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Optoacoustic, Noninvasive, Real-Time, Continuous Monitoring of Cerebral Blood Oxygenation: An In Vivo *Study in Sheep*

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Background: **Current, invasive cerebral oxygenation monitors require either retrograde jugular venous bulb cannulation or intraparenchymal probe insertion. There is no accurate, noninvasive, continuous monitor of cerebral blood oxygenation.**

Methods: **The authors designed, built, and tested novel optoacoustic instrumentation that continuously measures blood oxygenation in the superior sagittal sinus (SSS) *in vivo* in 12 anesthetized sheep. In this technique, laser pulses generate acoustic signals, the amplitudes and slopes of which are proportional to oxyhemoglobin saturation in the SSS. Optoacoustic signals from the SSS measured through the scalp and cranium were compared with directly measured oxyhemoglobin saturation in blood withdrawn from the cannulated SSS.**

Results: **In the first experiments (feasibility), F_{IO_2} changes produced rapid corresponding changes in optoacoustic signals and arterial oxygen saturation. In the second experiments (validation), the authors correlated oxyhemoglobin saturation in the SSS with optoacoustic signals and developed quantifying algorithms. In eight of nine validation experiments, the authors quantified optoacoustic signals by subtracting the temporal profile at low F_{IO_2} (0.08–0.1) from profiles at higher F_{IO_2} and integrating those signals in the range from 3 to 5 μs. In each validation experiment, optoacoustic signals showed tight temporal association and good linear correlation with measured oxyhemoglobin saturation (r^2 0.75 to 0.99 for eight individual experiments).**

Conclusions: **The optoacoustic system detects signals induced in the SSS and optoacoustic signals from the SSS linearly correlate with oxyhemoglobin saturation. The data suggest that the optoacoustic technique merits clinical evaluation.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

COMPELLING clinical evidence suggests that monitoring cerebral oxygenation can detect otherwise unrecognized cerebral ischemia and be used to guide therapeutic interventions in such diverse situations as craniotomy and intensive care of traumatic brain injury.[1–7] Evidence demonstrates a strong association between cerebral hypoxia and worse outcome in traumatic brain injury and cardiac surgery using cardiopulmonary bypass.[8,9]

To date, the two primary clinical methods used to monitor brain oxygenation are invasive; one requires percutaneous insertion of a catheter into the jugular bulb to continuously measure cerebral venous oxygenation[1] and the other requires insertion of a probe through the cranium into the brain parenchyma to measure tissue P_{O_2}.[5,7] Jugular venous bulb monitoring is based on the following equation:[10]

$$Cjv_{O_2} = Ca_{O_2} - CMRO_2/CBF \quad (1)$$

where Cjv_{O_2} = jugular venous bulb oxygenation content, Ca_{O_2} = arterial oxygen content, $CMRO_2$ = the cerebral metabolic rate for oxygen, and CBF = cerebral blood flow. As a surrogate for jugular venous bulb oxygen content, jugular venous bulb oxygen saturation (Sjv_{O_2}) can be measured or monitored. Continuous oximetric monitoring of jugular venous bulb hemoglobin saturation provides a global assessment of brain oxygenation but requires frequent recalibration, which has been a major factor limiting wider use.[1] In addition, the time and effort necessary to insert a catheter usually precludes introduction before an acutely ill patient has been stabilized. More recently, brain tissue P_{O_2} monitoring has been highly correlated with outcome in patients with traumatic brain injury.[7] However, although brain tissue P_{O_2} monitoring provides a precise regional measurement of tissue oxygenation, it provides no information about inadequate tissue oxygenation in remote sites and is clearly unsuitable for clinical situations in which intracranial devices are not customarily inserted.

A noninvasive monitor would greatly expand the population of surgical and critically ill patients in whom

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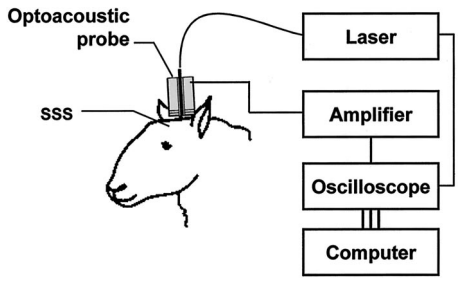

Fig. 1. Optoacoustic system for *in vivo* assessment of changes in oxyhemoglobin saturation in the superior sagittal sinus in sheep.

changes in cerebral venous saturation could be used to direct therapy and could permit earlier monitoring. Encouraging reports of the use of near-infrared spectroscopy, a noninvasive method of monitoring cerebral blood oxygenation, during carotid endarterectomy[11] and cardiac surgery[12] must be balanced against the fact that current technology is qualitative rather than quantitative and can only be used to detect trends rather than to provide accurate measurements. In contrast, laser optoacoustics represents a potential quantitative method for assessing cerebral oxygenation. Recently proposed as a technique for tissue characterization and diagnostic imaging,[13–16] laser optoacoustics combines the merits of optical tomography (high optical contrast) and ultrasound imaging (minimal scattering of acoustic waves) to yield a noninvasive diagnostic modality with high contrast, sensitivity, and resolution.

We developed and built an optoacoustic system that includes an Nd:YAG laser (capable of generating pulses of nanosecond durations; Ultra CFR model, Big Sky Laser Technologies, Inc., Bozeman, MT) and an optoacoustic probe specifically designed to monitor cerebral blood oxygenation. We previously tested the system *in vitro* by experimentally varying oxygenation in sheep blood.[17] In the current study, we tested the feasibility of optoacoustic monitoring of cerebral blood oxygenation *in vivo* in sheep.

Materials and Methods

This study was approved by the Institutional Animal Use and Care Committee of the University of Texas Medical Branch, Galveston, Texas.

Our optoacoustic system (fig. 1) consists of: 1) a compact pulsed Nd:YAG laser operating at 1064-nm wavelength with a pulse duration of 10 nanoseconds and a repetition rate of 2 Hz, 2) an optoacoustic probe that combines a light delivery system and an acoustic detector (transducer) with a preamplifier, and 3) a registration system (an oscilloscope and a laptop computer). Light at this wavelength penetrates deeply through skin, bone, and other tissues because of relatively low absorption, reduced scattering, and effective attenuation coefficients: 0.1–0.5 cm^{-1}, 10–20 cm^{-1}, and 1.5–5 cm^{-1}, respectively. Moreover, at this wavelength the absorption coefficient of oxygenated blood exceeds that of deoxygenated blood by at least five times.[18,19]

The radiation from the Nd:YAG laser (Big Sky Laser Technologies, Inc.) was coupled into FT SILICA/TECSTM (Thorlabs Inc., Newton, NJ) multimode optical fiber (1.5-mm core diameter), the other end of which was centered in a ring-shaped piezoelectric element (for acoustic detection) with outer and inner diameters of 12 mm and 4 mm, respectively. The piezoelectric element was constructed of polyvinylidenefluoride film (PIEZOFLEX™, Airmar Technology Corporation, Milford, NH), which had a thickness of 0.5 mm and was covered with 10-μm layer of copper to provide electrical contact. Copper electrodes were attached using special low-temperature solder. The piezoelectric element was covered with aluminum foil to reduce unwanted signal generated by backscattered light and to limit electromagnetic interference. The piezo element was glued to a block of epoxy (Hysol Electronic Chemicals, Industry, CA) that matched the acoustical impedance of polyvinylidenefluoride film. The detected pressure profiles were amplified by a voltage preamplifier (Airmar Technology Corporation, Milford, NH) and were recorded and digitized with a digital oscilloscope TDS 220 (Tektronix, Inc., Wilsonville, OR) and averaged over 32 pulses (*i.e.*, 16 s) to increase the signal-to-noise ratio. The recorded signals were transmitted to a laptop computer (Inspiron 3800; Dell Computer Corporation, Round Rock, TX) through a general purpose interface bus. We developed an algorithm in Lab-VIEW (National Instruments Corp., Austin, TX) to acquire, record, and process optoacoustic signals in real time.

We evaluated the performance of our system *in vivo* in 12 adult sheep (weight 35–40 kg). We chose sheep as the experimental animal because the thickness of the sheep skull (5–6 mm) is sufficient to demonstrate the capability of the optoacoustic technique to measure venous saturation beneath a substantial layer of bone. Although in adult sheep the superior sagittal sinus (SSS; diameter, 2–3 mm) is much smaller than that in most adult humans (diameter, 8–10 mm), it is within the limits of resolution of the optoacoustic technique. The animals were housed in the Animal Resources Center at the University of Texas Medical Branch, which is staffed by full-time veterinarians who monitor the humane care of each animal on a daily basis. All surgical procedures were performed under sterile technique, and all catheterization/surgical procedures were performed under 1.5% to 2.0% isoflurane anesthesia. We continuously monitored cardiac rate and rhythm (by electrocardiogram) and arterial saturation (by a pulse oximeter applied to the lip). An arterial catheter was inserted percutaneously into a femoral artery for blood sampling and continuous blood pressure monitoring. After nontermi-

nal experiments, all animals were observed postoperatively for level of consciousness, bleeding, or evidence of discomfort. Analgesia consisted of buprenorphine administered intramuscularly. Euthanasia was performed under pentobarbital anesthesia.

To sample blood for comparison with optoacoustic measurements, a catheter was inserted through a small craniotomy into the SSS to permit blood sampling directly from the SSS without arterial and capillary blood contamination. The hemoglobin saturation of venous blood (1 ml) withdrawn slowly from the SSS was measured using a co-oximeter (IL 813 Instrumentation Laboratories, Lexington, MA) and was compared to simultaneously recorded optoacoustic signals. The *in vivo* validation was accomplished using a range of P_{ACO_2} values from 20 to 40 mmHg and a range of F_{IO_2} values from 0.07 to 0.21, which was sufficient to produce a range of arterial P_{AO_2} from 40 to 100 mmHg. This produced a wider range of cerebral venous saturations (8–100%) than would be encountered in neurologic intensive care.

We used a custom-designed head holder to minimize motion artifacts. After a midline incision, the left and right scalp and temporalis muscles were reflected laterally, and the skull surface was cleaned to avoid the high attenuation of acoustic and optical waves produced by numerous air pockets in dense wool even after shaving. The optoacoustic probe was applied to the surface of the sheep skull overlying the SSS. The acoustical contact was provided by standard ultrasound gel (Aquasonic 100, Parker Laboratories Inc., Fairfield, NJ). Before each experiment the probe was scanned laterally over the skull to identify the best signal from the SSS. The best signal for all sheep was within 2 mm of the midline.

The experiments proceeded in two phases. In the first (feasibility) phase (n = 3 sheep), the temporal profiles of the optoacoustic signals were recorded during a series of incremental decreases and increases in F_{IO_2}. In this phase, the SSS was not catheterized and optoacoustic signals were qualitatively compared with changes in arterial hemoglobin saturation. In the second (validation) phase (n = 9 sheep) the SSS was cannulated, the sheep were heparinized, and cerebral venous blood oxygenation was measured directly by withdrawing blood samples immediately after optoacoustic signal acquisition. As in the first phase, each sheep went through at least one sequence of incremental decreases. Because of the extreme range of hypoxemia used in these studies, some sheep became hemodynamically unstable after one cycle of decreasing F_{IO_2}. If one cycle of decreasing F_{IO_2} was well tolerated, F_{IO_2} was increased and the comparisons continued. If, at the end of one complete cycle of decreasing and increasing F_{IO_2} the animal continued to tolerate the procedure well, we performed a second cycle. In one sheep, a third cycle was performed.

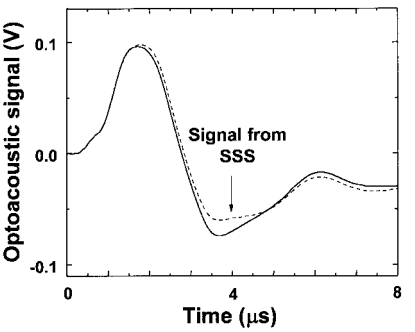

Fig. 2. Typical optoacoustic signal measured *in vivo* from the sheep head by using the optoacoustic probe placed above the superior sagittal sinus (SSS) at high (*dashed line*) and low (*solid line*) oxygenation.

Statistical Analysis

In the first phase of the study, in which sheep did not have catheters in the SSS, we qualitatively evaluated concurrent changes in the optoacoustic signals and pulse oximetry. In the second phase of the study, correlation coefficients between the optoacoustic signals and actual hemoglobin saturations in the SSS were derived for each individual sheep. Although the catheter inserted in the SSS is comparable (approximately 1 mm) to the sheep SSS diameter (approximately 2–3 mm) and may influence the optoacoustic signal detected from the SSS, the optoacoustic system was capable of detecting signals from the SSS in eight of the nine sheep. To quantify the signal from the SSS, we based our primary algorithm on the integral of the difference between the signals at experimental F_{IO_2} and minimal F_{IO_2} (0.08–0.1) in the range from 3 to 5 μs (fig. 2). The calculation at 3 to 5 μs after the laser pulse corresponds to the time necessary for the acoustic signal to be transmitted through the cranium. The integrated signals were then correlated with oxyhemoglobin saturation in the SSS.

Results

Laser fluence at the tissue surface during these experiments ranged from 100 to 600 mJ/cm^2. For comparison, the maximum permissible exposure (not the threshold for actual skin damage which is approximately 100-fold higher) of human skin to laser light at this wavelength is 100 mJ/cm^2.[20] No gross damage to illuminated tissues was evident in any experiments.

Figure 3 shows the time course of F_{IO_2} (bottom), optoacoustic signals from the SSS (bottom), and arterial hemoglobin saturation (by pulse oximetry, top) in one of three sheep from the first, feasibility, phase of the experiment. Variation of F_{IO_2} produced rapid corresponding changes in the optoacoustic signal and in arterial oxygen saturation.

Figure 4, left, from eight sheep in the second, validation phase of the experiment, compares the time course

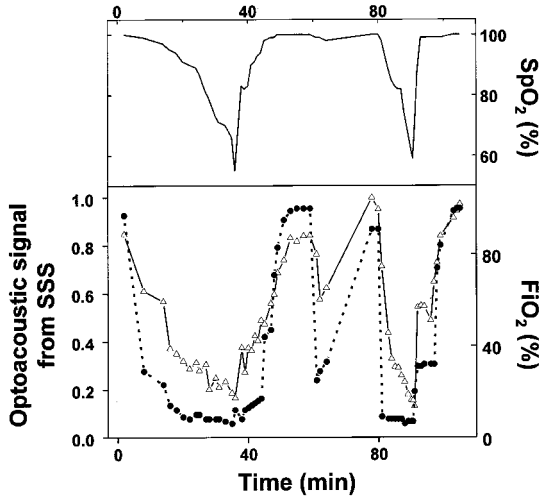

Fig. 3. Time course of the optoacoustic signal from superior sagittal sinus (SSS; *triangles, solid line,* bottom) and arterial hemoglobin saturation (by pulse oximetry; top) during changes in F_{IO_2} (*circles, dashed line*, bottom) during an *in vivo* experiment with a sheep from the first feasibility phase of the experiment (no catheter in the SSS).

of oxyhemoglobin saturation that was directly measured with cooximetry in blood from the SSS of each of the sheep and the optoacoustic signals from the SSS. In one of nine sheep in the second phase, we were unable to obtain a satisfactory optoacoustic signal. At autopsy, the tip of the catheter completely filled the SSS and extended directly beneath the optoacoustic probe; we speculated that the catheter tip interfered with the signal. In each of the other eight sheep in the validation phase, the optoacoustic signal closely followed the changes in oxyhemoglobin saturation. The correlation coefficients of the same signals with oxyhemoglobin saturation are presented in figure 4, right (r^2 0.75 to 0.99).

In three of eight sheep from the second phase the signals were superior to those from the other five sheep. When a distinct peak was detected from the SSS (one sheep in phase one and first three sheep in the second phase), we applied an alternative algorithm. In those three sheep, in addition to comparing oxyhemoglobin saturation with the integral of the difference between the signals, we also compared the areas (in arbitrary

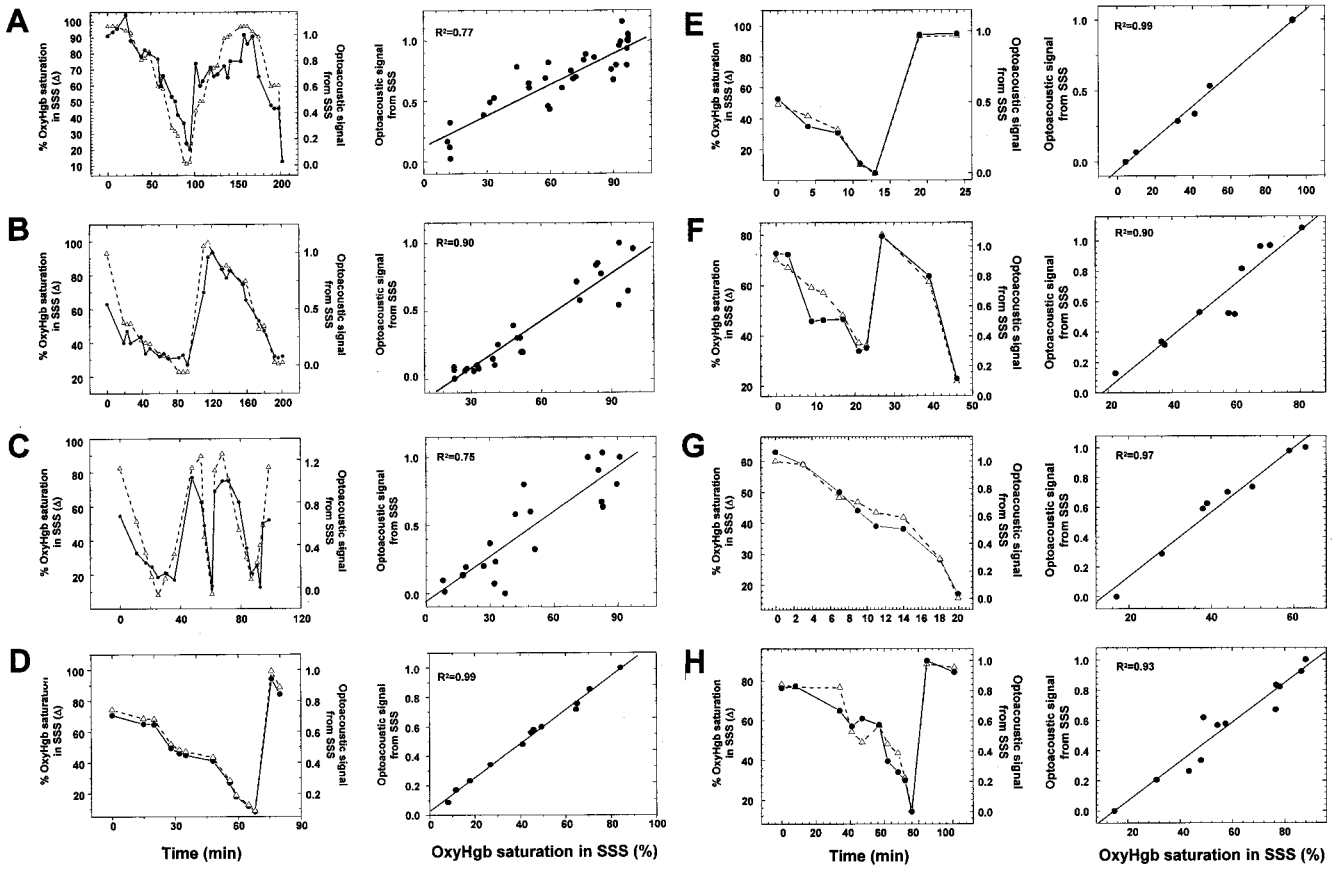

Fig. 4. *Left*: Time course of oxyhemoglobin saturation in the superior sagittal sinus (SSS) of eight anesthetized sheep in which F_{IO_2} was progressively decreased and then, if the initial hypoxemia was well tolerated, increased. Several sheep had two or more cycles of decreasing and increasing F_{IO_2}. At intervals during each experiment, oxyhemoglobin in blood withdrawn from the SSS was measured by a co-oximeter (*triangles, dashed lines*) and compared with the optoacoustic signals from the SSS (*circles, solid lines*) calculated with the first algorithm. *Right*: Linear correlation of the optoacoustic signals compared with oxyhemoglobin saturation in the SSS.

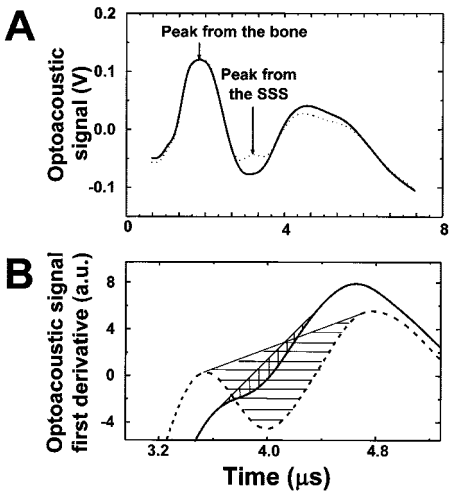

Fig. 5. (*A*) Optoacoustic signal (with a distinct peak from the SSS) measured *in vivo* from the sheep head at an F_{IO_2} of 1.0 (*dashed line*) and an F_{IO_2} of 0.07 (*solid line*). (*B*). First derivatives (in arbitrary units; au) of the optoacoustic signals from the sheep head at an F_{IO_2} of 1.0 (*dashed line*) and an F_{IO_2} of 0.07 (*solid line*). First derivatives were obtained from the signals presented in (*A*). Dashed areas represent the signals from the SSS calculated by using the second algorithm.

units) of the negative peaks of the first derivative of the signal (fig. 5). No reference signal, *i.e.*, a signal at very low oxygenation, was required for this algorithm. Figure 5A shows typical optoacoustic signals recorded *in vivo* at different F_{IO_2} values in a sheep in which the first derivative method was used. The horizontal axis is time in μs. The time to recording of each signal is determined by the transmission of acoustic waves through tissue (approximately 1.5 and 3.0 mm/μs for soft tissue and bone, respectively). The first, positive, peak was produced by generation of optoacoustic waves directly on the surface of the optoacoustic probe and on the surface of the irradiated tissue. The negative peak was caused by diffraction of the induced waves as a result of their propagation toward the probe. The signal at 4 μs was induced in blood circulating in the SSS. One signal was recorded at an F_{IO_2} of 0.07, and the other signal was recorded at an F_{IO_2} of 1.0. The area of the first derivative of the negative peak of the signal (fig. 5B) represents the optoacoustic signal from the SSS in figure 5A in arbitrary units. In the other five sheep in phase two, we speculate that the optoacoustic signals induced in the SSS were sensitive to probe misalignment because of the small size of the sheep SSS relative to the thickness of the skull.

The optoacoustic signals that were obtained using the first derivative algorithm are displayed in figure 6 (A-C). Data presented in figure 6A (left) were recorded during the experiment with the first sheep from the second phase. At t = 0 min the F_{IO_2} was 1.0 and oxyhemoglobin saturation in the SSS measured by the co-oximeter was 97%. As we gradually decreased F_{IO_2} to 0.05 over the course of 90 min, pulse oximeter saturation and oxyhemoglobin saturation in the SSS gradually decreased to 28% and 12%, respectively. During the next 70 min we slowly increased the F_{IO_2} to 0.80, resulting in an increase of the oxyhemoglobin saturation in the SSS. During the last 50 min of the experiment we again decreased F_{IO_2}. The optoacoustic signal measured from the SSS and calculated from the first derivative closely followed the oxyhemoglobin saturation in the SSS (r^2 = 0.90; fig. 6A, right). In the second sheep from this group (fig. 6B, left), F_{IO_2} was changed rapidly between high and low values with prolonged (1 h) intervals between changes. Figure 6B (right) shows good correlation (r^2 = 0.90) between oxyhemoglobin saturation and the optoacoustic signal. In the third sheep (fig. 6c, left), we rapidly changed oxyhemoglobin saturation in the SSS to determine whether the system could detect sharp changes in oxyhemoglobin saturation in real time. The alternative algorithm provided better correlation between the optoacoustic signal from SSS and blood oxygenation in SSS: r^2 values ranged from 0.75 to 0.90 and from 0.90 to 0.95 for the first and second algorithm, respectively. We anticipate that this algorithm will be applied in clinical studies because the human SSS is greater than that of sheep and will induce a distinct peak.

Discussion

These data are the first to demonstrate the feasibility of monitoring SSS oxyhemoglobin saturation noninvasively using an optoacoustic technique. Changes in the optoacoustic data correlated highly with a standard measurement of SSS saturation and rapid variation of the oxyhemoglobin saturation in the SSS produced correspondingly rapid, highly correlated changes in the optoacoustic signal. Furthermore, optoacoustic signals correlated well with SSS saturations across a greater range than is likely to be encountered in clinical use. Even with one wavelength, the characteristics of the signal are encouraging for ultimate clinical use if the second algorithm (which does not utilize any reference signals) is applied.

However, there are a number of limitations to this study. These experiments used only one wavelength and therefore could only demonstrate strong correlations between the optoacoustic signal and oxyhemoglobin saturation in the SSS. We speculate that addition of one or more wavelengths could accurately quantify SSS oxyhemoglobin saturation. In addition, the use of sheep introduced several difficulties despite their relatively large body size and skull thickness that is comparable to adult humans. Specifically, sheep have a much smaller SSS than adult humans. Our *in vivo* optoacoustic measurements suggest several potentially confounding variables in sheep, including the small diameter of the SSS, changes in the SSS diameter (as a result of dilation, for instance) and motion artifacts. Because the probe has

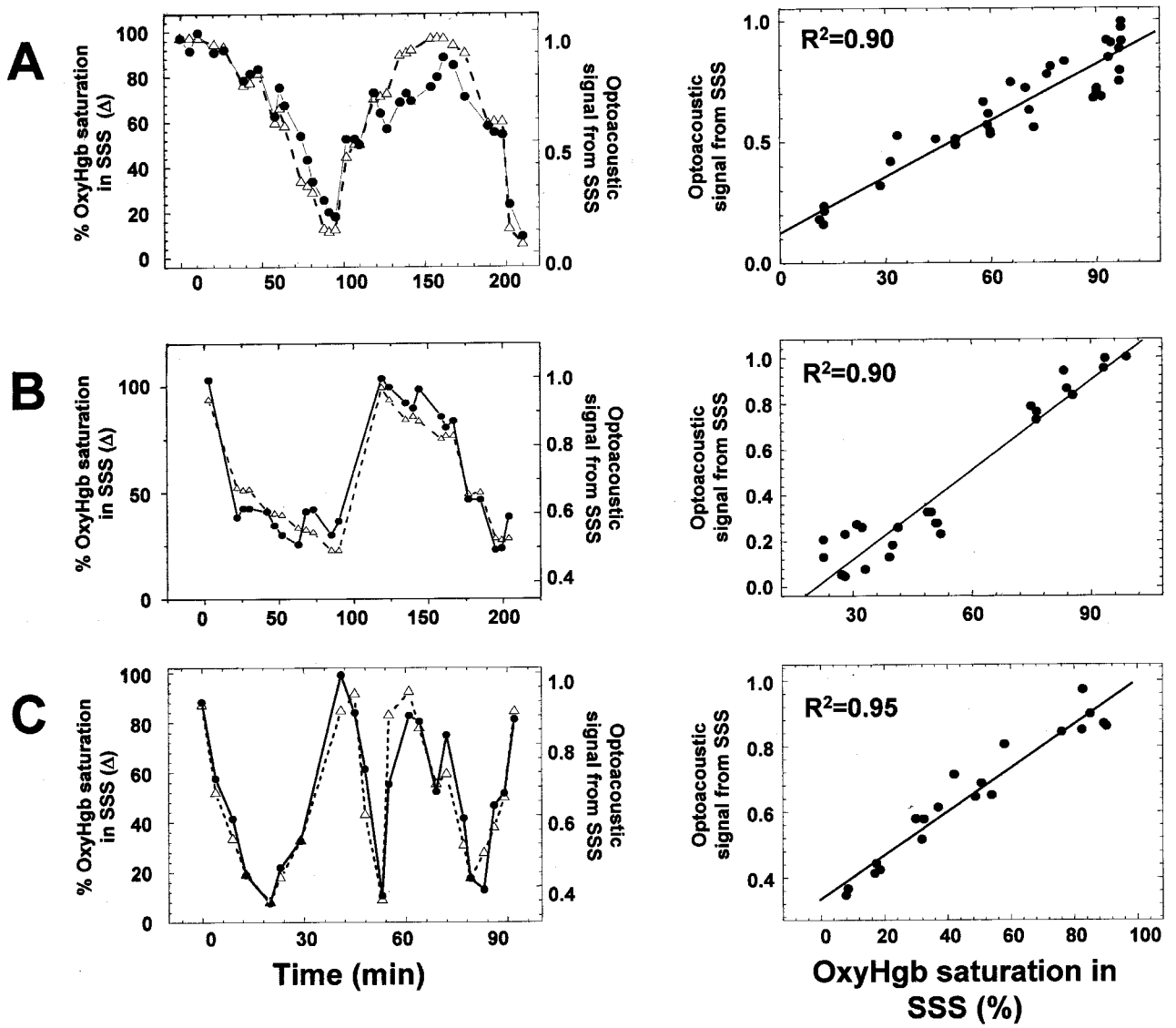

Fig. 6. ***Left*****: Time course of oxyhemoglobin saturation in the SSS (*triangles, dashed lines*) of three anesthetized sheep (same sheep as in figure 4, A-C, left) and optoacoustic signals (*circles, solid lines*) calculated with the second algorithm.** ***Right*****: Linear correlation of the optoacoustic signals compared with oxyhemoglobin saturation in the SSS. The data demonstrate better correlation between the optoacoustic signal and actual oxyhemoglobin saturation when the second algorithm was used for the same sheep.**

high lateral resolution (1.5 mm) that is close to the diameter of the sheep SSS (2–3 mm), variation in the SSS diameter or minor displacement of the probe (up to 1 mm) can alter the signal detected from the SSS. Finally, sheep wool, which is highly insulating, has multiple air pockets that preclude transmission of an acoustic signal.

Perhaps the most encouraging aspect of these data are that these experiments in sheep pose greater logistical difficulties than we anticipate with clinical experiments. The greater size of the human SSS (8–10 mm) should result in detection of the distinct peak from the SSS that will be less prone to motion artifacts. Moreover, the application of the second algorithm (which does not require the low-saturation reference signal) should provide more accurate optoacoustic measurement of blood oxygenation in the SSS. Our next studies will consist of *in vivo* tests of two-wavelength and multi-wavelength optoacoustic systems in sheep and the first clinical tests of the optoacoustic technique in healthy volunteers.

For clinical use, a two-wavelength or multiple-wavelength system will be necessary to provide accurate SSS blood oxygenation measurements because optoacoustic signals are dependent not only on oxyhemoglobin saturation but also on total hemoglobin concentration. To accurately measure absolute values of oxyhemoglobin saturation, despite variations of total hemoglobin concentration, one can record and analyze optoacoustic waves induced at two or more different wavelengths. Any nanosecond lasers (including laser diodes) operating in the near-infrared spectral range in which oxy- and

deoxyhemoglobin have different absorptions can be used as sources of pulsed laser radiation for the two-wavelength system. Based on measurement of optoacoustic signals at two wavelengths (1 and 2), blood oxygenation can be calculated by solving two equations:

$$\mu a(1) = C[oxy] \times K[oxy,1] + C[deoxy] \times K[deoxy,1]$$

$$\mu a(2) = C[oxy] \times K[oxy,2] + C[deoxy] \times K[deoxy,2]$$

where $\mu a(1)$ and $\mu a(2)$ are the absorption coefficients of blood measured at the two wavelengths, C[oxy] and C[deoxy] are concentrations of oxyhemoglobin and deoxyhemoglobin in blood, and K [oxy, 1], K [deoxy, 1], K [oxy, 2] and K [deoxy, 2] are known values of extinction coefficients of oxyhemoglobin and deoxyhemoglobin at these two wavelengths. Having the two equations and the two unknowns C[oxy] and C[deoxy], one can calculate C[oxy] and C[deoxy] and, hence, oxygenation of blood circulating in a specific targeted vessel by determining the ratio: C[oxy]/(C[oxy] + C[deoxy]). Therefore, the use of the two-wavelength approach can calculate blood oxygenation despite fluctuating hemoglobin concentrations.

Application of an optoacoustic system with more than two wavelengths may further improve the accuracy of measurement of oxyhemoglobin saturation. A multi-wavelength near-infrared spectroscopy system was tested *in vivo* in dogs and provided more accurate measurement of cerebral oxyhemoglobin saturation when special algorithms for analysis of the near-infrared transmittance spectra obtained from the dog head were used.[21] However, because of the uncertain direction and path length of reflected light, techniques based on near-infrared spectroscopy cannot distinguish between arterial and venous blood. In contrast, because the optoacoustic technique has high resolution and because the acoustic signal is transmitted linearly through tissue, a multi-wavelength optoacoustic assessment of a specific vessel, *e.g.*, the SSS, may accurately quantify cerebral venous oxyhemoglobin saturation measurement.

These studies suggested that the optoacoustic system is capable of accurately tracking rapid changes of cerebral oxyhemoglobin saturation *in vivo* in sheep despite the small dimensions of the sheep SSS. We anticipate that the larger diameter of the human SSS and internal jugular vein will permit cerebral blood oxygenation monitoring in adult humans.

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