





**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<sup>2</sup> 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.<sup>7</sup> 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.<sup>9</sup> 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











