Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans

Babs R. Soller, PhD; Kathy L. Ryan, PhD; Caroline A. Rickards, PhD; William H. Cooke, PhD; Ye Yang, PhD; Olusola O. Soyemi, PhD; Bruce A. Crookes, MD; Stephen O. Heard, MD; Victor A. Convertino, PhD

Objective: **To compare the responses of noninvasively measured tissue oxygen saturation (St_{O_2}) and calculated muscle oxygen tension (Pm_{O_2}) to standard hemodynamic variables for early detection of imminent hemodynamic instability during progressive central hypovolemia in humans.**

Design: **Prospective study.**

Setting: **Research laboratory.**

Subjects: **Sixteen healthy human volunteers.**

Interventions: **Progressive lower body negative pressure (LBNP) to onset of cardiovascular collapse.**

Measurements and Main Results: **Noninvasive measurements of blood pressures, heart rate, and stroke volume were obtained during progressive LBNP with simultaneous assessments of St_{O_2}, Pm_{O_2}, and muscle oxygen saturation (Sm_{O_2}). Forearm Sm_{O_2} and Pm_{O_2} were determined with a novel near infrared spectroscopic measurement device (UMMS) and compared with thenar St_{O_2} measured by a commercial device (HT). All values were normalized to the duration of LBNP exposure required for cardiovascular collapse in each subject (i.e., LBNP maximum). Stroke volume was significantly decreased at 25% of LBNP maximum, whereas blood pressure was a late indicator of imminent cardiovascular collapse. Pm_{O_2} (UMMS) was significantly decreased at 50% of maximum LBNP while Sm_{O_2} (UMMS) decreased at 75% of maximum LBNP. Thenar St_{O_2} (HT) showed no statistical change throughout the entire LBNP protocol.**

Conclusions: **Spectroscopic assessment of forearm muscle Po_2 and Sm_{O_2} provides noninvasive and continuous measures that are early indicators of impending cardiovascular collapse resulting from progressive reductions in central blood volume. (Crit Care Med 2008; 36:176–182)**

KEY WORDS: tissue oxygen saturation; near infrared spectroscopy; physiologic monitoring; hypovolemia

Early diagnosis of blood loss is a high priority for treatment of circulatory shock since hemorrhage is a leading cause of death in civilian and military trauma (1, 2). Unfortunately, compensatory mechanisms that buffer against changes in regulated variables, such as blood pressure and arterial oxygen saturation, make standard physiologic measurements poor indicators for early assessment of shock (3). Even standard examinations of mental status, pulse character, and pulse rate provide late information about the severity of blood loss. Subsequently, the appearance of hypotension and other signs and symptoms of shock does not mark the beginning of circulatory compromise but rather represents the beginning of decompensation when it may be too late to introduce effective life-saving interventions (4). The resulting challenge is that the early diagnosis of circulatory shock is difficult in the absence of measurements that represent physiologic responses associated with the underlying mechanisms of shock. It is therefore critical to identify and measure novel physiologic signals that will be altered during the earliest time period of blood volume loss before changes in blood pressure and arterial oxygen saturation.

In a human model of progressive hypovolemia, we have demonstrated that one of the most sensitive and specific measures of early reductions in central blood volume is cardiac output (5–7). A common denominator in the development of shock is inadequate oxygen delivery to the tissue, which is associated with reductions in systemic blood flow (cardiac output) and metabolic alterations (reduced pH or base excess). Therefore, a measurement that includes an indicator of the moment-to-moment changes in tissue dysoxia may be a better tool for the early detection of circulatory shock than current standard hemodynamic measurements.

Near infrared spectroscopy (NIRS) is a technology that has been employed to

From the Department of Anesthesiology, University of Massachusetts Medical School, Worcester, MA (BRS, YY, OOS, SOH); U.S. Army Institute of Surgical Research, Fort Sam Houston, TX (KLR, CAR, VAC); Department of Health and Kinesiology, University of Texas at San Antonio, San Antonio, TX (WHC); and the Division of Trauma, Burns and Critical Care, Department of Surgery, University of Vermont College of Medicine (BAC).

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Dr. Soller is a cofounder of Reflectance Medical Inc., which intends to commercialize the deep muscle oxygenation monitoring technology. Drs. Soller, Yang, and Soyemi are co-inventors of this technology and could gain financially from its commercial development, in agreement with the University of Massachusetts' policy on sharing of its license income with inventors. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: babs.soller@umassmed.edu

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noninvasively and continuously assess tissue oxygen saturation (Sto_2). A number of different spectroscopic systems have been developed and tested in animal models of hemorrhagic shock and resuscitation (8–11). One system, manufactured by Hutchinson Technologies (HT), is commercially available and was recently evaluated in a large series of trauma patients (12). In this study, the HT system could adequately identify patients in severe shock but could not distinguish patients in mild or moderate shock from patients who were not in shock. One of the limitations of this study was the very heterogeneous nature of the enrolled patient population in terms of the severity of shock. To further examine the sensitivity of the HT monitor to detect mild reductions in blood volume, we employed the system in a controlled laboratory environment where hemorrhage was simulated in healthy human volunteers using lower body negative pressure (LBNP). Increasing levels of negative pressure applied to the lower body induce central hypovolemia that elicits hemodynamic responses similar to those reported during acute hemorrhage, such as tachycardia and reductions in stroke volume (7). While the application of LBNP does not mimic all of the responses observed in traumatic hemorrhage (e.g., lack of tissue trauma and pain), the similar cardiovascular responses indicate its value as a surrogate for studying hemorrhage in conscious humans (7).

The HT monitor uses NIRS to determine an average Sto_2 across skin, fat, and muscle (13) using algorithms unique to that particular instrument. Recently, our group from the University of Massachusetts Medical School (UMMS) has developed a new method of determining oxygen saturation specifically from muscle (Smo_2) using a simple, inexpensive, continuous-wave spectroscopic instrument. The UMMS group has previously demonstrated that muscle oxygen tension (Pmo_2) can also be calculated from near infrared spectra collected from human muscle (14). To better understand the response of the HT Sto_2 monitor during early stages of central hypovolemia, we compared results using the HT instrument with those obtained from matched subjects measured with the UMMS instrument (Smo_2, Pmo_2) using an identical LBNP protocol.

MATERIALS AND METHODS

Subjects. A total of 32 healthy, nonsmoking, normotensive men and women were initially screened to participate as subjects for this investigation. Ten subjects were tested with the HT Sto_2 sensor (Hutchinson Technologies, Inspectra, Hutchinson, MN) (HT group). As a result of technical problems with data collection, the data of eight subjects were eventually used for analysis of the HT group. The remaining 22 subjects were tested at a later date using the UMMS Smo_2/Pmo_2 sensor because this system was not available at the time of the HT testing. One UMMS subject was eliminated from the analysis because of technical problems with data collection. Eight subjects were chosen from the UMMS cohort for comparison with the HT group based on statistical matching of gender, reduction in stroke volume (SV) during LBNP, and age. All procedures and risks associated with the study were explained to the subjects, and their voluntary written informed consent was obtained. A complete medical history and physical examination were also completed. Subjects refrained from exercise and abstained from caffeine and other autonomic stimulants, such as prescription or nonprescription drugs, for ≥24 hrs before the experimental protocol. All experimental procedures and protocols were reviewed and approved by the Institutional Review Board for the use of human subjects at the Brooke Army Medical Center at Fort Sam Houston, Texas.

Protocol. With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen. This model therefore provides conditions of controlled, experimentally induced hypovolemic hypotension, offering a unique method for investigating new monitoring devices, such as NIRS. Although absolute equivalence between the magnitudes of negative pressure applied and actual blood loss cannot be determined at this time, review of available human and animal data has revealed ranges of effective blood loss (or fluid displacement) caused by LBNP. Considering the magnitude of induced central hypovolemia, we have previously proposed that 10–20 mm Hg negative pressure produces hemodynamic responses equivalent to those resulting from blood loss of 400–550 mL, 20–40 mm Hg LBNP induces hemodynamic responses equivalent to blood loss of 550–1000 mL, and >40 mm Hg LBNP induces responses equivalent to blood loss of ≥1000 mL (7).

Each subject reported to the laboratory for a progressive LBNP protocol that was designed to test his or her tolerance to experimentally induced hypotensive hypovolemia. The subject was first instrumented with noninvasive devices for hemodynamic and tissue oxygenation measurements (described subsequently). The LBNP protocol consisted of a 5-min baseline period followed by 5 mins of chamber decompression to −15, −30, −45, and −60 mm Hg and additional increments of −10 mm Hg every 5 mins until either the onset of cardiovascular collapse or the completion of 5 mins at −100 mm Hg. Cardiovascular collapse was defined by one or a combination of the following criteria: a) a precipitous fall in systolic blood pressure (SBP) >15 mm Hg and/or a sudden bradycardia; b) progressive diminution of SBP <70 mm Hg; or c) voluntary subject termination due to discomfort from presyncopal symptoms, such as sweating, nausea, dizziness, or gray-out. At the onset of cardiovascular collapse, the chamber vacuum was released to ambient pressure to rapidly restore blood flow and blood pressure. To ensure subject safety, an Advanced Cardiac Life Support provider or physician was present in the laboratory building during all LBNP tests.

Hemodynamic Measurements. Continuous heart rate was measured from a standard electrocardiogram. Beat-by-beat SBP and diastolic blood pressure were measured noninvasively using an infrared finger photoplethysmograph (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The Finometer blood pressure cuff was placed on the middle finger of the left hand which, in turn, was laid at heart level. Excellent estimates of directly measured intra-arterial pressures during various physiologic maneuvers have been demonstrated with this device (15–18). Mean arterial pressure was calculated by dividing the sum of SBP and twice diastolic blood pressure by three.

Beat-to-beat SV was measured noninvasively using thoracic electrical bioimpedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC). The thoracic electrical bioimpedance technique is based on the resistance changes in the thorax to a low-intensity (4 mA), high-frequency (70 kHz) alternating current applied to the thorax by band electrodes placed at the root of the neck and at the xiphoid process at the midaxillary line. Ventricular SV was determined via the Kubicek equation (19): SV (in mL) = $\rho \times (L/Z_0)^2 \times$ LVET $\times$ (dZ/dt), where ρ (in ohms/cm) is the blood resistivity, a constant of 135 ohms/cm *in vivo*; L (in cm) is the mean distance between the inner band electrodes (front and back); Z_0 (in ohms) is the average thoracic background impedance; LVET (in seconds) is the left ventricular ejection time; and dZ/dt is the maximum height of the dZ/dt peak. Correlation coefficients of .70–.93 have been reported in SV measurements simultaneously made with thoracic electrical bioimpedance and thermodilution techniques (20).

Hemodynamic data were sampled at 500 Hz and recorded directly to data acquisition software (WINDAQ, Dataq Instruments, Akron, OH). Analysis of the data was subse-

quently accomplished using commercially available analysis software (WinCPRS, Absolute Aliens, Turku, Finland).

Noninvasive Measurement of Thenar Sto_2. Readings of Sto_2 were recorded using a commercially available NIRS InSpectra Tissue Spectrometer HT probe (Hutchinson Technology, Hutchinson, MN). The NIRS HT probe, with a nonsterile polyethylene cover (Optoshield, Hutchinson Technology), was placed on intact skin over the thenar eminence muscle of the left hand following the manufacturer's instructions. The instrument applies a mathematical algorithm to the tissue spectrum that accentuates the spectral contribution due to oxyhemoglobin and deoxyhemoglobin and removes unwanted baseline effects that are related to tissue scattering. An empirical model for calculating Sto_2 is generated by correlating a variable that is derived from the modified spectrum to *in vitro* hemoglobin at known oxygen saturation levels. Tissue measurements are made at four wavelengths, resulting in a relatively simple instrument configuration. As NIRS HT measurements were taken without regard to systole or diastole, and as only 20% of blood volume is intraarterial, spectroscopic measurements were primarily indicative of the venous oxyhemoglobin concentration.

Noninvasive Measurement of Smo_2 and Pmo_2. Smo_2 and Pmo_2 were determined noninvasively using a monitor developed jointly by personnel from the Anesthesiology Department of University of Massachusetts Medical School (Worcester, MA) and Luxtec Corporation (West Boylston, MA). The sensor was placed over the flexor digitorum profundus muscle in the right forearm. Light is collected with two sensors contained in the same housing. One sensor collects light that illuminates only the skin and fat layer. The second sensor collects light that illuminates the skin, fat, and muscle layer. Mathematical processing removes the light reflected from the skin and fat, leaving only the absorption spectrum of muscle (21). Removal of spectral interference from skin pigmentation and fat is critical to determining absolute chemical concentrations from muscle spectra. The corrected absorption spectrum is analyzed with a Taylor series expansion attenuation model (22) to calculate oxygen saturation from deep muscle, Smo_2, and is described briefly in the Appendix and in more detail by Yang et al (22a). Pmo_2 is calculated from Smo_2, which are related through the hemoglobin oxygen dissociation curve, also described in the Appendix.

The light output of the system is calibrated with three NIST-traceable reflectance standards (Avian Technologies, LLC, Wilmington, OH) with nominal values of 2%, 50%, and 99%, before use on each subject to allow for determination of the absolute values of Smo_2 and Pmo_2 (23).

Data and Statistical Analysis. Values for NIRS measurements and hemodynamic variables are presented as the mean ± 1 SEM. Data from all the noninvasive sensors were collected continuously. For each LBNP level, the last 3 mins of data for each measured variable were averaged to provide a single value for the LBNP level.

Subjects completed the study at different LBNP levels based on their individual tolerance to this hypovolemic stress. Since there was significant subject-to-subject variability in both hemodynamic and NIRS-determined variables, percent changes from baseline values were determined. To allow comparisons between the two groups of subjects, responses to LBNP were reapportioned to equal fractions between 0% maximum LBNP (baseline) and 100% maximum LBNP, the level where cardiovascular collapse occurred and the LBNP protocol was stopped. This approach allowed all subjects' data to be included at the LBNP level that elicited their cardiovascular collapse.

Absolute values of measured and calculated variables were analyzed using a linear mixed model analysis of variance with a first order autoregressive covariance structure to determine whether there was a significant variation during progressive LBNP. This type of analysis takes into account the repeated nature of the experimental design. If statistical differences were found, Bonferroni-corrected comparisons with baseline measurements were performed to determine the first level of LBNP that could be distinguished statistically from baseline ($p < .05$). Statistical analysis was performed using SPSS (version 14.0, SPSS, Chicago, IL).

RESULTS

NIRS data were collected on eight subjects using the HT Sto_2 device on the eminentia thenaris (thenar eminence) muscle and eight matched subjects using the UMMS Smo_2/Pmo_2 device on the flexor digitorum profundus (forearm) muscle. The subject demographics for each group are shown in Table 1. There were no statistical differences between the subject groups, except that the UMMS group had a higher percentage of non-Caucasian subjects. All non-Caucasian subjects in this study were Hispanic. The progressive reductions in SV during LBNP for both groups were statistically indistinguishable ($p = .15$) (Fig. 1).

Absolute values for HT Sto_2, UMMS Smo_2, and UMMS Pmo_2 during progressive reduction of negative pressure and stroke volume are presented in Table 2. Baseline HT Sto_2 was 83.1% ± 3.2% and did not change significantly throughout the entire LBNP protocol (Fig. 2). UMMS Smo_2 decreased proportionately from baseline (66.2% ± 2.0%) with decreasing LBNP and SV (amalgamated $R^2 = .92$), becoming statistically different ($p < .05$) from baseline at 75% of maximum LBNP (Fig. 2). UMMS Pmo_2 was statistically different ($p < .05$) from baseline at 50% of maximum LBNP and was also highly cor-

Table 1. Subject demographics (mean ± SE)

Study Group	Gender, % Male	Age, yrs	Ethnicity, % Non-Caucasian[a]	Height, cm	Weight, kg
HT	62.5	30 ± 1	12.5	171 ± 4	77 ± 6
UMMS	62.5	29 ± 1	37.5	178 ± 5	83 ± 6

HT, Hutchinson Technology monitor; UMMS, University of Massachusetts Medical School monitor.
[a]All non-white subjects were Hispanic.

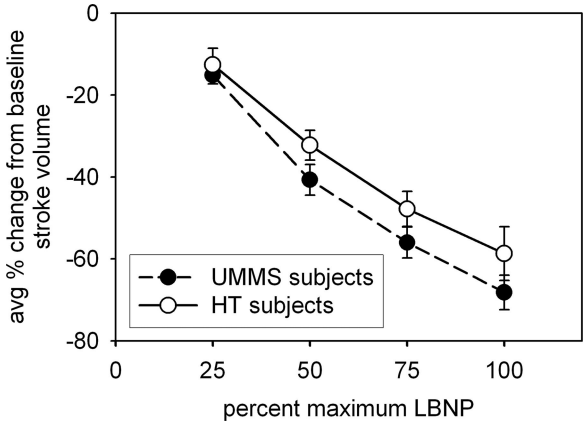

Figure 1. Reduction in stroke volume (percent change from baseline) during progressive lower body negative pressure (*LBNP*). Changes in stroke volume were not significantly different between the subjects using the Hutchinson Technologies (*HT*) and University of Massachusetts Medical School (*UMMS*) devices.

Table 2. Absolute values of tissue oxygen saturation (St_{O_2}), muscle oxygen saturation (Sm_{O_2}), and muscle oxygen tension (Pm_{O_2}) for each normalized level of progressive lower body negative pressure

	HT St_{O_2}, %	UMMS Sm_{O_2}, %	UMMS Pm_{O_2}, mm Hg
Baseline	83.1 ± 3.2	66.2 ± 2.0	34.8 ± 1.1
25% max	81.9 ± 2.9	63.0 ± 2.4	33.1 ± 1.3
50% max	83.5 ± 3.0	59.8 ± 2.3	31.4 ± 1.1[a]
75% max	84.6 ± 2.5	55.4 ± 2.5[a]	29.4 ± 1.1[a]
100% (max)	83.1 ± 2.6	50.3 ± 4.7[a]	27.2 ± 2.0[a]

HT, Hutchinson Technology monitor; UMMS, University of Massachusetts Medical School monitor. [a]$p < .05$ compared with baseline. n = 8; values are mean ± SE.

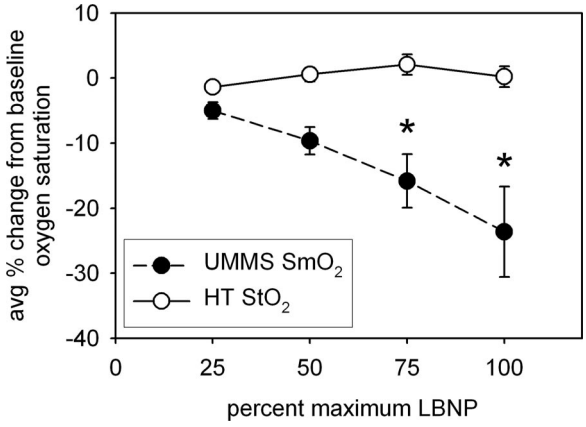

Figure 2. Percent change from baseline for Hutchinson Technologies (*HT*) tissue oxygen saturation (St_{O_2}) (*open circles*) and University of Massachusetts Medical School (*UMMS*) muscle oxygen saturation (Sm_{O_2}) (*filled circles*) during progressive lower body negative pressure (*LBNP*). *$p < .05$ compared with baseline.

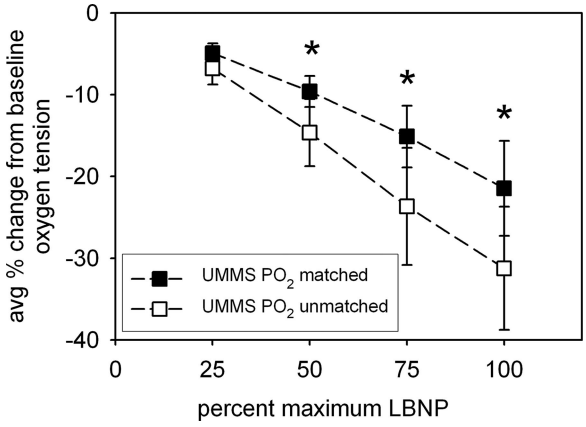

Figure 3. Percent change from baseline for University of Massachusetts Medical School (*UMMS*) muscle Po_2 for matched subjects (*filled squares*, n = 8), and UMMS muscle Po_2 for unmatched subjects (*open squares*, n = 13) during progressive lower body negative pressure (*LBNP*). *$p < .05$ compared with baseline. Muscle Po_2 for both matched and unmatched UMMS subjects is significantly different at LBNP levels ≥50% of maximum LBNP.

related with decreases in stroke volume (amalgamated $R^2 = .94$) (Fig. 3). For comparison, Pm_{O_2} responses for the remaining, unmatched UMMS cohort (n = 13) are also shown in Figure 3 and were also statistically different from baseline at 50% of maximum LBNP.

DISCUSSION

The major finding of this study is that the HT St_{O_2} measurement at the eminentia thenaris is not sensitive to early and significant reductions in central blood volume. In contrast, the UMMS determinations of Sm_{O_2} and Pm_{O_2} at the flexor digitorum profundus were highly correlated with SV and significantly decreased before cardiovascular collapse. These measurements proved to be sensitive indicators of the reduction in central blood volume as demonstrated by early and large reductions compared with the HT thenar St_{O_2} measurement.

One of the earliest compensatory mechanisms during hemorrhage is sympathetically mediated reflex vasoconstriction. During hemorrhage, vasoconstriction is heterogeneous throughout the body, predominantly affecting skeletal muscle and splanchnic circulations to redirect blood flow to the heart and brain (24–26). We have previously shown that our model of progressive LBNP produces a steady increase in total peripheral resistance (27), suggesting that this model mimics the peripheral vasoconstrictor response to hemorrhage in healthy volunteers. In this study we demonstrated that UMMS Sm_{O_2} and Pm_{O_2} are strongly correlated with SV, but HT St_{O_2} is not. We suggest that LBNP-induced decreases in SV are compensated by vasoconstriction, proportionately reducing both free oxygen (Pm_{O_2}) and oxygen bound to hemoglobin (Sm_{O_2}) in the capillaries.

One of the limitations of this study is that Sm_{O_2} and St_{O_2} were not measured simultaneously on the same subject. However, the two groups of subjects were matched on gender, age, and SV changes, and there was no difference in weight and height between the groups. Figure 3 compares Pm_{O_2} in the UMMS matched subjects with Pm_{O_2} in the unmatched subjects. Both groups of subjects showed significant reductions in Pm_{O_2} with decreasing SV. The unmatched group of subjects happened to tolerate LBNP better than the matched subjects, however, resulting in a larger percentage decrease in Pm_{O_2}.

It is possible that vasoconstriction in the thenar muscle is different from that in the profundus muscle, resulting in differing performance of oxygen saturation measurements between the HT and UMMS sensors. However, the UMMS system has previously been used on the hypothenar muscle and was shown to be highly sensitive to changes in hypoperfusion (Pm_{O_2}) during cardiopulmonary bypass (14). The thenar HT sensor has detected significant reductions in St_{O_2} during severe shock in trauma patients (12, 28), so it is possible that it may provide an earlier indication of shock if it were used on the flexor digitorum muscle like the UMMS sensor. However, the studied, commer-

cially available, HT sensor is not designed to collect light from deep within the muscle. Depth of penetration of near infrared light is determined primarily by the separation of the light source and the light detector and the thickness of the fat layer (29, 30). Because the source-detector spacing for the HT sensor is approximately half that of the UMMS sensor, the HT sensor is likely too small to collect light from the muscle through fat on the forearm of most patients.

The major difference in the oxygen saturation results obtained between the two sensors is most likely related to both the difference in the design of the sensor and the algorithms used for calculating oxygen saturation from NIR spectra. The HT St_{O_2} measurement reflects an average of tissue oxygen saturation in the skin, fat, and muscle, and no corrections are made for subject variation in skin color and fat thickness. It is possible that spectral contributions from skin and fat obscure St_{O_2} changes and/or that vasoconstriction in these tissue layers is different from that in the muscle. In contrast, the UMMS Sm_{O_2} sensor employs correction algorithms that remove subject-specific spectral variation from skin and fat (21), producing spectra and oxygen saturation measurements specifically from the deep muscle. This difference between St_{O_2} and Sm_{O_2} measurements with LBNP provides new evidence to support the use of deep muscle oxygen saturation as a more sensitive indicator to track the severity of blood loss in trauma patients.

Hutchinson Technologies has recently published information on the algorithms used to calculate St_{O_2} (13). Their system is calibrated to an *in vitro* flowing blood system; they do not account for tissue oxygen extraction in their calibration methodology. This approach likely results in the surprisingly high baseline St_{O_2} value of 83% observed in the present study and 87% reported in the study of 700 control subjects (12). In contrast, other investigators who have used direct, rather than empirical methods to calculate tissue oxygen saturation from near infrared spectra have arrived at baseline values in humans near 60% (31, 32). The latter value is more consistent with the oxygen saturation values expected for capillary blood (33) and was approximated by the baseline Sm_{O_2} value of 66 ± 2% obtained with the UMMS device. Near infrared light is so strongly absorbed by large blood vessels that there is no detectable light returning from these vessels. Therefore, absorbance spectra can only be obtained from the capillaries, resulting in a measurement of oxygen saturation from these small vessels. Since the HT algorithms do not account for oxygen consumed by the tissue, the system may not be sensitive to early changes in capillary oxygen saturation, which primarily reflects an increase in oxygen extraction by cells near the capillaries.

The UMMS NIRS system also measures absorbance spectra from the small blood vessels in the tissue, but since the portion of the absorbance that results from skin pigment and fat is removed, the spectra describe capillary absorbance from the muscle alone. A Taylor series expansion attenuation method (22) is used to directly calculate Sm_{O_2} in a manner that compensates for changing blood volume in the tissue during LBNP. Pm_{O_2} is calculated directly from the determination of Sm_{O_2} using the hemoglobin oxygen dissociation curve (Appendix). Previously we have used an empirical method to calculate Pm_{O_2} for individual patients and showed that it was in good agreement with interstitial fluid P_{O_2} measured with an invasive sensor placed in the muscle (14). This is the first report of a direct method for calculating tissue or capillary P_{O_2} from NIR spectra.

Clinical Implications. In clinical practice, multiple variables are used to identify the presence of shock: Blood pressure, arterial lactate, serum base deficit, and mixed venous oxygen saturation are the most common examples. All, however, suffer from significant deficiencies, especially when applied to field (i.e., triage or military) conditions. Blood pressure, while automated, is unreliable and may be a poor indicator in the young and those patients who are taking β-blockers. Both arterial lactate and serum base deficit are invasive and require laboratory testing. Depression of these two variables may also occur in the setting of other systemic pathology (i.e., ethylene glycol poisoning or alcohol intoxication). Last, while helpful, mixed venous oxygen saturation requires the placement of a pulmonary artery flotation catheter and subsequent central venous pressure monitoring and reflects a global state of oxygen consumption. The ideal device for the early identification of shock would be noninvasive and continuous and could be used easily in a variety of conditions.

A number of recent investigations have evaluated the utility of noninvasive or minimally invasive monitoring during hemorrhagic or traumatic shock. Sublingual capnometry has been shown to be a good predictor of outcome in hypotensive trauma patients and is equivalent to the predictive power of both arterial lactate and base deficit (34). Near infrared spectroscopy using the HT sensor is useful to identify the severity of shock in trauma patients (12) and predicts the development of organ dysfunction or death in trauma patients who have suffered severe torso trauma (28). The disadvantage of sublingual capnometry is that measurements are not continuous, the disposable sensors are expensive, and the monitor is no longer clinically available. Although LBNP does not mimic all of the features of hemorrhagic shock, our data suggest that the UMMS monitor will discern hypoperfusion earlier than the HT monitor in patients with hemorrhagic or traumatic shock. Furthermore, prediction of outcome of these patients should be at least as accurate as the HT monitor although prospective clinical trials will be needed to confirm this hypothesis.

CONCLUSIONS

We have compared two different NIRS systems in a controlled setting of progressive central hypovolemia. We found that the HT thenar St_{O_2} sensor was not sensitive to decreases in SV and peripheral perfusion induced by LBNP. In contrast, the UMMS system calculates Sm_{O_2} and Pm_{O_2}, which are both highly correlated with the reduction in SV with progressive LBNP and are early indicators of central hypovolemia. Changes in peripheral muscle NIR spectra measured by the UMMS system during progressive hypovolemia reflect a decrease in tissue blood volume and an increase in oxygen extraction.

Near infrared spectroscopy (NIS) is a general term for the collection of reflectance spectra from tissue. The instrumentation used to collect and process spectra is highly dependent on the manufacturer, which strongly influences the subsequent results. Algorithms used to calculate oxygen saturation also vary significantly and affect application of the technique. When properly implemented, this new technology has the promise of providing the intensive care unit with a noninvasive monitor that will be a significantly earlier indicator of hemorrhage-induced blood loss. Early notification and subsequent treatment are expected to re-

duce the incidence of shock and the associated complications.

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APPENDIX

Muscle oxygen saturation (Smo_2) is defined by Equation *1*:

$$SmO_2 = \frac{C_{(HbO_2+MbO_2)}}{C_{(HbO_2+MbO_2)} + C_{(Hb+Mb)}} \quad [1]$$

where $C_{HbO_2+MbO_2}$ is the oxygenated heme concentration, C_{Hb+Mb} is the deoxygenated heme concentration, Hb is hemoglobin, and Mb is myoglobin. Equation *1* is true for any near infrared spectroscopic system when considering light collected from the muscle, even if convoluted with light reflected from skin and fat.

In the UMMS system, attenuation of light by the subject's tissue, A(λ) at wavelength λ is defined in Equation *2*:

$$A(\lambda) \approx \ln\left(\frac{I_{ref}(\lambda)}{I(\lambda)}\right) \qquad [2]$$

where $I_{ref}(\lambda)$ is the measured diffuse reflectance intensity from a 99% diffuse reflectance reference standard (SRT-99-050, Labsphere, North Sutton, NH) at wavelength λ, and I(λ) is the measured diffuse reflectance intensity from the subject at wavelength λ. Incident light attenuation by tissue is caused by both absorption and scattering events. Light is absorbed by hemoglobin in the small blood vessels and myoglobin in the cells as well as both intravascular and extravascular water and melanin pigment in the skin. Light is scattered away from physical structures in the tissue such as blood vessels and muscle fibers as well as fat, which lies over the muscle.

To calculate muscle oxygen saturation (Smo_2), we first remove the components of spectrum that result from skin pigment absorption and fat scattering by using a two-source, single detector fiberoptic probe. One source is placed close (2.5 mm) to the fiber optic bundle, which transmits light to the spectrometer. This captures light from only the skin and fat layers. The second source, farther from the detector bundle (30 mm), captures light from the skin, fat, and muscle layers. Light collected from the short distance pair is orthogonalized with the light from the long distance pair to generate a spectrum that describes attenuation from only the muscle layer. The details of this method are described in a prior publication (21).

The resulting muscle attenuation spectrum can be approximated with the Taylor series expansion model described by Stratonnikov and Loschenov (22):

$$A(\lambda) = (c_0 + c_1\lambda) + \langle L \rangle \left\{ c_{Hb+Mb}\varepsilon_{Hb}(\lambda) + c_{HbO_2+MbO_2}\varepsilon_{HbO_2}(\lambda) + c_{wat}\varepsilon_{wat}(\lambda) \right\} \ln(10) \qquad [3]$$

where c_0 and c_1 are constants, λ is the wavelength, <L> is the average photon path length through the tissue, and c_{Hb+Mb}, $c_{HbO_2+MbO_2}$, and c_{wat} are concentrations of the light absorbers deoxygenated and oxygenated hemoglobin and myoglobin and water, respectively. ε_{Hb}, ε_{HbO_2} and ε_{Wat} are known extinction coefficients of Hb, HbO_2, and water, respectively. Since hemoglobin and myoglobin have nearly identical extinction coefficients, only the extinction coefficients of hemoglobin are required. The function $(c_0 + c_1\lambda)$ describes the portion of the spectrum resulting from light that is scattered, where the remaining portion of the relationship describes light absorption from the chromophores hemoglobin, myoglobin, and water.

c_0, c_1 as well as c_{Hb+Mb}, $c_{HbO_2+MbO_2}$, c_{wat}, and <L> are obtained by nonlinear least square fitting of the measured attenuation spectrum to the modeled spectrum described by Equation *3*. Once c_{Hb+Mb} and $c_{HbO_2+MbO_2}$ are obtained, Smo_2 is calculated using equation *1*.

One of the limitations of tissue near infrared spectroscopy is the inability to separate the deoxygenation of myoglobin from hemoglobin, hence, the general name muscle or tissue oxygen saturation.

The partial pressure of oxygen in the muscle (Pmo_2) can be calculated from Smo_2 determined with this method. Severinghaus described (35) the relationship between oxygen saturation (So_2) and tension (Po_2) under standard physiological conditions:

$$PO_2 = \exp(0.385 \cdot \ln(SO_2^{-1} - 1)^{-1} + 3.32 - (72 \cdot SO_2)^{-1} - (SO_2^6)/6) \qquad [4]$$

For our application, Smo_2 is calculated from skin pigment and fat corrected spectra. Then Pmo_2 is calculated using Equation *4*. Again, Pmo_2 represents an average of hemoglobin and myoglobin oxygen tension, although in this experimental model we suggest that myoglobin saturation is relatively unchanged because the partial pressure of oxygen is well above the P_{50} for myoglobin. We also recognize that calculation of Pmo_2 should be compensated for variation in pH and Pco_2. In a related study we determined that changes in pH were minimal in this LBNP model, with significant decreases in pH occurring late in the progression. For this reason, calculation of Pmo_2 during early hypovolemia will be unaffected by this omission.

The calculations were implemented in software written in Matlab (version 7.0.4.365 (R14) Service Pack 2, Mathworks, Natick, MA). The fitting algorithm was implemented with the "lsqcurvefit" function in the Matlab optimization toolbox version 3.0.2.