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Esophageal oxyhemoglobin saturation as a resuscitative metric in hemorrhagic shock

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ABSTRACT

Background Mixed venous saturation (SvO2) is considered the gold standard to assess the adequacy of tissue oxygen delivery (DO2) in shock states. However, SvO2 monitoring is challenging as it requires an invasive catheter and frequent blood sampling. Non-invasive methods, including near-infrared spectroscopy, have demonstrated low sensitivity to tissue dysoxia.

Methods We fabricated a new device that uses resonance Raman spectroscopy (RRS) to quantify oxyhemoglobin saturation (ShbO2) in the esophagus (eShbO2), tongue (tShbO2), and liver (hShbO2). In two rat models of hemorrhagic shock, we quantified (1) The correlation of RRS-measured ShbO2 to SvO2 during progressive hemorrhage (n=20) and (2) The value of these metrics to predict near-term mortality in fixed, severe hemorrhage (mean blood pressure =25 mm Hg; n=18).

Results In model 1, eShbO2 (r=0.705, p<0.0001) and tShbO2 (r=0.724, p<0.0001) correlated well with SvO2 and with serum lactic acid (eShbO2-lactate r=0.708, p<0.0001; tShbO2-lactate r=0.830, p<0.0001). hShbO2 correlated poorly with both SvO2 and lactic acid. Using time-matched ShbO2-SvO2 pairs, the performance of ShbO2 to detect severe tissue hypoxia (SvO2<20%) was excellent (AUC 0.843 for eShbO2, 0.879 for tShbO2). In model 2, eShbO2 showed a maximized threshold of 40% with 83% of animals dying within 45 minutes of this cut-off, demonstrating accuracy as a monitoring device. This was similar for tShbO2, with a threshold of 50%, predicting death within 45 minutes in 76% of animals. ShbO2 showed superior sensitivity to invasive monitoring parameters, including MABP<30 mm Hg (sensitivity 59%), pulse pressure<15 mm Hg (sensitivity 50%), and heart rate>220 bpm (sensitivity 39%, p=0.004).

Conclusions eShbO2 represents a new paradigm to assess the adequacy of DO2 to a tissue. It constitutes a promising monitoring method to evaluate tissue oxygen saturation in real time and non-invasively, correlating with SvO2 and time to death.

Level of evidence Level III, therapeutic/care management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mixed venous oximetry and serum lactic acid are commonly used to quantify the state of the circulation, but require blood sampling and are intermittently measured.

WHAT THIS STUDY ADDS

⇒ Oxyhemoglobin saturation in the esophagus or tongue can be assessed using Raman spectroscopy, which correlates well with invasively measured mixed venous saturation and serum lactic acid.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Raman spectroscopy-based oximetry may be a useful, continuous monitor of the health of the circulation.

BACKGROUND

Adequate tissue oxygenation is vital to the maintenance of structure and function. An imbalance between oxygen delivery (DO2) and oxygen consumption is a key driver of abnormality in a number of critical illness states, including shock.[1] The assessment and optimization of DO2 is essential to the treatment of patients after major surgery, severe trauma, heart failure, and sepsis.[2] Currently, assessment of tissue oxygenation takes place primarily through venous oximetry, that is, mixed venous oxyhemoglobin saturation (SvO2). When the oxygen supply is insufficient to meet the metabolic demands of tissues, tissue hypoxia develops, increasing oxygen extraction from hemoglobin and decreasing SvO2.[3]

The most common approach to SvO2 monitoring is co-oximetry of blood sampled after complete venous admixture, typically from the pulmonary artery (PA).[4] Because of the invasive nature of PA catheters, SvO2 is more commonly sampled from a central venous catheter (CVC) positioned in the superior vena cava as a surrogate for central SvO2.[5] This technique still requires a CVC and inherits a risk of complications such as infection, pneumothorax, hematoma, and thrombosis.[6–8] Further, this approach to monitoring is intermittent and only as frequent as blood is sampled; this approach significantly limits its use in small children, in whom repeat phlebotomy contributes significantly to transfusion requirements.[9 10] Indwelling fiberoptic oximetric catheters may theoretically allow continuous monitoring,[11 12] though these catheters are still invasive, large in caliber, and require frequent recalibration due to drift; thus, their use is not widespread. Regional oximetry using near-infrared spectroscopy (NIRS) is broadly used to continuously monitor regional oxyhemoglobin saturation. However, several studies have demonstrated a low sensitivity and specificity to detect even the most extreme episodes of tissue hypoxia.[13–15] Thus, an alternate approach to monitoring the adequacy of oxygen delivery is needed.

Here, we present an alternative approach to monitoring the adequacy of oxygen delivery that measures tissue ShbO2 in central tissues using an optical technique known as resonance Raman spectroscopy (RRS). Distinct from absorbance spectroscopy, a single wavelength of light is emitted and the spectral shift of reflected light is captured, which is indicative of the vibrational characteristics of the molecules it encounters. This wavelength shift creates a spectral signature of a substance,[16] and thus effectively distinguishes the oxidized versus reduced state of the porphyrin structures in hemoglobin.[17 18] Measurement of tissue ShbO2 has been previously described by this method.[19] Here, we describe the correlation between hemoglobin saturations measured using RRS in a tissue versus central SvO2, and the sensitivity and specificity of these metrics in predicting death in models of hemorrhagic shock.

MATERIALS AND METHODS

All animals were maintained in accordance with the National Research Council guidelines.

RRS system

Three custom-built lasers were designed for these experiments, each with a single wavelength laser source, a collection fiber optic probe, and a high-resolution spectrometer (figure 1A,B). The spectrometer contains a custom-built charge-coupled device driver and laser control board, as well as an internal acetaminophen control, which autocalibrates the device each time the laser is turned on (figure 1A). As previously described,[20] a 405 nm wavelength excitation light is projected onto the surface of a tissue of interest and collected then projected into a high-resolution spectrometer. The use of a wavelength near the Soret absorption band (400 nm to 450 nm) results in a dominant RRS peak between 1350/cm and 1380/cm, which has been established as a spectral marker of oxygenation/deoxygenation of the iron center of hemoproteins. By setting a spectral range from 700/cm to 1700/cm (figure 1C) we were able to detect the characteristic vibrations of the porphyrin ring. The laser power was set to 4 mW, which has been previously demonstrated to be safe,[21] illuminating an area of 1.5 mm of tissue in diameter and less than 1 mm depth. The resulting signal was averaged during a 60-second period for analysis.

Instrumentation

Male Sprague-Dawley rats (400 g to 500 g weight) were obtained from Charles River. Animals were housed in pairs, under controlled conditions (temperature, 21°C to 22°C; humidity, 40% to 50%) and a 12-hour dark-light cycle with free access to food and water. On the day of experimentation, anesthesia was induced by inhalational isoflurane (2.5%), followed by an injection of ketamine (45 mg/kg to 75 mg/kg intraperitoneal [IP]) and xylazine (5 mg/kg to 10 mg/kg IP). Thereafter, animals were intubated and ventilated (CWE, Incorporated, SAR-1000 ventilator) with positive end-expiratory pressure 5 cm H2O, tidal volume 8 mL/kg to 10 mL/kg, respiratory rate 35 bpm to 45 bpm and fraction of inspired oxygen (FiO2) 30% to 35%. The esophageal RRS probe was advanced orally into the proximal esophagus under direct vision; after positioning, the tongue probe was placed. Finally, a transverse incision was made in the abdomen for direct placement of the hepatic probe over the right medial lobe (figure 1C).

Anesthesia was maintained throughout the experiment with isoflurane (1% to 2%) and titrated to ensure non-responsiveness to painful stimuli. Core temperature was maintained at 37°C by a closed loop thermoregulated heating pad. Instrumentation included femoral arterial catheter for phlebotomy, arterial pressure catheter (SPR-671 catheter, 1.4 French, Millar), and tail vein catheter. The chest and pericardium were opened to permit intermittent pulmonary arterial punctures for SvO2 and lactate measurement; this approach was favored after failed attempts to reliably sample venous blood from CVCs. After instrumentation, a baseline arterial and pulmonary artery blood gas was obtained, and all the animals underwent a 20-minute baseline period.

Experiment 1: Progressive hemorrhagic shock

In experiment 1, blood was withdrawn to achieve mean arterial blood pressure (MABP) of 35 mm Hg (time=0). After 20 minutes of maintaining this MABP, SvO2 and lactate were measured from a pulmonary artery blood gas sample and analyzed (ABL90 Flex Plus, Radiometer America). Afterwards, more arterial blood was drawn as necessary to reach MABP 30 mm Hg (time=20). The same procedure was repeated for MABP 25 mm Hg, 20 mm Hg, and 15 mm Hg or until the animal died of exsanguination, defined as pulse pressure (systolic blood pressure minus diastolic blood pressure) less than 5 mm Hg.

Experiment 2: Fixed blood pressure

In the second experiment, a fixed-pressure hemorrhagic shock was established by continuous blood draw for a MABP of 25 mm Hg to 30 mm Hg. Afterwards, the animals were monitored until the pulse pressure was less than 5 mm Hg, when the animal was considered deceased.

Statistical analysis

Statistical analysis and graphing were performed using Prism V.9.00 software (GraphPad, California, USA). For all tests, a value of $p<0.05$ was considered statistically significant.

Comparison between groups was performed analyzing averages during the different intervals using two-way repeated measures analysis of variance. When results were statistically significant, time-dependent differences between groups were evaluated using the Holm-Sidak multiple comparison method. Association between variables was studied by Spearman's correlation coefficient, and curve fitting with regression models. Sensitivity and specificity analyses were performed calculating sensitivity and specificity of every 5-minute average. The probability of survival was calculated by survival proportions analysis by the log-rank test. The receiver operating characteristics (ROC) curve was used to estimate the diagnostic ability of ShbO2, MABP, pulse pressure, and heart rate. Area under the ROC curve was calculated for these analyses.

RESULTS

Experiment 1

A total of 21 animals completed this experimental protocol. Achieving the initial MABP target (35 mm Hg) required phlebotomy of 9 mL to 14 mL of blood, representing 30% to 45% of equivalent blood volume. One animal did not survive the initial 20-minute period and was excluded from the analysis.

Esophageal (eShbO2) and tongue (tShbO2) ShbO2s decreased significantly during the different intervals of hemorrhagic shock (figure 2). eShbO2 decreased from a baseline of 67.4±16.0% to a nadir of 37.8±22.8% ($p=0.0004$ for change during time) at MABP 15 mm Hg, and tShbO2 decreased from a baseline of

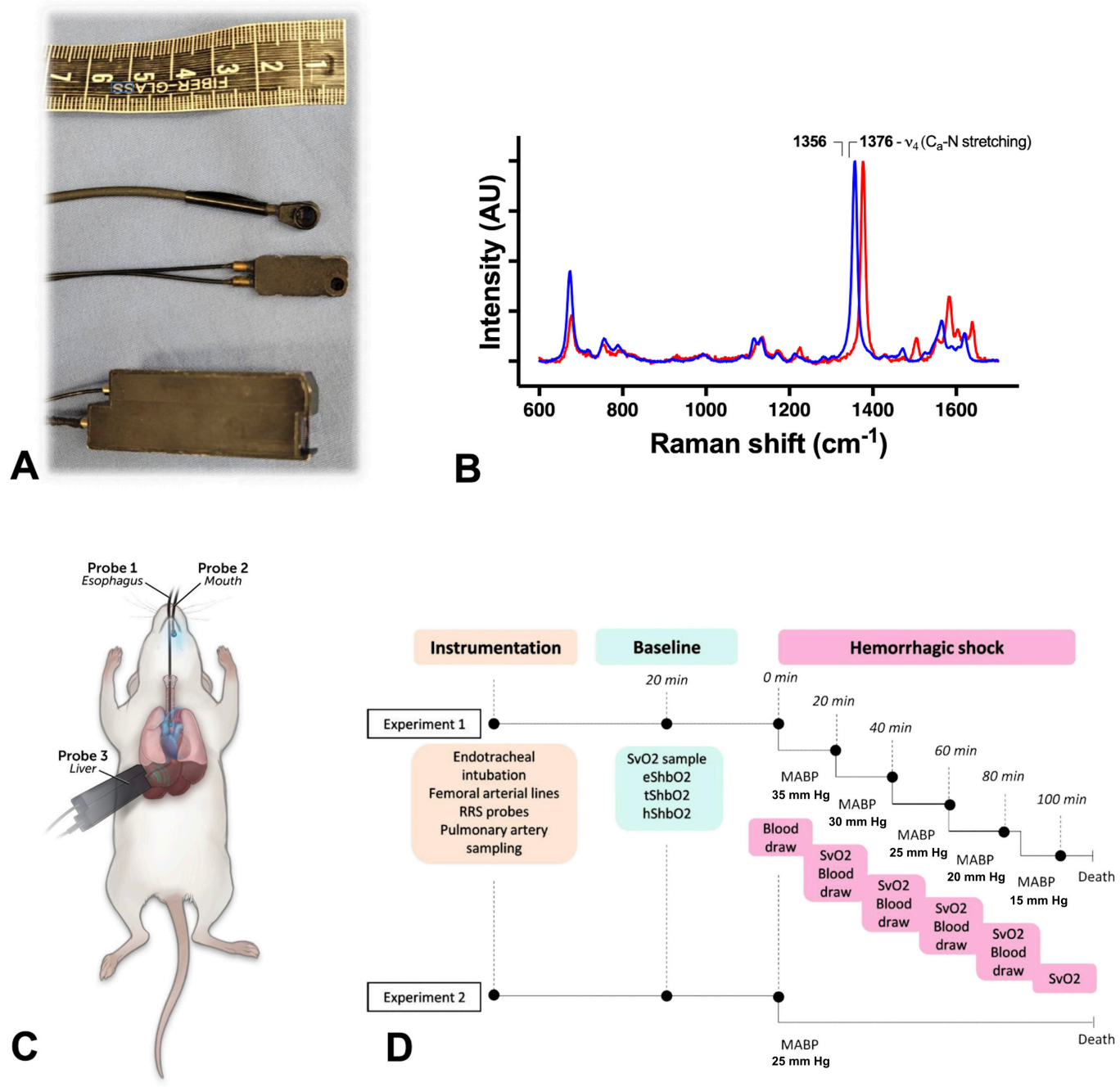

Figure 1 (A) The device features multiple lasers (1) whose emissions are split between an acetaminophen reference (2) and the outgoing fiber bundle, which connects to a quick disconnect probe interface (B) at (3). Returning light passes through a collimating lens (4), reflects off of a mirror (5) and onto a custom grating (6) which separates light according to wavelength onto a lens (7). The array is then analyzed by a CCD image sensor (8) stabilized by a thermoelectric cooler. The 2D signal intensity image is outputted to an electronic board (9) which controls the laser and CCD. Fiberoptic cable paths not shown for image clarity. (C) Raman spectra for oxygenated (red) and deoxygenated (blue) hemoglobin; these isoforms can be clearly distinguished based on the peak differential at 1356/cm (deoxygenated) versus 1376/cm (oxygenated). (D) Positioning of the RRS probes in the animal model. (E) Study schematic. In Model 1, hypovolemic shock was induced by controlled phlebotomy to a target MABP 35 mm Hg, followed by a 20-minute period of observation, then SvO2 sampling. Thereafter, blood was withdrawn to decrease MABP by 5 mm Hg and the observation and blood sampling repeated; this cycle was iterated until death, defined as pulse pressure<5 mm Hg. In Model 2, blood was withdrawn to achieve MABP 25 mm Hg, and animals were monitored until death. CCD, charge-coupled device; eShbO2, oxyhemoglobin saturation in the esophagus; hShbO2, oxyhemoglobin saturation in the liver; MABP, mean arterial blood pressure; RRS, resonance Raman spectroscopy; SvO2, mixed venous saturation; tShbO2, oxyhemoglobin saturation in the tongue.

76.1±15.9% to a nadir of 24.9±24.4% (p<0.0001). In the same way, SvO2 (pulmonary artery) decreased from 42.1±7.3% at baseline to 7.1±1.8% at the end of the experiment (p=0.0026). In contrast, hShbO2 (liver) was preserved throughout the hemorrhage period (69.0±13.3% at baseline to 59.3±4.8% at the end of the experiment, p=0.847).

Time-matched eShbO2-SvO2 pairs exhibited a positive correlation (Spearman's correlation coefficient r=0.705, p<0.0001,

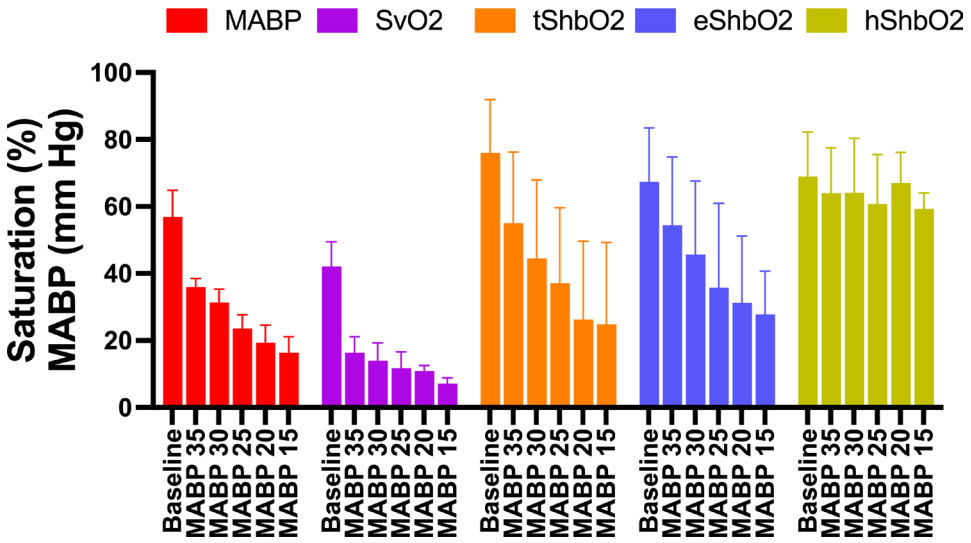

Figure 2 Average MABP during the 20-minute intervals (red), pulmonary artery saturation (SvO2) (purple), tissue oxyhemoglobin saturation (ShbO2) in tongue (orange), esophagus (blue), and liver (yellow) in rats undergoing progressive fixed-pressure hemorrhagic shock. Data are means, error bars are SD. eShbO2, oxyhemoglobin saturation in the esophagus; hShbO2, oxyhemoglobin saturation in the liver; MABP, mean arterial blood pressure; tShbO2, oxyhemoglobin saturation in the tongue.

figure 3A) and tShbO2-SvO2 correlation (r=0.724, p<0.0001, figure 3B) was strong. However, hShbO2 correlated poorly with SvO2 (r=0.271, p=0.475, figure 3C). The sensitivity and specificity of ShbO2 to categorically detect severe tissue hypoxia (defined as SvO2<20%) was excellent: AUC for eShbO2 was 0.843 (95% CI 0.747 to 0.900, p<0.0001) and for tShbO2 was 0.879 (95% CI 0.789 to 0.969, p<0.0001, figure 3D).

Time-matched eShbOo2-lactate pairs exhibited a strong, inverse correlation (Spearman's correlation coefficient r=0.708, p<0.0001, figure 4A), as did tShbO2-lactate (r=0.830,

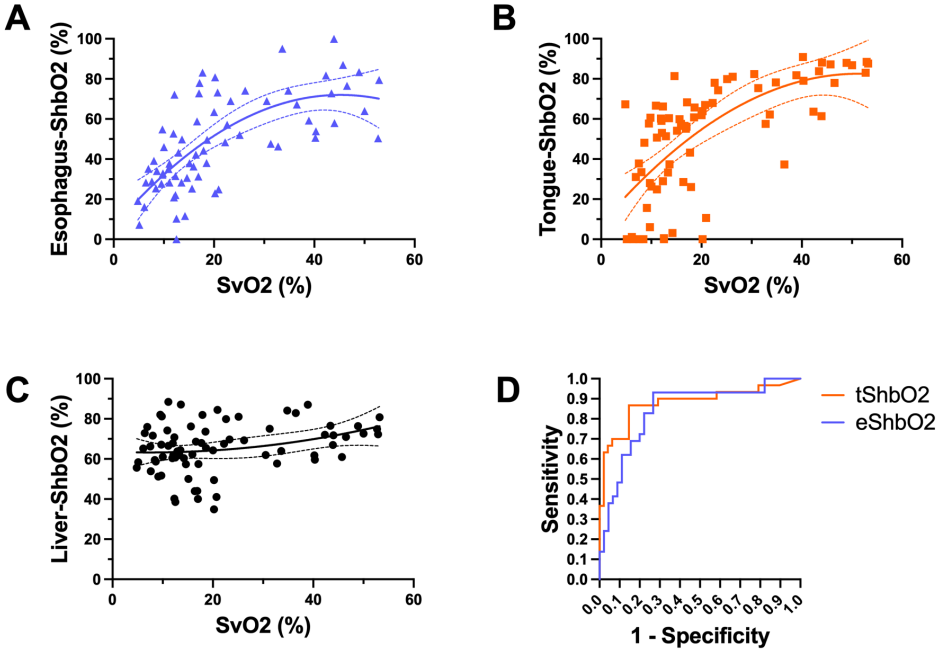

Figure 3 ShbO2 is associated with SvO2 during graded hemorrhagic shock. ShbO2 values are average of the oxyhemoglobin measured by RRS during the 2 minutes prior to the SvO2 sample. The line represents a quadratic regression with 95% CI. (A) Time-matched pairs of esophageal ShbO2 and SvO2. Spearman's correlation coefficient r=0.705, p<0.0001, r^2=0.492. (B) Tongue ShbO2. Spearman's correlation coefficient r=0.724, p<0.0001, r^2=0.467. (C) ShbO2 in the liver. Spearman's correlation coefficient r=0.271, p=0.475, r^2=0.089. (D) Defining SvO2<20% as presence of severe shock state, receiver operating characteristics curve analysis of ShbO2 to detect SvO2<20%. Tongue-ShbO2 (orange line) AUC 0.8795 (95% CI 0.789 to 0.969, p<0.0001). Esophageal-ShbO2 (blue line) AUC 0.843 (95% CI 0.747 to 0.9, p<0.0001). eShbO2, oxyhemoglobin saturation in the esophagus; ShbO2, oxyhemoglobin saturation; RRS, resonance Raman spectroscopy; SvO2, mixed venous saturation; tShbO2, oxyhemoglobin saturation in the tongue.

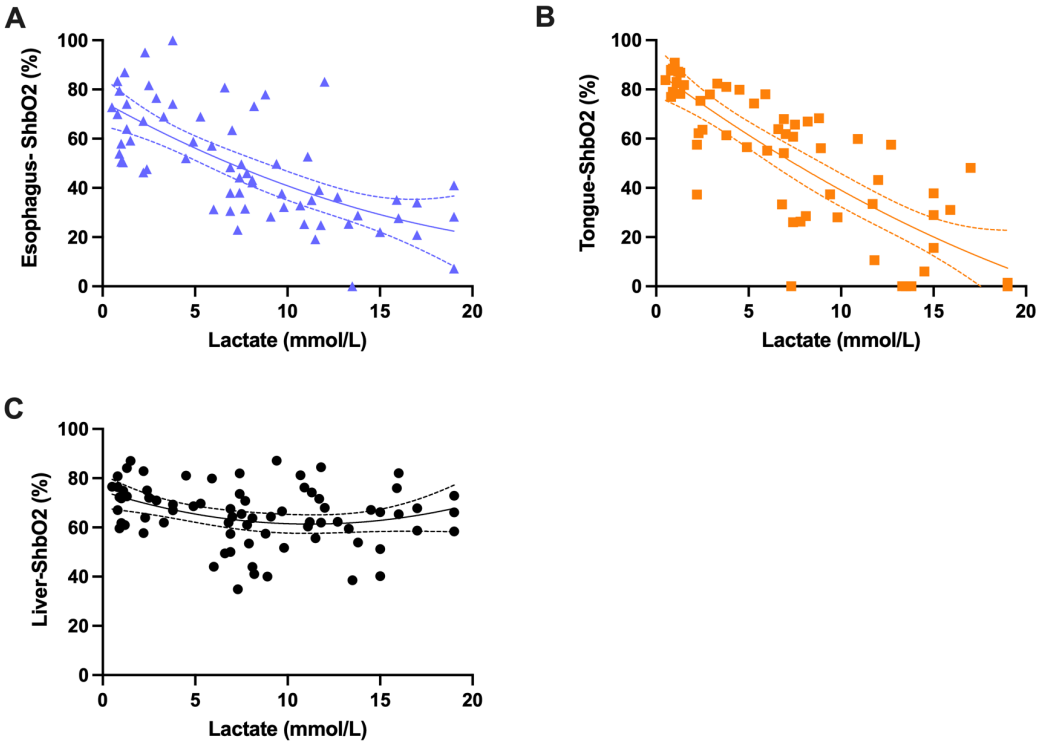

Figure 4 ShbO2 is associated with lactate during graded hemorrhagic shock. (A) Time-matched pairs of esophageal ShbO2 and lactate. Spearman's correlation coefficient r=−0.708, p<0.0001, r^2=0.478. (B) ShbO2 in the tongue. Spearman's correlation coefficient r=−0.830, p<0.0001, r^2=0.657. (C) ShbO2 in the liver. Spearman's correlation coefficient r=−0.247, p=0.033, r^2=0.111. ShbO2 values are average of the oxyhemoglobin measured by RRS during the 2 minutes prior to the lactate sample. The line represents a quadratic regression with 95% CI. ShbO2, oxyhemoglobin saturation; RRS, resonance Raman spectroscopy.

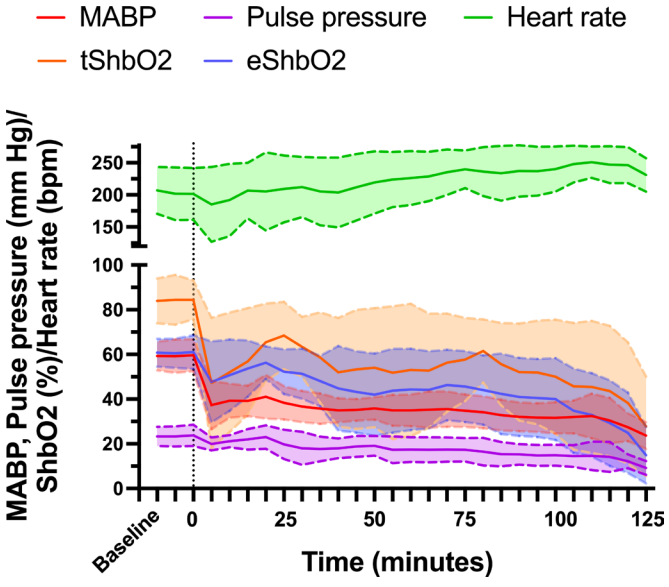

Figure 5 MABP (mm Hg), pulse pressure (mm Hg), heart rate (beats per minute) and ShbO2 (%) during baseline and shock. Data are 5-minute averages of measurements and presented as mean and error bars as SD. eShbO2, oxyhemoglobin saturation in the esophagus; MABP, mean arterial blood pressure; ShbO2, oxyhemoglobin saturation; tShbO2, oxyhemoglobin saturation in the tongue.

p<0.0001, figure 4B). hShbO2 had no correlation with lactate (r=0.247, p=0.033, figure 4C).

Experiment 2

A total of 22 animals were instrumented as described; two animals died within 10 minutes of the initial shock and were excluded from the analysis. The phlebotomy volume required to reach the target MABP ranged between 12 mL and 17 mL, approximately 40% to 65% of the total blood volume.

ShbO2 decreased abruptly immediately after the hemorrhage parallel to the MABP (figure 5). Baseline MABP was 59±6 mm Hg, decreasing to 24±6 mm Hg just before death. Accordingly, pulse pressure decreased from 23±4 mm Hg to 9±3 mm Hg and heart rate increased from 207±37 bpm to 231±26 bpm. eShbO2 decreased from 60.8±6.3% to 14.9±12.7% and tShbO2 decreased from 84.0±10.0% to 27.8±22.3%.

We then assessed the performance of a single point in time ShbO2 measurement as a diagnostic test for impending death, compared with invasive hemodynamic monitoring. Thresholds were established for each variable (online supplemental figure 1): the optimal threshold of eShbO2 was 40%, tShbO2 was 50%, MABP was 30 mm Hg, pulse pressure was 15 mm Hg, and heart rate was 220 bpm. We computed time to death from the first instance (based on a computed 1-minute average) of any of these findings to death and screened the sensitivity of each to detect death within 45 minutes. eShbO2<40% was 83.3% sensitive for death within 45 minutes, tShbO2<50% to 72.2% sensitive,

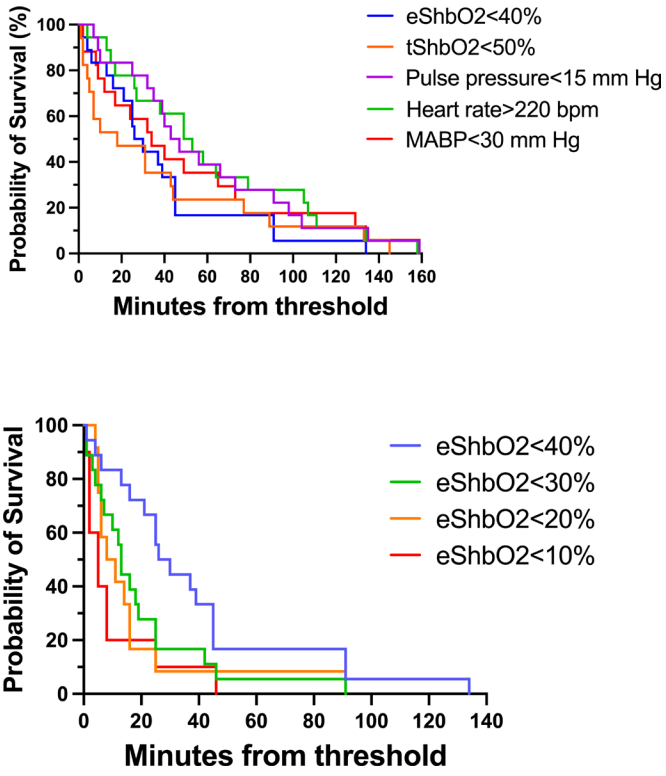

Figure 6 (A) After the first occurrence of eShbO2<40% (blue), 83% of the animals died within 45 minutes; in contrast 72% of animals died within the same window after tShbO2<50%. An optimized threshold of MABP<30 mm Hg, pulse pressure<15 mm Hg and heart rate>215 bpm, predicted death within 45 minutes in 59%, 50%, and 39% of animals, respectively, (p=0.004). (B) Down-scale thresholds of eShbO2 to predict death from reaching the cut-off. eShbO2, oxyhemoglobin saturation in the esophagus; MABP, mean arterial blood pressure; tShbO2, oxyhemoglobin saturation in the tongue.

MABP<30 mm Hg was 58.8% sensitive, pulse pressure<15 mm Hg was 50% sensitive, and heart rate>215 bpm was 39% sensitive (figure 6A).

Finally, having observed that eShbO2 was optimally sensitive in detecting impending death, we explored the predictive impact of lower thresholds. Overall, 83.3% of animals with single point measurements of eShbO2<40% died within 45 minutes, 83.3% of animals with single point eShbO2<30% died within 25 minutes, 83.3% of animals with single point eShbO2<20% died within 16 minutes, 80.0% of animals with single point eShbO2<10% died within 8 minutes of the measurement (figure 6B).

DISCUSSION

We have shown that central site monitoring of ShbO2 in the esophagus or tongue correlates well with invasively measured markers of perfusion. Specifically, we found that RRS-measured eShbO2 and tShbO2 responsively decrease (within minutes) during hemorrhagic shock and correlate well with SvO2 and lactate. We found that the diminution of ShbO2 from the liver was of much smaller magnitude than that in the esophagus and tongue, a phenomenon that has been previously reported in this vital organ.[22 23] Perhaps more importantly, we found that eShbO2 and tShbO2 outperform other commonly used metrics (including invasively measured vital signs) for the detection of near-term death in a model of hemorrhagic shock, with a progressively narrower prediction window with more extreme hypoxia. It is therefore possible that eShbO2 may be a useful tool to predict death and may perhaps represent a continuously measured physiologic target for resuscitative efforts.

Most oximeters, including pulse oximeters and NIRS devices, use absorbance spectroscopy of emitted light in the red and/or near-infrared range to quantify local ShbO2. Our approach used RRS within a small probe head form factor which allowed its use within the confines of the rat esophagus. This anatomic location is optically favorable because it minimizes ambient light interference, which improves spectroscopic performance.[24] It also represents a practical, easily accessible location to stabilize a probe during resuscitation. In addition to a small form factor, RRS-based oximetry affords a high degree of confidence in distinguishing oxyhemoglobin and deoxyhemoglobin isoforms due to the distinct peaks of the ν_4 band. An excellent correlation between oxyhemoglobin saturation as measured by co-oximetry and RRS has been previously demonstrated with the same instrument.[20]

The correlation of local ShbO2 with central SvO2s is likely affected by several factors. First, the RRS laser wavelength chosen permits a depth of penetration of only ~1 mm;[20] thus, the region sampled likely represented capillary blood at a tissue level rather than venous (or arterial) blood. Second, oxygen extraction and therefore local tissue oxygen tension (PO2) and regional SvO2 are known to differ based on local tissue factors, including local metabolic activity (different in each organ), temperature, and regional blood flow.[25 26] Thus, rather than representing error in measurement, the non-linear correlation between SvO2 and eShbO2 and tShbO2 are likely related to changes in the degree of sparing of each of these sites relative to other sites that contribute to the global state of venous ShbO2. Thus, in addition to being used as a reasonable surrogate of SvO2 (certainly outperforming the performance of NIRS to detect local hypoxia[14]), eShbO2 or tShbO2 may also represent easily accessible, responsive predictors of near-term mortality, allowing the sickest patients to be treated first in a multicasualty incident.

This technique opens the possibility of several future improvements. Incorporation of additional wavelengths may allow for the isolation of arterial blood that allows for esophageal detection of arterial ShbO2 (using a substraction algorithm similar to that used in photoplethysmography) and arteriovenous oxyhemoglobin difference. As have other absorbance techniques,[27] this technique may also allow for an estimate of hemoglobin concentration, adding dimension to resuscitation in the setting of blood loss. Further, the use of certain wavelengths of light may allow for the responsive monitoring of mitochondrial redox state,[20] a pure measure of the adequacy of oxygen delivery to its cellular target.

One potential limitation of this technology is the relatively small area-of-interest laser, which has a coverage diameter of 1.5 mm. This restricted field of view provides an understanding of local energetics, but heterogeneity with the surrounding tissue should be considered. Further, the effects of melanin, adipose tissue, and skin thickness on measurement accuracy will be important to explore in future work.

To fully understand the effectiveness of the laser, future human studies must explore its accuracy across a range of skin colors and adipose tissue volumes, as these variables may impact the signal. In future work, it will be important to investigate whether RRS is performant in detecting subclinical hemorrhage or represents an endpoint for resuscitation.

CONCLUSION

eShbO2 and tShbO2 correlate well with SvO2 and predict death with excellent sensitivity and specificity. eShbO2 may represent a new monitoring paradigm in far-field trauma environments.

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Contributors JGM and KS: data collection, analysis of data, article preparation, literature search, review of the article. PR: analysis of data and review of the article. YP: data collection, analysis of data, and review of the article. JK: study design, data collection, analysis of data, article preparation, literature search, review of the article, and response to reviewers.As guarantor, JK accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests JK and PR are inventors of a patent for this technology filed by Boston Children's Hospital.

Patient consent for publication Not applicable.

Ethics approval The protocol was approved by the Institutional Animal Care and Use Committee at our institution (protocol number 20-04-4158R).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request.

Author note Social media information (280 characters, 3 hashtags): Monitoring esophageal oxygen saturation predicts death in hemorrhagic shock and correlates well with mixed venous oxyhemoglobin saturation. #hemorrhagicshock #resuscitationmonitoring #bostonchildrens

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