Development and Validation of a Cerebral Oximeter Capable of Absolute Accuracy

David B. MacLeod, MBBS, FRCA,* Keita Ikeda, PhD,* Charles Vacchiano, PhD, CRNA,† Aaron Lobbestael, MS,‡ Joyce A. Wahr, MD,§ and Andrew D. Shaw, MBBS, FRCA, FCCM‖

Objective: **Cerebral oximetry may be a valuable monitor, but few validation data are available, and most report the change from baseline rather than absolute accuracy, which may be affected by individuals whose oximetric values are outside the expected range. The authors sought to develop and validate a cerebral oximeter capable of absolute accuracy.**

Design: **An in vivo research study.**

Setting: **A university human physiology laboratory.**

Participants: **Healthy human volunteers were enrolled in calibration and validation studies of 2 cerebral oximetric sensors, the Nonin 8000CA and 8004CA. The 8000CA validation study identified 5 individuals with atypical cerebral oxygenation values; their data were used to design the 8004CA sensor, which subsequently underwent calibration and validation.**

Interventions: **Volunteers were taken through a stepwise hypoxia protocol to a minimum saturation of peripheral oxygen. Arteriovenous saturation (70% jugular bulb venous saturation and 30% arterial saturation) at 6 hypoxic plateaus was used as the reference value for the cerebral oximeter. Absolute accuracy was defined using a combination of the bias and precision of the paired saturations (A_{RMS}).**

Measurements and Main Results: **In the validation study for the 8000CA sensor (n = 9, 106 plateaus), relative accuracy was an A_{RMS} of 2.7, with an absolute accuracy of 8.1, meeting the criteria for a relative (trend) monitor, but not an absolute monitor. In the validation study for the 8004CA sensor (n = 11, 119 plateaus), the A_{RMS} of the 8004CA was 4.1, meeting the prespecified success criterion of <5.0.**

Conclusions: **The Nonin cerebral oximeter using the 8004CA sensor can provide absolute data on regional cerebral saturation compared with arteriovenous saturation, even in subjects previously shown to have values outside the normal population distribution curves.**

KEY WORDS: cerebral oximetry, cerebral saturation, Bland-Altman analysis, hypoxic protocol, near-infrared spectroscopy

THE INTRODUCTION OF pulse oximetry 30 years ago to monitor the saturation of arterial blood (SaO_2) continuously led to dramatic improvements in patient safety.[1,2] Knowledge of SaO_2, however, provides only part of the clinical picture, because adequate tissue oxygenation depends not only on supply (oxygen delivery, ie, oxygen content of blood and regional blood flow) but also on demand (regional oxygen consumption.) A monitor that continuously and accurately reports the regional oxygen saturation of brain tissue (rSO_2), which is critically susceptible to hypoxia, has been sought for a long time.

The first commercially available cerebral oximeters were accepted as trend monitors, not as absolute monitors. There has been no proven gold standard for determining the absolute or precise level of rSO_2, and, therefore, it was impossible to know whether an oximeter-generated rSO_2 value agreed absolutely with true cerebral saturation. Cerebral oximeters, however, have been accepted as relative or trend monitors, where changes from the baseline of rSO_2 values could accurately reflect the magnitude and direction of changes in cerebral saturation.[3-5] These trend, or relative, monitors have been validated in laboratory settings,[6] and many reports have demonstrated their ability to detect potentially devastating changes in cerebral saturation.[7-9] Two randomized trials have demonstrated the ability of these monitors to improve outcomes after abdominal surgery or cardiac surgery when used to direct interventions to maintain a minimum saturation.[10,11]

Discussion continues on the ability of any monitor to provide absolute measurement, ie, whether the value presented absolutely agrees with the true cerebral tissue oxygen saturation. Part of the issue is that there has not been an accepted "gold standard" against which the accuracy of an oximeter could be tested.[12] Over time, however, laboratory data have accumulated showing that cerebral tissue saturation can be estimated using SaO_2 and jugular bulb venous saturation ($SjvO_2$) in a ratio of 1:3.[13,14]

$$\text{Cerebral arteriovenous saturation } [SavO_2] = (0.25 \times SaO_2) + (0.75 \times SjvO_2)$$

This ratio has been used in clinical studies and in validation studies performed in volunteers.[6]

This study was designed to test the accuracy of a cerebral oximetric system (Equanox Cerebral Oximetry System; Nonin Medical, Inc, Plymouth, MN) in a prospective, single-center, nonrandomized study. During the validation of the Equanox system using the 8000CA sensor, a subject with significantly atypical light scattering and absorbing characteristics was identified. Data from this volunteer and 4 others with unusual light-scattering characteristics were used in the development of a second-generation sensor, the 8004CA, which was validated subsequently.

METHODS

Two separate, sequential, prospective, single-center, nonrandomized investigations to calibrate and validate the accuracy of the 2 oximetric sensors were performed with approval from the medical center institutional review board. Calibration and validation of the 8000CA sensor were completed entirely before initiating the development and calibration and validation studies for the 8004CA sensor. The 2 sensors were evaluated with the same study design and methods.

*From the *Human Pharmacology Laboratory, Department of Anesthesiology, and †School of Nursing, Duke University, Durham, NC; ‡Nonin Medical, Inc, Plymouth, MN; §Department of Anesthesiology, University of Michigan, Ann Arbor, MI; and ‖Department of Anesthesiology, Duke University/Durham VAMC, Durham, NC.*

Funding for this study was provided by Nonin Medical, Inc.

Address reprint requests to David MacLeod, MD, FRCA, Assistant Professor of Anesthesiology Human Pharmacology Laboratory, Department of Anesthesiology, Duke University Medical Center, Durham, NC 27710. E-mail: david.macleod@duke.edu

1053-0770/2606-0007$36.00/0
http://dx.doi.org/10.1053/j.jvca.2012.06.010

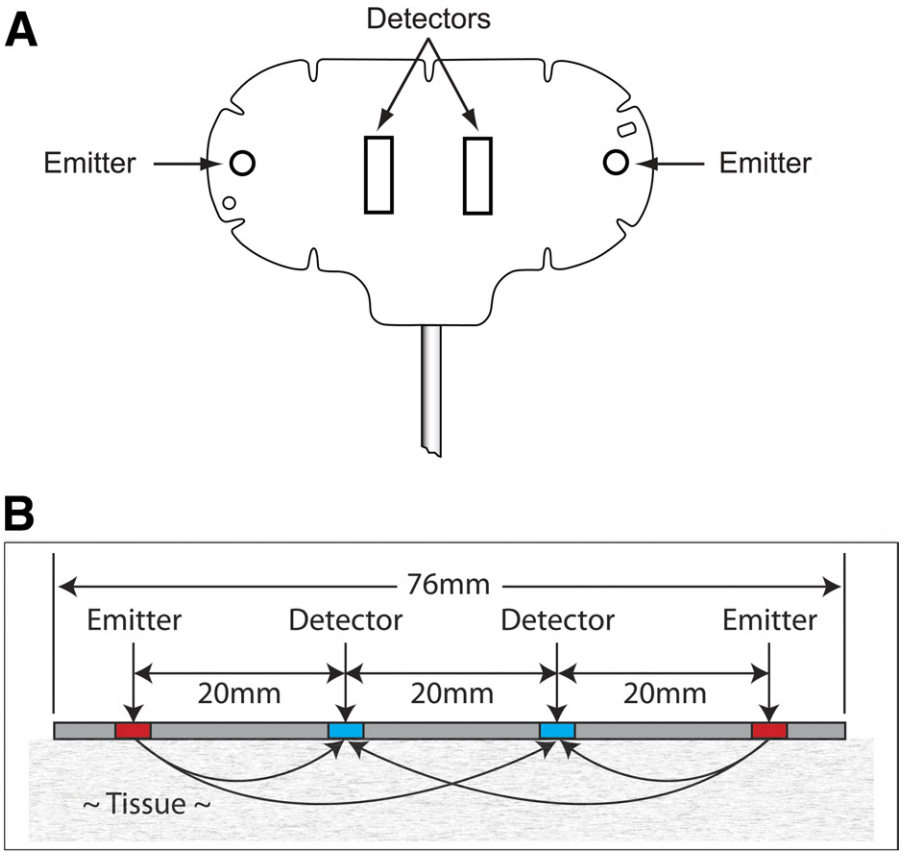

Fig 1. Schematic of the Equanox 8000CA and 8004CA sensors. (A) The Equanox cerebral oxygen saturation monitor (Nonin Medical, Inc, Plymouth, MN) contains 2 light-emitting diodes, each generating 3 or 4 near-infrared spectroscopic wavelengths, and 2 detection sensors, each separated from the next optode by a distance of 20 mm. (B) Measurements from the emitters to the closer detector (20 mm) represent shallow (extracranial) tissue saturation; measurements from emitters to farther detectors (40 mm) represent shallow (extracranial) and deep (intracranial) tissue saturations. (Color version of figure is available online.)

Normal, healthy volunteers 21-35 years old and with a body mass index $\geq$18 and $\leq$30 kg/m^2 who gave written informed consent were enrolled. Subjects were not eligible to be enrolled in a validation study if they had participated previously in the calibration of the same sensor (the calibration was done separately). A completely separate cohort of subjects was enrolled in the validation part of each study. Subjects underwent the hypoxia protocol outlined below. At each study session, 2 anesthesiologists were present; 1 to oversee the safe conduct of the study and be responsible for each subject's safety, the other to oversee the study procedure and data validity.

Device Description

Nonin 8000CA

The initial cerebral oximeter tested was the Nonin Equanox 8000CA (Fig 1). This sensor is based on dual-emitter and dual-detector sensor topology and uses 3 wavelengths in each emitter (730, 810, and 880 nm). Typical oximeters use a single emitter with 2 detectors: 1 detector spaced to capture light from skull and skin only (short path, extracranial saturation), the second detector spaced to capture light from the skin, skull, and brain (long path, extra- and intracranial saturation). Subtracting the extracranial saturation from that of the longer path (intracranial and extracranial saturations) is assumed to isolate intracranial oxygen saturation.[7] However, any difference in the optical properties of the skull and forehead beneath the near versus the far detector will influence the calculated intracranial saturation measurement. The 8000CA sensor has dual emitters and dual detectors, with the long and short paths reversed for each emitter, causing the skull and forehead optical differences associated with each detector to be canceled out.

Nonin 8004CA

During the validation study of the 8000CA sensor, 1 individual was identified with significantly atypical light-scattering characteristics. This individual and 4 others with atypical light-scattering characteristics were used to direct the design of the 8004CA sensor; specifically, an additional wavelength was added to account for tissue-related light absorption and refraction.

Hypoxia Protocol

Enrolled subjects fasted overnight; no sedation or anesthesia was administered. Standard monitors were applied (5-lead electrocardiography, pulse oximetry), and an intravenous catheter and a radial artery catheter were placed. A 5-F catheter (PreSep Central Venous Oximetry Catheter; Edwards Lifesciences, Irvine, CA) was placed in the right or left jugular venous bulb with ultrasound guidance, and its position was confirmed with a lateral skull x-ray. Two Equanox sensors of the same model (8000CA in the first study, 8004CA in the second study) were placed on each side of the forehead for bilateral monitoring. A dedicated facemask and breathing apparatus with a tight seal (RespirAct; Thornhill Research, Inc, Toronto, ON, Canada) were used to induce hypoxia to a predetermined degree and to control precisely the blood carbon dioxide levels despite a variable ventilatory rate. The RespirAct breathing apparatus is a device available for research purposes that uses a prospective, feed-forward, low-gas-flow system to provide precise and independent control of blood carbon dioxide and oxygen levels.[9] End-tidal oxygen and carbon dioxide are monitored and controlled continuously to maintain the target partial pressure of arterial oxygen and end-tidal carbon dioxide.

The hypoxic protocol is depicted in Fig 2. Each plateau lasted 6 minutes, with arterial and venous blood samples collected after a