIRS correlation.

Other methods of CBF measurement exist and their relative advantages and disadvantages are noted in Table 1. The CT perfusion method is a commonly used method in the neurointensive care unit, using iodinated contrast to measure CBF, due to its ease of use, speed of imaging, and wide availability.[6,21,22] However, acquiring measurements by means of CT perfusion requires transportation of critically ill patients, which poses patient safety risks of invasive catheter dislodgement (central venous lines or invasive brain catheters/probes), lowering the head of the bed during transport (increasing the risk of ventilator-associated pneumonia or raised intracranial pressure in patients with borderline intracranial compliance), exposure to ionizing radiation, and risk of possible allergic or anaphylactic reaction due to iodinated contrast material, or even contrast-induced nephropathy.[15,23] The peak dose from ionizing radiation in CT perfusion is approximately 325–435 mGy and depends on many factors including acquisition technique and type of scanner.[21] Early transient erythema may occur in some patients at a skin dose of 2000 mGy.[7] It is apparent that several CT perfusion scans in a short period of time could cause transient erythema and even "stripe alopecia."[7] There has been increasing scrutiny by the public of radiation dosing within the hospital.[7] Xenon-enhanced CT is another method used to measure CBF and is regarded as a potential gold standard for regional CBF measurement due to its superior spatial resolution, accuracy, and reproducibility.[6,17] However, xenon-derived CBF or xenon-enhanced CT is not widely available in many ICUs. Also, xenon has been known to be a vasodilator and may increase CBF (up to 100%).[8] One key advantage of the use of NIRS is its availability to be performed at the bedside, even in unstable patients who cannot be transported to the CT suite.[12]

Another method of measuring cerebral O_2 metabolism is the jugular venous catheter and jugular venous O_2 saturation by placement of a venous catheter into the internal jugular vein in the patient's neck. Jugular venous O_2 saturation estimates jugular venous oxygenation via a jugular vein catheter oximeter within the internal jugular vein and typically requires recalibration every 8–12 hours.[21] Jugular venous O_2 saturation can provide an indirect measurement of CBF by "supply and demand physiology" similar to NIRS, albeit with some differences explained below. When jugular venous O_2 saturation is low (< 50% for > 10 minutes in duration), it generally indicates decreased "supply physiology" such as very low hemoglobin defined by the delivery of O_2 equation: de-

TABLE 1: Different methods of CBF measurement

Method of CBF Measurement	Advantages	Disadvantages
Kety-Schmidt model	reliable measurement of global CBF[25]	inhalation mixture of O_2 & N_2O[25]
xenon-enhanced CT	accurate, high spatial quality, extensively researched[4]	not widely available, xenon known as a vasodilator[19]
CT perfusion	perhaps more widely used than xenon-enhanced CT, quantifies CBF, CBV, MTT, & time to peak[26]	x-ray exposure, bolus injection of iodine dye (dye allergy & anaphylactic risks), risk of contrast nephropathy, & transportation of critically ill[4]
PET	standardized, quantitative measurements of CBF & CBV, excellent spatial resolution[26]	not widely available to most ICUs, radioactive components[26]
MRI w/ perfusion-weighted imaging	can demonstrate structural brain changes as well as perfusion, & does not require use of ionizing radiation; measures CBF, CBV, MTT, & time to peak[13,26]	Gd intravenous contrast agent administration, may be problematic in renal failure, longer scan time vs CT[26]
NIRS w/ indocyanine green dye (animals)	noninvasive, no major side effects reported w/ use[5]	not standardized in humans, complex distortion by skin tissue[2]

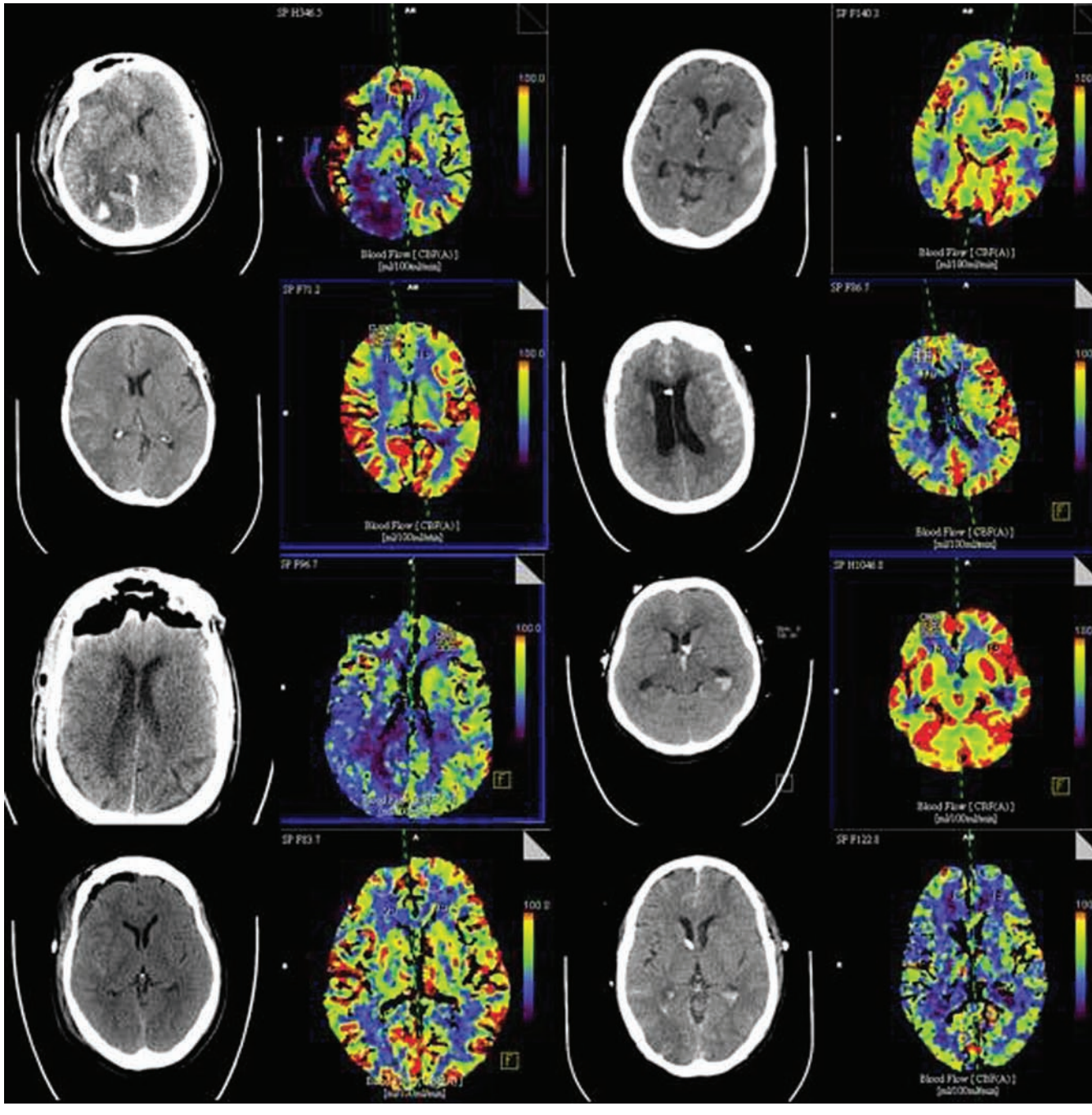

Fig. 2. Axial CT head and CT perfusion images of all 8 patients included in the study.

livery of O_2 = cardiac output × carrying capacity of O_2. The carrying capacity of O_2 is further defined as follows: (hemoglobin × 1.36 × saturation of O_2) + (partial pressure of O_2 × 0.0031). Other low "supply" physiological considerations include low cardiac output or poor oxygenation via the variables partial pressure of O_2, low hemoglobin, or saturation of O_2. Conversely, an increase in cerebral metabolism (increased demand) can similarly change the jugular venous O_2 saturation (or NIRS) by increased cerebral consumption of O_2 or increased O_2 extraction fraction. In fact, the arteriovenous O_2 content difference (carrying capacity of O_2 – the venous O_2 content of the blood) multiplied by the cardiac output is defined as O_2 demand by the Fick Principle.[21] Downsides to jugular venous O_2 saturation monitoring include invasive venous puncture and risks of central bloodstream-related infection (which is a national benchmark of inpatient quality), jugular vein thrombosis, and potential raised intracranial pressure from jugular venous outflow obstruction.[13]

The NIRS method is an emerging technology for measuring O_2 content via near-infrared light (approximately 600–900 nm) originally described by Jobsis,[11] in which near-infrared light emitted light through a cat's head. Neural activity is ultimately fueled by glucose-

oxidative metabolism and is dependent upon delivery of oxygenated hemoglobin transported from the blood to the tissue and results in exchange of oxygenated hemoglobin to the deoxygenated hemoglobin form.[21] In mammals, hemoglobin is a strong "chromophore" or light-absorbing molecule. Oxygenated and deoxygenated hemoglobin consist of different optical absorbing properties, which allows for its detection by NIRS; the maximum absorption of oxygenated hemoglobin is approximately 900 nm of near-infrared light and is approximately 760 nm in deoxygenated hemoglobin.[3] Lambert-Beer described a relationship that is a ratio of oxygenated hemoglobin versus deoxygenated hemoglobin via NIRS technology and is used in commercial and patent-specific NIRS measurement algorithms.[20]

Aoyagi described the NIRS method for isolating arterial O_2 saturation, which was described in 1985.[18] This noninvasive technology has emerged as a fairly ubiquitous tool for anesthesia and intraoperative, noninvasive, O_2 saturation monitoring to detect desaturation events in a real-time fashion. Therefore, cerebral NIRS measures combined arteriovenous oxygenated hemoglobin saturation (1/3 arterial and 2/3 venous), which has values that are higher than jugular venous O_2 saturation data and trend up and down depending on supply and demand cerebral physiology. The NIRS light is emitted at the level of the scalp, but measures deeper cerebral brain oxygenation via a "spatially resolved optode technique." Two optodes are separated by a finite distance from the light emitter, and the closer optode measures the superficial scalp tissues' contribution to tissue oxygenation, which is then subtracted from the distal optode measurement, which receives deeper cortical-subcortical brain tissue information.[3,4,21]

Therefore, NIRS indirectly measures CBF via supply and demand cerebral O_2 consumption and O_2 delivery, but not actual CBF directly. However, NIRS oximetry can indirectly assess CBF via a surrogate technique, which can provide some assessment of cerebral ischemia and physiology. To date, the isolation of the pure brain arterial oxygenation saturation via the noninvasive NIRS method remains difficult due to contamination of scalp, bone, and tissues external to underlying brain tissue. The cerebral oximetry devices have difficulty isolating the pulsatile arterial waveform that is distinct from extracerebral tissue compared with the "finger arterial saturation devices" that are commercially available and originally derived from Aoyagi's invention.[13] The NIRS cerebral oximetry technology nonetheless provides clinicians with a potentially useful method of indirectly assessing regional CBF that is noninvasive and provides some insight into neurometabolic states.

This study demonstrates that CT perfusion CBF has a significant linear correlation with NIRS measurement ($p > 0.0001$), although with several limitations. These limitations include the small sample size, a retrospective study design, and lack of a baseline comparative study between CT perfusion and NIRS methodology. Near-infrared spectroscopy is also limited by the thickness of the skull or frontal scalp swelling after craniotomy, which increases the distance from the light emitter and deeper tissues and can be further distorted if large amounts of CSF are present between skin and brain tissue or underlying severe brain atrophy.[12] Also, NIRS sensors are placed in the frontal head location only, which could complicate the estimation of the exact region of interest in CT perfusion imaging based on the depth from the optodes and penetration of NIRS light.

Disclosure

Dr. Hanel serves as a consultant to NeuroVasx and Codman.

Author contributions to the study and manuscript preparation include the following. Conception and design: Taussky, Daugherty, Pooley, Evans, Hanel, Freeman. Acquisition of data: Taussky, O'Neal, Luke, Thorpe, Pooley, Freeman. Analysis and interpretation of data: Taussky, O'Neal, Thorpe, Freeman. Drafting the article: Taussky, O'Neal, Freeman. Critically revising the article: Taussky, O'Neal, Hanel, Freeman. Reviewed submitted version of manuscript: Taussky, O'Neal, Luke, Thorpe, Pooley, Evans, Hanel, Freeman. Approved the final version of the manuscript on behalf of all authors: Taussky. Statistical analysis: Taussky, Luke. Administrative/technical/material support: Thorpe.

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