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Continuous, Noninvasive, and Localized Microvascular Tissue Oximetry Using Visible Light Spectroscopy

David A. Benaron, M.D., Ilian H. Parachikov, Ph.D.,† Shai Friedland, M.D.,‡ Roy Soetikno, M.D.,§ John Brock-Utne, M.D., Ph.D.,‖ Peter J. A. van der Starre, M.D., Ph.D.,# Camran Nezhat, M.D.,** Martha K. Terris, M.D.,†† Peter G. Maxim, Ph.D.,‡‡ Jeffrey J. L. Carson, Ph.D.,§§ Mahmood K. Razavi, M.D.,‖‖ Hayes B. Gladstone, M.D.,## Edgar F. Fincher, M.D.,*** Christopher P. Hsu,††† F. Landon Clark,††† Wai-Fung Cheong, Ph.D.,‡‡‡ Joshua L. Duckworth, M.D., L.T., M.C., U.S.N.,§§§ David K. Stevenson, M.D.‖‖‖*

Background: **The authors evaluated the ability of visible light spectroscopy (VLS) oximetry to detect hypoxemia and ischemia in human and animal subjects. Unlike near-infrared spectroscopy or pulse oximetry (Spo_2), VLS tissue oximetry uses shallow-penetrating visible light to measure microvascular hemoglobin oxygen saturation (Sto_2) in small, thin tissue volumes.**

Methods: **In pigs, Sto_2 was measured in muscle and enteric mucosa during normoxia, hypoxemia (Spo_2 = 40–96%), and ischemia (occlusion, arrest). In patients, Sto_2 was measured in skin, muscle, and oral/enteric mucosa during normoxia, hypoxemia (Spo_2 = 60–99%), and ischemia (occlusion, compression, ventricular fibrillation).**

Results: **In pigs, normoxic Sto_2 was 71 ± 4% (mean ± SD), without differences between sites, and decreased during hypoxemia (muscle, 11 ± 6%; $P < 0.001$) and ischemia (colon, 31 ± 11%; $P < 0.001$). In patients, mean normoxic Sto_2 ranged from 68 to 77% at different sites (733 measures, 111 subjects); for each noninvasive site except skin, variance between subjects was low (*e.g.*, colon, 69% ± 4%, 40 subjects; buccal, 77% ± 3%, 21 subjects). During hypoxemia, Sto_2 correlated with Spo_2 (animals, r^2 = 0.98; humans, r^2 = 0.87). During ischemia, Sto_2 initially decreased at −1.3 ± 0.2%/s and decreased to zero in 3–9 min (r^2 = 0.94). Ischemia was distinguished from normoxia and hypoxemia by a widened pulse/VLS saturation difference ($\Delta < 30\%$ during normoxia or hypoxemia *vs.* $\Delta > 35\%$ during ischemia).**

Conclusions: **VLS oximetry provides a continuous, noninvasive, and localized measurement of the Sto_2, sensitive to hypoxemia, regional, and global ischemia. The reproducible and narrow Sto_2 normal range for oral/enteric mucosa supports use of this site as an accessible and reliable reference point for the VLS monitoring of systemic flow.**

MONITORING of low cardiac output and ischemia remains problematic. Standard techniques for monitoring the systemic circulation, such as mixed venous saturation (Svo_2) and cardiac index, require indwelling, costly pulmonary catheters that cause complications,[1,2] may be absent when required, and typically do not provide continuous data. Early regional ischemia may not be detected by systemic monitoring, closing the window of opportunity for intervention when an ischemic injury is reversible.

In the search for noninvasive, continuous ways to monitor ischemia, electrical bioimpedance cardiac output monitoring has been advocated, but comparative studies show a lack of agreement with thermodilution methods.[3,4] Near-infrared spectroscopy (NIRS)[5] is responsive to both hypoxemia[6,7] and ischemia,[8–13] but clinical use has been restricted to large organs such as the brain,[14–16] where the broad normal ranges (reported as wide as 48–88%[17,18]) limit clinical utility. Sublingual capnography[19–21] exhibits similarly wide normal ranges (44–64 mmHg).[22] Polarographic oximetry probes (*e.g.*, Eppendorf needle[23]) and fiber-enabled pulmonary catheters[24] are invasive.

We evaluated the ability of a recently introduced method, visible light spectroscopy (VLS) oximetry,[25] to detect hypoxemia and ischemia. Unlike NIRS or pulse oximetry (Spo_2), VLS oximetry uses shallow-penetrating visible light to measure a local estimate of the microvascular hemoglobin oxygen saturation (Sto_2) in thin, small tissue volumes.

Materials and Methods

VLS Oximeter

We studied a VLS oximeter[25] (T-Stat, model 303; Spectros Corp., Portola Valley, CA). Briefly, this oximeter emits white light from a probe placed on, in, or near tissue, collecting any light returning to the probe from the tissue (tissue contact is not required for VLS mea-

* Head, Biomedical Optics Laboratory, Associate Professor, Department of Pediatrics, ‡ Assistant Professor, Department of Gastroenterology, Stanford Hospital and Livermore Veterans Affairs Medical Center, § Assistant Professor, Chief of Endoscopy and Associate Chief of Gastroenterology, †† Chief, Department of Urology, Palo Alto Veterans Affairs Health Care System, ‖ Professor, Anesthesia, # Associate Professor, Department of Anesthesia, ** Director, Center for Special and Minimally Invasive Surgery, Clinical Professor (Adjunct) of Surgery and OB/GYN, Stanford University School of Medicine, ‡‡ Research Assistant, §§ Research Associate, Department of Radiation Oncology, ‖‖ Associate Professor, Department of Diagnostic Radiology, ## Director, Division of Dermatologic Surgery, Clinical Instructor of Dermatology, *** Resident, Department of Dermatology, ‖‖‖ Harold K. Faber Professor of Pediatrics, Senior Assoc Dean for Academic Affairs, Professor (Courtesy), Obstetrics and Gynecology, Department of Pediatrics, ††† Medical Student, Stanford University School of Medicine. † VP Product Development, Spectros Corporation, ‡‡‡ Research Associate, Spectros Corporation. §§§ Resident, Neurology, Department of Neurology, National Naval Medical Center, Bethesda, Maryland.

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Address reprint requests to Dr. Benaron: Division of Neonatal Medicine, 750 Welch Road, No. 315, Mail Code 5731, Stanford University School of Medicine, Palo Alto, California 94305. Address electronic mail to: dbenaron@stanford.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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surement). The collected light is separated by wavelength into 2,048 bins, measured simultaneously. For oximetry, the blue-to-yellow (476–584 nm) portion of the visible spectrum is then used to solve for light scattering and for the concentration of each of the major forms of hemoglobin (deoxyhemoglobin, oxyhemoglobin, and optionally methemoglobin and carboxyhemoglobin) using first differential spectroscopy and least-squares fitting to known hemoglobin spectra. Tissue hemoglobin is estimated as [deoxyhemoglobin + oxyhemoglobin], and the tissue hemoglobin oxygen saturation (Sto_2) is determined as [oxyhemoglobin]/[deoxyhemoglobin + oxyhemoglobin]. The oximetry measurements are continuous, with each measurement typically requiring 5–50 ms, depending on the intensity of the reflected light.

Probes

Probes used in this study included (1) a hand-held wand (6 mm diameter × 12 cm), (2) an endoscopic catheter (2 mm diameter × 2 m), (3) a clip-on surface probe, (4) an invasive needle probe (27 gauge), (5) an oral-esophageal catheter (5 mm diameter × 1 m cm), and (6) a flexible rectal probe (12 mm diameter × 20 cm).

Hypotheses

There were two hypotheses in this study: (1) that VLS oximetry is sensitive *in vivo* to normoxia, hypoxemia, and ischemia; and (2) that VLS saturation measures correlate with pulse oximetry during hypoxemia.

Animal Study Methods

Porcine studies were performed under institutional animal care committee approval at the Palo Alto Veterans Affairs System Hospital (Palo Alto, California).

Porcine Normoxia. After induction with ketamine, six 40-kg pigs were intubated and ventilated with room air, nitrous oxide, and isoflurane. An arterial line was placed for blood sampling, and a venous line was placed for administration of medication and fluids. A pulse oximeter probe (Nellcor, Pleasanton, CA) placed on the ear was used to monitor arterial saturation (Spo_2). A blood gas cartridge-based analysis system (i-STAT, East Windsor, NJ) was used to intermittently monitor pH and arterial partial pressure of oxygen (Po_2). Measurements of muscle oxygenation were performed using an invasive needle probe inserted 5 cm past the skin into the thigh of the pig; measurements of gastrointestinal mucosa were made using an endoscopic catheter passed down the accessory channel of a flexible colonoscope and held with the probe tip 1–20 mm from the mucosal surface, with adjustment as needed by the endoscopist to maintain this distance.

Porcine Hypoxemia. After collection of the data during normoxia, three pigs were ventilated with progressively lower inspired oxygen fraction (Fio_2) mixtures, with pauses near each target saturation (90%, 80%, 70%, 60%) for stabilization, unless cardiovascular instability was noted, followed by the immediate increase of Fio_2 back to room air until the Spo_2 had recovered and 5 min had elapsed. Each cycle required approximately 40 min from start to finish. On the final hypoxemic run, each animal was allowed to enter cardiac arrest (Fio_2 = 0). Sto_2 was monitored in muscle using a needle probe. In total, eight cycles were studied.

Porcine Regional Ischemia. In three normoxic ventilated pigs, the abdomen was surgically opened, and the sigmoid colon was exposed. A VLS endoscopic probe was inserted into the rectum *via* colonoscopy. Sto_2 measurements were collected before, during, and after a 3-min clamping of the local arcadial and radial arteries. Each pig underwent one local ischemia cycle, for a total of three regional ischemia cycles.

Human Study Methods

Human studies were performed under institutional review board approval at the Livermore Veterans Affairs Hospital, Stanford University, and the Palo Alto Veterans Affairs System Hospital and after written informed patient consent. Human subjects were studied under conditions of normoxia, hypoxemia, local ischemia, and global ischemia.

Clinical Normoxia. Normoxic Sto_2 was measured at enteric sites in the gastrointestinal clinic. In 40 patients undergoing routine colonoscopy and 10 patients undergoing esophageal–gastric–duodenal endoscopy, measurements of Sto_2 were made using a VLS probe passed down the accessory channel of the endoscope. Measurements were made of various segments of the gastrointestinal tract (in the esophagus, stomach, and small intestine or in the colon, depending on the procedure). In 21 patients undergoing surgery, buccal mucosal Sto_2 was measured using a cheek clip probe that maintains a small gap between the buccal surface and the probe sensor. In 25 patients in the dermatology clinic, facial skin Sto_2 was measured using a handheld probe, maintaining again a gap between the skin surface and the probe.

Clinical Hypoxemia. In three healthy volunteers breathing a mixture of room air and helium, hypoxemia was induced by increasing the helium:air ratio. An anesthesiologist was present at all times. Pulse oximetry Spo_2 was recorded at the left index finger. VLS oximetry was recorded as (1) buccal Sto_2 monitored using a cheek clip, (2) esophageal Sto_2 monitored using a catheter passed orally 25–30 cm beyond the lips and into the midesophagus without an endoscope and after topical benzocaine pharyngeal anesthesia (Cetacaine; Cetylite Industries, Pennsauken, NJ), or (3) sigmoid mucosa monitored using a rectal probe passed 10–20 cm beyond the sphincter without endoscopy after Fleet's enema. Each subject underwent three breathe-down cycles to 85% Spo_2 or, in one subject, to below 70% Spo_2. Only one site

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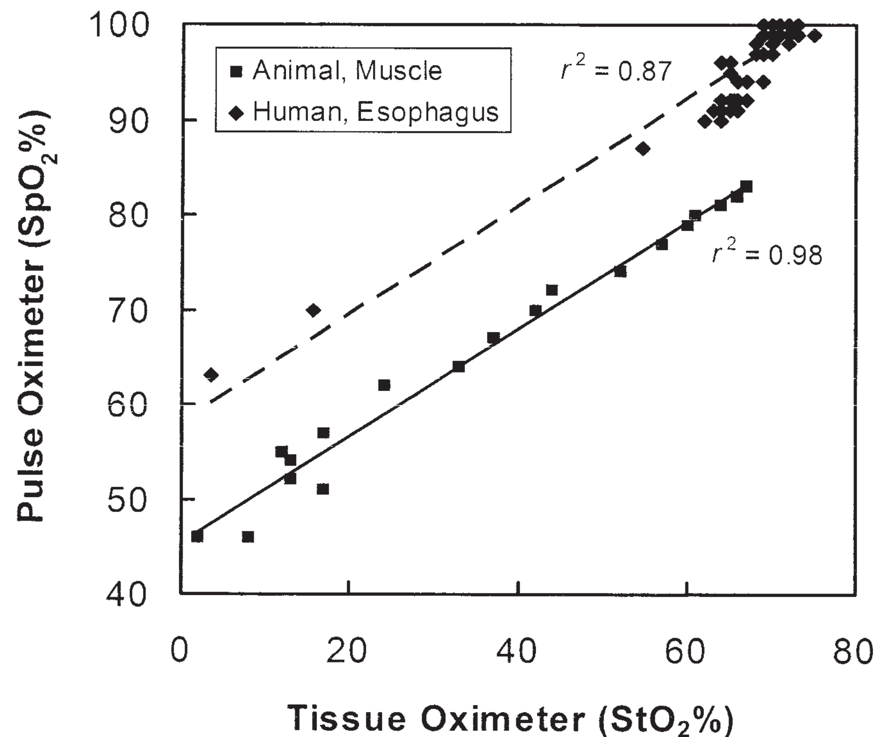

Fig. 1. Visible light spectroscopy *versus* pulse oximetry during hypoxemia. Muscle microvascular hemoglobin oxygen saturation (Sto_2) in pigs and esophageal Sto_2 in human subjects were linearly correlated with oxygen saturation measured by pulse oximetry (Spo_2) during the induction of hypoxemia (animals, r^2 = 0.98; humans, r^2 = 0.87).

was monitored during any single cycle. We recorded a total of nine cycles.

Clinical Regional Ischemia. Local ischemia was induced in healthy volunteers in two ways. In a first group of five subjects, digital ischemia was induced by gradually increasing tourniquet pressure at the base of the forefinger while Spo_2 and Sto_2 were monitored using pulse oximetry and a handheld VLS probe placed at the tip of the finger. In a second group of five subjects, localized cutaneous and muscular ischemia was induced by direct pressure of the flat tip of a hand-held VLS probe placed against the lip, and Sto_2 was monitored using the VLS probe. The lip compression pressure was selected such that a minimum of 10 μM hemoglobin remained detectable during the compression, as estimated by the VLS hemoglobin signal from the tissue.

Clinical Global Ischemia. In patients undergoing implantation of an automatic implantable cardioverter defibrillator in the operating room, buccal Sto_2 was monitored before, during, and after ventricular fibrillation for defibrillator testing. The onset of ischemia was defined as the start of fibrillation on the electrocardiogram.

Statistics

Demonstration of VLS sensitivity to hypoxia required Sto_2 measurements during normoxia, hypoxemia, and ischemia for both animal and human studies. *A priori* sample size estimates were based on an assumption of normally distributed VLS data, on pilot data in animals and humans suggesting that Sto_2 saturation values would cluster near 65 ± 5% (mean ± SD), and on a target confidence of 95%. In view of this, four measures were required to estimate a mean Sto_2 for each tissue site to a 95% confidence range in of ±5% in animals, 25 measures were required to estimate Sto_2 to ±2% in humans, and six measures were required to differentiate between conditions that change mean Sto_2 by ±5% in humans. A normal distribution of Sto_2 was tested using the Kolmogorov-Smirnov test. Correlation was estimated using least-squares linear regression; a Bland-Altman plot was determined to be less appropriate because there was no accepted standard against which Sto_2 values were postulated to be equivalent and which could be used in the same tissue.

Results

Animal Study Results

Porcine Normoxia. Tissue Sto_2 during normoxia was 72 ± 3% (mean ± SD) in the colonic mucosa and 69 ± 4% in the thigh muscle. There was no difference between mean Sto_2 values from different sites (all sites 71 ± 4%; P = not significant [NS]). The mean pulse/VLS saturation difference during normoxia was 27%.

Porcine Hypoxemia. Muscle Sto_2 was linearly correlated with Spo_2 during staged induction of hypoxemia (r^2 = 0.98; fig. 1). Below an arterial saturation of 90%, Sto_2 was significantly lower than during normoxia. After arrest, Sto_2 decreased to zero. The mean pulse/VLS saturation during hypoxemia ranged from 17 to 38%.

Porcine Regional Ischemia. Colon Sto_2 decreased to 31 ± 11% after clamping of the major vessels and re-

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Table 1. Visible Light Spectrometry (VLS) Oximetry during Normoxia in Human Subjects

Site of Measurement	Tissue Oximeter, % (mean Sto_2% ± SD)	No. of Subjects	Normal Range, % (mean Sto_2% ± 2 SD)
Colon	69 ± 4	40	61–77
Small intestine	71 ± 3	10	65–77
Stomach	70 ± 4	5	62–78
Esophagus	68 ± 4	10	60–76
Buccal mucosa	77 ± 3	21	71–83
Skin	72 ± 16	25	40–100

VLS Sto_2% values were measured at different sites. Colonic, intestinal, gastric, and esophageal saturation were similar (P = NS). Buccal saturation was significantly higher ($P < 0.001$); skin saturation was significantly more variable ($P < 0.001$).

turned to 72 ± 5% after clamp release. The mean pulse/VLS saturation difference at baseline was 19–25% and increased to as high as 66% during ischemia ($P < 0.001$ *vs.* normoxia and hypoxemia).

Human Study Results

Clinical Normoxia. Enteric mucosal Sto_2 during normoxia averaged 69 ± 4%, with no difference between colonic, small intestine, stomach, and esophageal values (P = NS; table 1). Skin Sto_2 mean values were similar but showed a wider variance (72 ± 16%, $P < 0.001$). Buccal Sto_2 was higher than Sto_2 for other tissues (77 ± 3%; $P < 0.001$). Sto_2 was normally distributed (Kolmogorov-Smirnov test, enteric Sto_2, D = 0.72, $P < 0.005$). The mean pulse/VLS saturation difference ranged from 20 to 29%.

Clinical Hypoxemia. Esophageal Sto_2 during helium breathe-down was linearly correlated with pulse oximetry ($r^2 = 0.87$; fig. 1). At an Spo_2 of 80%, Sto_2 was lower than during normoxia (56 ± 6 *vs.* 72 ± 4%; $P < 0.005$). The pulse/VLS saturation difference was 17% during normoxia *versus* 29% during hypoxemia. During recovery, Sto_2 returned to baseline values more rapidly than Spo_2 (5 *vs.* 12 s).

Table 2. Visible Light Spectrometry (VLS) and Pulse Oximetry after 120-s Occlusion Ischemia in the Human Forefinger

Intervention	Tissue Oximeter, % (Sto_2%)*	Pulse Oximeter, % (Spo_2%)	Mean ΔSp-to$_2$% (Spo_2% − Sto_2%)
Baseline	73	100	27
Partial occlusion	34	97	63
Total occlusion	8	—	—

The VLS oximeter continues to measure throughout ischemia.

Clinical Regional Ischemia. Tissue Sto_2 decreased during regional ischemia in the lip (fig. 2) and forefinger (table 2) subject groups. The initial rate of Sto_2 decrease was −1.3 ± 0.2%/s. After reversal of ischemia, Sto_2 and saturation difference returned to baseline in all tissues within seconds. The mean pulse/VLS difference increased significantly during ischemia (11–27% baseline *vs.* 91% peak ischemia; $P < 0.001$). During concurrent pulse and VLS oximetry in the forefinger, Sto_2 was measurable at all times, whereas pulse oximetry was not operative during maximal occlusion (table 2).

Clinical Global Ischemia. Buccal Sto_2 decreased during global ischemia with ventricular fibrillation (fig. 3). The initial rate of decrease in Sto_2 was similar to that during human regional ischemia (−1.2 ± 0.1%/s; P =

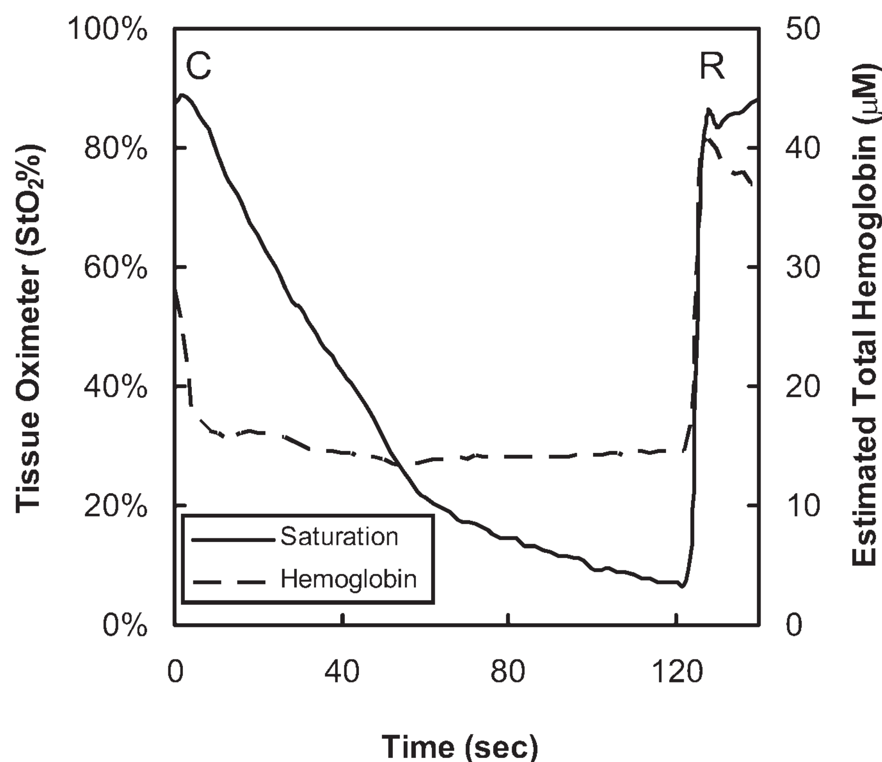

Fig. 2. Visible light spectroscopy lip oximetry during local ischemia in human subjects. Tissue microvascular hemoglobin oxygen saturation (Sto_2) decreased during regional compression ischemia in the lip. After reversal of compression, Sto_2 and saturation difference returned to baseline within seconds. C = compression; R = release.

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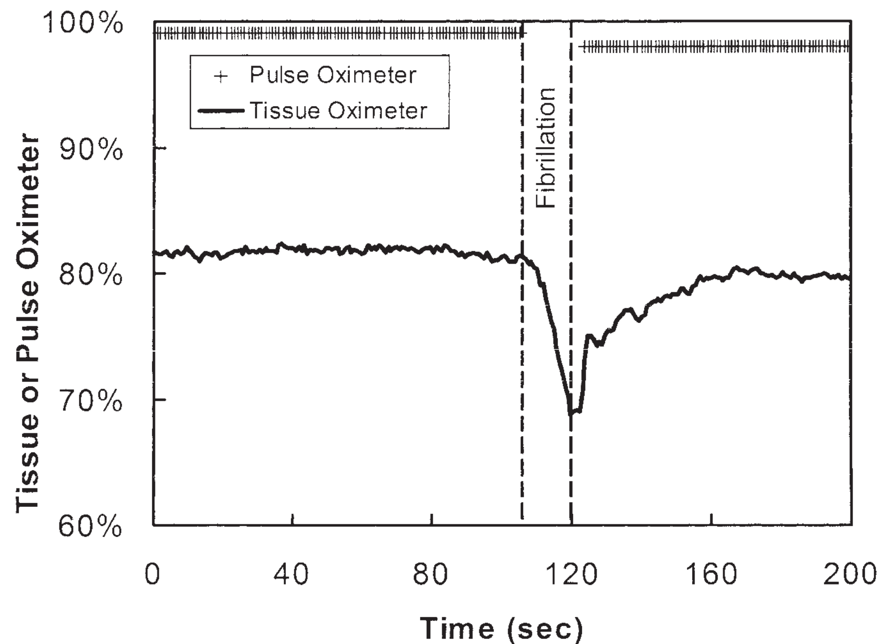

Fig. 3. Visible light spectroscopy buccal oximetry during global ischemia in human subjects. Tissue microvascular hemoglobin oxygen saturation decreased during ventricular fibrillation, and it decreased below the 95% normal range in an average of 9 s, recovering rapidly on restoration of rhythm.

NS). Sto_2 decreased below the 95% normal range in an average of 9 s (n = 3), recovering rapidly on restoration of rhythm. In contrast, pulse oximetry stopped recording entirely at the onset of ventricular fibrillation and remained inoperative until 7 s after cardiac rhythm was restored. In patients undergoing sustained cardiac arrest, Sto_2% decreases to zero after 3–9 min. The correlation between Svo_2 and Sto_2 was $r^2 = 0.94$ (plot not shown).

Discussion

The results show that VLS oximetry provides a continuous, noninvasive, and localized measurement of Sto_2 in thin, small tissue volumes. VLS is sensitive to hypoxemia, regional, and global ischemia, even during low or absent blood flow.

In view of the similar VLS saturations at different tissue sites within the gastrointestinal tract, and the narrow normal range, we speculate that VLS oximetry of the gastrointestinal mucosa can provide an accessible, reliable reference point for the monitoring of systemic flow. Precedent for use of the gastrointestinal mucosa to monitor systemic perfusion includes partial pressure of carbon dioxide (Pco_2) tonometry or capnometry (gastric/duodenal,[26] esophageal,[27] sublingual,[28–30] or buccal), esophageal pulse oximetry,[31,32] and Doppler flow.[33,34] In this respect, it would be interesting to verify whether VLS can be serve as a standard for monitoring changes in systemic circulation. The ability to perform localized gastrointestinal measures may also allow for detection and localization of focal hypoxic or ischemic bowel.

The narrow normal range of VLS differs from other noninvasive approaches such as NIRS and capnography, a potential advantage for clinical use in identifying the individual patient at risk for hypoxia. Compared with NIRS, the VLS normal range was significantly narrower (NIRS cerebral normal range is 36% wide,[17,18] VLS esophageal normal range was 16% wide; F = 0.14, $P < 0.0001$). The exception to this tight variability was skin, known to exhibit a wide variability in perfusion and saturation (reported SD range, 10–12%),[35] similar to our measured variance (SD = 16%, F = 0.56, P = NS).

Visible light spectroscopy may assist in the discrimination of ischemia from hypoxemia. The difference between pulse and VLS oximetry was significantly greater during ischemia than during normoxia or hypoxemia (typically $\Delta < 30\%$ during hypoxemia, $\Delta > 35\%$ during pure or mixed ischemia; table 3). In contrast to conventional arteriovenous difference measurements, pulse/VLS saturation difference is calculated using two noninvasive values, without need for blood sampling.

The ability of VLS probes to operate in a noninvasive, noncontact geometry may work to its advantage. Local blood flow in soft tissues is highly influenced by local factors such as compression. In this study, noninvasive VLS probes yielded a higher mean Sto_2 value ($t = 12.7$, $P < 0.0001$), and a tighter coefficient of Sto_2 variation ($F = 0.31$, $P < 0.0001$) than invasive VLS needle probes

Table 3. Visible Light Spectrometry (VLS) and Pulse Oximetry Difference during Normoxia, Hypoxemia, and Ischemia

Subject	Normoxia, % (ΔSp-to_2%)	Hypoxemic Hypoxia, % (ΔSp-to_2%)	Ischemic Hypoxia, % (ΔSp-to_2%)
Human	21–29	16–29	51–91
Animal	25–28	22–38	66–83

The difference between pulse and VLS oximetry was greater during ischemia than during normoxia or hypoxemia.

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used in this and other studies (*e.g.*, 61 ± 8% prostate and 65% ± 8% esophagus by invasive VLS needle), suggesting that local pressure impacts local tissue oximetry. In support of this view, we easily induced local lip ischemia with gentle probe pressure on the lip. Jiang *et al.*[36] recently reported a similar NIRS pressure sensitivity in breast studies. This suggests that the act of measurement using invasive or pressure-contact approaches, such as polarographic needles, NIRS probes, tonometry/capnography probes, or VLS needles, may depress the local tissue oxygenation.

Visible light spectroscopy oximetry in other forms has been previously demonstrated *in vivo*. Malonek and Grinvald[37] used visible light reflectance to monitor cortical activation in the exposed brain through oxygenation and scattering changes. Harrison *et al.*[38] and others[35] used VLS reflectance to monitor skin oxygenation and skin pigments. In the 1980s, both Feather *et al.*[39] and Kessler *et al.*[40] developed VLS oximeters based on portable scanning spectrophotometers. The current study differs in the use of a VLS instrument that can measure using small probes, clips, or needles. We introduce the term *VLS* in this article because VLS is the visible light analog of the widely used *NIRS* term, and the benefits and drawbacks of VLS *versus* NIRS result in large part from the differential behavior of visible and near-infrared light in tissue.

Visible light spectroscopy is similar to NIRS in some respects. First, mean VLS Sto_2 is in accord with NIRS Sto_2 reported in peer-reviewed human studies[5–18] (bias VLS–NIRS = −1 ± 5%; P = NS). Second, the fractional contribution of venous blood to the cerebral NIRS signal has been reported as 0.84 ± 0.21 (range, 0.60–1.00).[41–43] Using central venous and pulse oximetry saturation as estimates for local venous and arterial saturation, the fractional contribution of venous blood to the VLS signal in this study is estimated at 0.89 ± 0.04 (P = NS). This similar mean value and arteriovenous weighting between VLS and NIRS suggest that the two methods probe similar microvascular compartments.

Visible light spectroscopy clinically differs from NIRS in the tissues that can be monitored, and this difference may permit VLS to play a more versatile role in patient treatment. NIRS light sources and detectors must be spaced 2–5 cm apart or more to illuminate and monitor a large, homogenous volume of tissue (> 30 ml); this renders NIRS unsuitable for many tissue regions, such as thin tissues, such as the gastrointestinal mucosa, or small tumors, and forces NIRS sensors to be long and bulky. In contrast, the visible light used in VLS is strongly absorbed by tissue, making the VLS measurement highly localized; this renders VLS unsuitable for transcranial use or use over thick skin because the surface tissue properties will dominate.

Because VLS oximetry measures small, subsurface tissue volumes and NIRS; measures larger, deeper volumes of tissue, VLS oximetry may be complementary to NIRS; because the difference between VLS tissue oximetry and arterial pulse oximetry is increased in ischemia but not in hypoxemia, VLS oximetry may be complimentary to pulse oximetry.

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