Evidence for misleading decision support in characterizing differences in tolerance to reduced central blood volume using measurements of tissue oxygenation

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BACKGROUND: The physiological response to hemorrhage includes vasoconstriction in an effort to shunt blood to the heart and brain. Hemorrhaging patients can be classified as "good" compensators who demonstrate high tolerance (HT) or "poor" compensators who manifest low tolerance (LT) to central hypovolemia. Compensatory vasoconstriction is manifested by lower tissue oxygen saturation (StO_2), which has propelled this measure as a possible early marker of shock. The compensatory reserve measurement (CRM) has also shown promise as an early indicator of decompensation.
METHODS: Fifty-one healthy volunteers (37% LT) were subjected to progressive lower body negative pressure (LBNP) as a model of controlled hemorrhage designed to induce an onset of decompensation. During LBNP, CRM was determined by arterial waveform feature analysis. StO_2, muscle pH, and muscle H^+ concentration were calculated from spectrum using near-infrared spectroscopy (NIRS) on the forearm.
RESULTS: These values were statistically indistinguishable between HT and LT participants at baseline ($p \geq 0.25$). HT participants exhibited lower ($p = 0.01$) StO_2 at decompensation compared to LT participants.
CONCLUSIONS: Lower StO_2 measured in patients during low flow states associated with significant hemorrhage does not necessarily translate to a more compromised physiological state, but may reflect a greater resistance to the onset of shock. Only the CRM was able to distinguish between HT and LT participants early in the course of hemorrhage, supported by a significantly greater ROC AUC (0.90) compared with STO_2 (0.68). These results support the notion that measures of StO_2 could be misleading for triage and resuscitation decision support.

In an effort to maintain adequate perfusion to vital organs during conditions of reduced central blood volume such as hemorrhage, a sympathetically-mediated compensatory vasoconstriction occurs. Using lower body negative pressure (LBNP) as an experimentally-controlled model of progressive central hypovolemia similar to hemorrhage,[1–4] it has previously been demonstrated that compensatory vasoconstriction is manifested by lower tissue oxygen saturation (StO_2) with eventual reduction in muscle pH (pH_m).[4,5] Since shock is described as a condition of inadequate tissue perfusion and oxygenation,[6] interest has been expressed in obtaining real-time noninvasive measurements of StO_2 and metrics of anaerobic metabolism as potential early markers that might be used for triage and resuscitation decision support.[7,8]

In addition to measures of StO_2, a measurement of the capacity to compensate, known as the compensatory

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reserve measurement (CRM),[9–13] has been introduced which conceptually represents the sum total of all compensatory mechanisms (e.g., tachycardia, vasoconstriction, tachypnea) that together contribute to "protect" against inadequate tissue perfusion during blood loss and other low circulating blood volume states.[10,12] The CRM represents a relative capacity for compensation and is based on measurements of changes in multiple features of each arterial waveform obtained from a photoplethysmogram (PPG).[10,11,14] Measurement of the compensatory reserve has proven to be a more sensitive and specific indicator of physiological state than other physiological indicators of reduced central blood volume per se.[7,11,15–17] That is, 100%, 60%, 30%, and 0% compensatory reserve represent the equivalent physiological state across individuals independent of the degree of central hypovolemia.

Sensitivity and specificity are characteristics that define the usefulness of a metric as indicators of patient status. In addition to the ability to respond to a change in physiological condition, the sensitivity of these metrics is influenced by their magnitude and rate of change. On the other hand, specificity of CRM and StO_2 can be influenced by the existence of significant inter-individual variability in tolerance to reduction in central blood volume. There is evidence supporting the notion that healthy humans have either a high or low tolerance (LT) to hypovolemia based on their physiological capacity to compensate in conditions of low blood flow states.[1,10–12,15,18] Data obtained from progressive reduction in central blood volume of both humans[1,12] and non-human primates[2,3,19] have demonstrated that approximately one in every three individuals can be classified as "poor" compensators who display relatively LT to experimentally-induced central hypovolemia. An individual's tolerance to central hypovolemia is characterized by the depletion of one's compensatory reserve, or the sum total of all compensatory mechanisms that contribute to the capacity to maintain tissue perfusion as a result of a blood volume deficit.[7,10,12,16,17,20] In this regard, tolerance time to decompensation (i.e., presyncope) can be defined as a CRM of 0%. If the impact of both rate of change and inter-individual variability on tolerance to reduced central blood volume are not accurately defined by CRM and/or StO_2, triage decision could be erroneously misleading and compromise patient outcomes.

We previously demonstrated that the CRM can distinguish individuals with high tolerance (HT) to central hypovolemia from those with LT.[10,15] We have also demonstrated that StO_2 is a sensitive metric for the early stages of progressive reductions in central blood volume.[4,5] However, the capability to distinguish individuals with HT from those with LT with measures of responses in StO_2 has not been reported. In the present study, we compare for the first time measurements of StO_2 in "poor" compensators who have LT to "good" compensators who have HT during experimentally-induced progressive reductions in central hypovolemia using CRM values of 60%, 30%, and 0% (i.e., hemodynamic decompensation). We used measures of compensatory reserve as a physiologically equivalent marker to differentiate tolerance to hypovolemia and associated changes in StO_2 in "good" (HT) and "poor" (LT) compensators. Our objective was to test the hypothesis that LT would be associated with earlier maximal reductions in StO_2 compared to HT despite similar StO_2 values at the time of hemodynamic decompensation. In other words, we expected LT participants to display equal StO_2 compared to HT participants at all percentages of CRM.

MATERIALS AND METHODS

Experiment participants

Fifty-one healthy, non-smoking, normotensive men and women volunteered as participants for this investigation after all procedures and potential risks were explained and voluntary written informed consent was obtained. Prior to experimentation, a complete medical history and physical examination was performed on each participant to assure that they were healthy. Participants were instructed to maintain their normal sleep pattern, refrain from physical exercise, and abstain from consuming alcoholic substances, nicotine in any form, caffeine products, herbal medications, and other autonomic stimulants such as prescription or non-prescription drugs (antihypertensive drugs, cold medication, allergy medication, dietary supplements) for at least 24 hours prior to the experimental protocol. Other exclusions included obesity (BMI > 30), history of fainting spells, family history of abnormal blood clotting, known or suspected abdominal hernia, history of severe allergic reactions, and breathing illnesses (asthma, etc.). Additionally, female participants with a positive urine pregnancy test before the experiment were excluded from testing. Based on measurements obtained from a subset of our subjects, "normal" hydration status without anemia was verified with hematocrit and hemoglobin levels within normal clinical ranges.[5] All experimental procedures, protocols, and informed consent documents were reviewed and approved by the U.S. Army Medical Research and Development Command Institutional Review Board for the use of human participants.

Each participant underwent an experimental protocol designed to measure tolerance to hypovolemia by applying progressive LBNP. Our previous work indicated that −30, −60, and − 90 mmHg LBNP is equivalent to approximately 450; 1,000; and 1,600 mL blood loss in a human with 70 kg body weight.[2] The experimental LBNP protocol consisted of a 5-minute baseline period followed by 5 minutes of chamber pressures set at −15, −30, −45, −60, −70, −80, −90, and − 100 mmHg, continuing until either the onset of clinical decompensation or the completion of 5 minutes at −100 mmHg. Decompensation was defined by a fall in systolic blood pressure (SBP) to <80 mmHg and/or the onset of pre-syncopal symptoms such as bradycardia, sweating, nausea, dizziness, tunnel vision, or gray-out (loss of color

vision). At the onset of clinical decompensation, the chamber vacuum was immediately released to ambient pressure, resulting in rapid restoration of blood volume to the central circulation.

Participants were categorized as those with HT or LT using statistical analysis of Kaplan–Meier "survival" curves.[1] By definition, LT participants experienced pre-syncopal symptoms and test termination prior to completing LBNP of −60 mmHg, while HT participants tolerated LBNP > −60 mmHg.

Hemodynamic measurements

Continuous heart rate (HR) was measured from a standard lead-II electrocardiogram (ECG). Beat-by-beat systolic (SBP) and diastolic (DBP) blood pressures were measured noninvasively using an infrared finger photoplethysmograph (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation). The Finometer® blood pressure cuff was placed on the middle finger of the left hand which was laid at heart level. Excellent estimates of directly measured intra-arterial pressures during various physiological maneuvers have been demonstrated with this device.[21] Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice DBP by three. Analysis of data was accomplished using commercially-available software (WinCPRS, Absolute Aliens).

Noninvasive determination of tissue StO_2 and pH_m

Spectra were collected using a Near-Infrared Spectroscopy (NIRS) system designed with mathematical preprocessing techniques to correct for variation in skin pigmentation, fat, and muscle optical properties as described previously.[4] The NIRS sensor was placed on the skin over the forearm muscle. The sensor contained two fiber optic bundles for illumination and one bundle for detection. The source-detector distances of the two illumination bundles were chosen such that light detected from illumination arose only from the skin and fat layers, while light detected from the on-axis bundle arose from the skin, fat and muscle layers.

The calculated muscle absorbance spectrum was fitted to a Taylor expansion attenuation model based upon Beer's Law modified for a scattering component.[22–24] The concentrations of oxygenated (HbO_2) and deoxygenated (Hb) hemoglobin were estimated on a subset of 36 participants (25 HT, 11 LT) from this fit, such that total hemoglobin (HbT), or the amount of hemoglobin in the volume of tissue sampled by the NIRS sensor, can be defined as $HbT = HbO_2 + Hb$. Spectra were also interpreted by a previously determined model which calculated pH_m from each spectrum.[4] Values of pH_m were converted to hydrogen ion concentration ($[H^+]$) for analysis. The spectral system's light output was assessed using 3 NIST-traceable reflectance standards (Avian Technologies, LLC) prior to use on each participant to allow for determination of the absolute values of StO_2.[25]

Measurement of compensatory reserve (CRM)

As detailed previously,[10,26] state-of-the-art feature extraction and machine-learning techniques were used to collectively process the arterial waveforms obtained from the Finometer blood pressure cuff during LBNP experiments. The CRM algorithm estimates the remaining proportion of physiological reserve available to compensate for changes in effective circulating blood volume by comparing waveforms over a 30-heartbeat window to >650,000 reference waveforms obtained from >200 humans (43% women) with age ranging from 18 to 55 years of age with an effort to meet proportional inclusion of race and ethnicity during progressive central hypovolemia induced by the LBNP protocol.[15] As such, robust CRM estimates required assessment of the entire waveform and comparison to the reference waveforms. The estimated CRM value corresponds to the CRM value of the most similar reference waveform in the training set.

The CRM is normalized on a scale of 100% to 0%, where "100%" reflects the maximum capacity of physiological mechanisms (e.g., baroreflexes, respiration) to compensate for reduced central blood volume and "0%" implies imminent cardiovascular instability and decompensation. Values between "100" and "0" indicate the proportion of compensatory reserve remaining. The time to hemodynamic decompensation can be defined as tolerance, where hemodynamic decompensation is defined by 0% CRM. CRM data were analyzed at equal compensatory reserve, such that 100%, 60%, 30%, and 0% CRM represent the equivalent physiological state across individuals. The 60% and 30% points were based on results of univariate logistical regression analysis of CRM values prospectively assessed in 300 adult trauma patients with hemorrhagic injury that revealed an optimal threshold cut point of 33% (Receiver Operating Characteristic Area Under the Curve [ROCAUC = 0.78] and an optimal upper threshold cut point at a CRM of 60% [ROCAUC = 0.67]).[27]

Data analysis

Values are presented as the mean ± 95% confidence interval (95%CI), such that the mean value lies in the middle of the full 95% CI, unless otherwise stated. Data from all the noninvasive sensors were collected continuously. For each LBNP level, the last 3 minutes of data for each measured parameter were averaged to provide a single value for that level. The total time to pre-syncope was also recorded. Differences between HT and LT participants were analyzed using two-sample, unpaired Student's *t-test*s in Matlab (Mathworks, Inc.). Two-sample F-tests were conducted to check for equal variance for all variables and the *t-tests* on those variables found to be unequal were adjusted using the Behrens-Fisher problem. Receiver operating characteristic (ROC) analysis was conducted by performing GEE repeated measures logistic regression on the dichotomous outcome of decompensation, which was measured at each level of LBNP. The ROCAUC with sensitivity and specificity

TABLE 1. Demographics (mean ± SD)

	High Tolerant (HT) N = 34	Low Tolerant (LT) N = 17	p-value
Percent female	41.2%	76.5%	0.02
Age (yrs)	28 ± 3	27 ± 3	0.67
Height (cm)	173 ± 4	168 ± 5	0.11
Weight (kg)	72 ± 5	67 ± 8	0.27
BMI	24 ± 1	24 ± 2	0.76

at the optimal threshold cut-off values was calculated to assess the ability of each independent variable to predict decompensation. ROC curves were compared using the chi-square test. The probability that any differences between measured parameters did not exist by greater than chance were expressed as exact p values.

TABLE 2. Measurements at baseline and presyncope, difference between baseline and presyncope for total hemoglobin (HbT) tissue oxygen saturation (StO_2), muscle pH (pH_m), hydrogen ion concentration ([H+]), and compensatory reserve measurement (CRM). HbT measurements were made on a subset of 36 participants (25 HT, 11 LT). All measurements are compared between participants with high (HT) and low (LT) tolerance. Values are expressed as mean ± 95% CI

	High tolerant (HT) N = 34	Low tolerant (LT) N = 17	p-value
Baseline			
Mean arterial pressure (mmHg)	94 ± 3	91 ± 2	0.28
Heart rate (beats/min)	62 ± 4	69 ± 4	0.03
Total hemoglobin (HbT)	96.4 ± 7.0	100.8 ± 8.4	0.45
Tissue oxygen saturation (StO_2, %)	62.8 ± 3.1	65.6 ± 2.2	0.25
Muscle pH (pH_m)	7.4 ± 0.0	7.4 ± 0.0	0.40
Hydrogen ion concentration ([H^+], nmol/L)	39 ± 2	38 ± 1	0.28
Compensatory reserve measurement (CRM, %)	87 ± 3	85 ± 3	0.27
Presyncope			
Mean arterial pressure (mmHg)	84 ± 3	80 ± 4	0.22
Heart rate (beats/min)	118 ± 8	102 ± 7	0.002
Total hemoglobin (HbT)	83.1 ± 6.6	94.7 ± 6.4	0.03
Tissue oxygen saturation (StO_2, %)	44.6 ± 5.6	56.0 ± 4.6	0.002
Muscle pH (pH_m)	7.4 ± 0.03	7.4 ± 0.03	0.18
Hydrogen ion concentration ([H^+], nmol/L)	45 ± 3	42 ± 3	0.16
Compensatory reserve measurement (CRM, %)	10 ± 3	18 ± 9	0.03
Difference between baseline & presyncope			
Mean arterial pressure (mmHg)	10 ± 3	11 ± 3	0.66
Heart rate (beats/min)	−56 ± 7	−33 ± 6	0.26
Total hemoglobin (HbT)	−13.3 ± 3.7	−6.1 ± 5.5	0.03
Tissue oxygen saturation (StO_2, %)	−18.8 ± 5.4	−9.6 ± 4.5	0.01
Muscle pH (pH_m)	−0.056 ± 0.01	−0.041 ± 0.02	0.35
Hydrogen ion concentration ([H^+], nmol/L)	6 ± 2	4 ± 2	0.31
Compensatory reserve measurement (CRM, %)	−77 ± 5	−67 ± 10	0.03

RESULTS

Thirty-four participants were categorized as HT (67%) and 17 participants categorized as LT (33%). The demographic information for these two groups of participants is presented in Table 1. Females accounted for 14 of the HT participants and 13 of the LT participants. As a population, HT and LT participants were statistically indistinguishable ($p \geq 0.11$) in age, height, weight, and body mass index (BMI).

Table 2 presents the data at baseline and decompensation, as well as the change from baseline to decompensation for physiological measurements. There were no statistical differences ($p \geq 0.25$) in group means of the baseline values for MAP, HbT, StO_2, pH_m, [H+], and CRM, while baseline HR was higher in LT participants compared to HT participants ($p = 0.03$). Average LBNP tolerance times were 22.2 ± 1.8 minutes for the LT group compared to 31.2 ± 1.8 minutes for the HT group ($p < 0.001$). At decompensation, values of MAP, pH_m, and [H^+] were statistically indistinguishable ($p \geq 0.16$) between HT and LT participants, though, the HT group had higher HR ($p = 0.002$), lower HbT ($p = 0.03$), and lower StO_2 ($p = 0.002$) compared to LT participants. The difference from baseline to decompensation in HbT, StO_2, and CRM was higher in HT participants compared to LT participants ($p \leq 0.03$). HT participants decreased StO_2 (−18.8 ± 5.4% vs. -9.6 ± 4.5%, $p = 0.01$) and HbT (−13.3 ± 3.7 vs. −6.1 ± 5.5, $p = 0.03$) more than LT

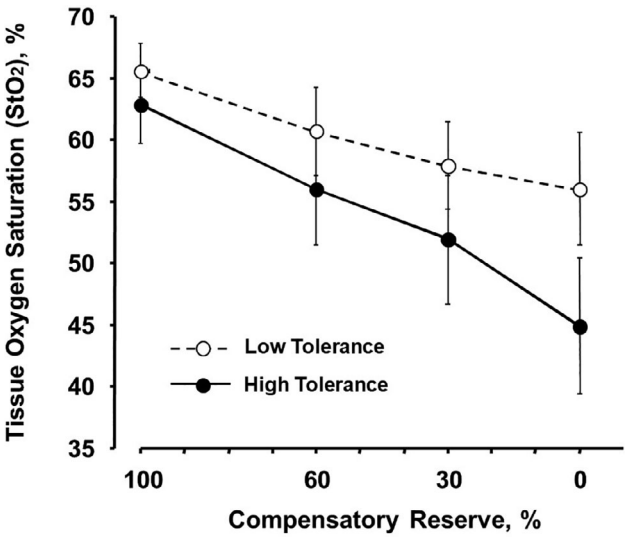

Fig. 1. The relationship between compensatory reserve measurement (CRM) and tissue oxygen saturation (StO_2) for participants with high tolerance (HT) (closed circles, *solid line*) and low tolerance (LT) (open circles, *dashed line*). Values are express as mean ± 95% CI.

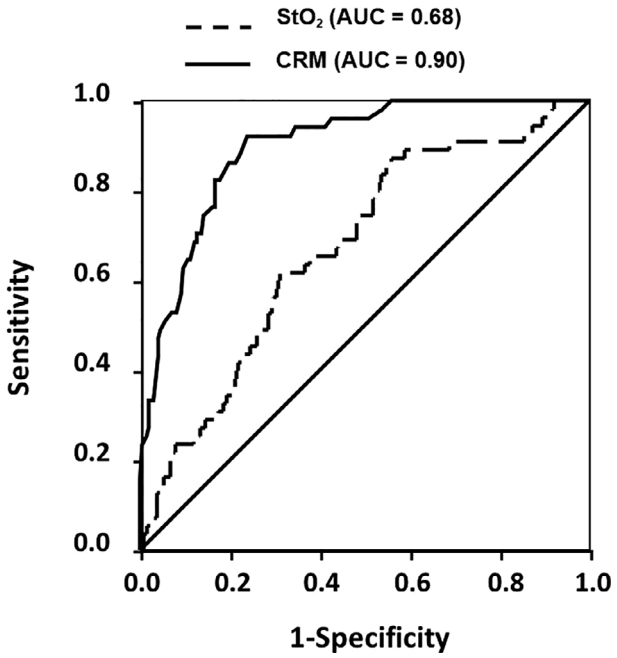

Fig. 2. Receiver operating characteristic area under the curves (ROC AUC) for predicting hemodynamic decompensation for the compensatory reserve measurement (CRM) and tissue oxygen saturation (StO_2).

participants. The reduction in CRM from baseline to decompensation was greater ($p = 0.03$) in HT participants (-77 ± 5 vs. $-67 \pm 10\%$, $p = 0.03$) than LT participants, such that HT participants reached lower levels of CRM at decompensation.

Figure 1 presents the relationship between CRM and StO_2 for each group (HT vs. LT) at 100%, 60%, 30%, and 0% (i.e., hemodynamic decompensation). CRM was able to distinguish between HT and LT participants early in the time course of progressive hemorrhage, such that times to reach 30% and 0% CRM occurred sooner ($p \leq 0.01$) in LT participants compared to HT participants, while StO_2 was significantly distinguishable at 0% CRM ($p = 0.01$). Due to the lesser time required to reach hemodynamic decompensation in LT participants, the slope of the CRM-StO_2 relationship was steeper in the HT participants (Fig. 1). The steeper slope in the HT group resulted in lower StO_2 at 0% CRM. In addition, Fig. 2 presents the ROC analysis comparing CRM and StO_2. The CRM demonstrated a superior ability to predict the onset of hemodynamic decompensation compared with StO_2 as indicated by a significantly higher ROC AUC (0.91; 95%CI = 0.87-0.94) compared to the ROC AUC of 0.68 (95%CI = 0.60-0.75) generated by measures of StO_2 (Fig. 2).

DISCUSSION

With the use of a physiological model designed to distinguish human participants with HT and LT to LBNP (i.e., "good" vs. "poor" compensators), we tested three hypotheses: 1) cardiovascular decompensation to central hypovolemia occurs because participants reach an intolerable reduction in StO_2; 2) lower tolerance to progressive reductions in central blood volume would be associated with earlier maximal reductions in StO_2; and 3) LT participants would display equal StO_2 as HT participants at equal percent of the CRM while times to reach hemodynamic decompensation would be higher in the HT group. Using NIRS-determined StO_2, we assessed microvascular metabolic differences in the forearm of participants with LT and HT to LBNP. If hemodynamic decompensation to progressive reduction in central blood volume occurs because participants reach intolerable reductions in StO_2, we would expect no statistical differences in either of these tissue metabolic indices at hemodynamic decompensation. Contrary to this hypothesis, we found that HT participants were able to sustain a larger decrease in forearm muscle oxygenation (i.e., lower StO_2) than LT participants at the time of clinical decompensation. Measurements of pH_m and [H+], however, were not distinguishable between HT and LT participants at the time of decompensation, suggesting that "good" compensators are able to maintain adequate cellular oxidative metabolism at similar levels of pH_m and [H+] despite lower levels of StO_2 compared to "poor" compensators. Contrary to expectations, StO_2 proved to be a misleading indicator of clinical compromise, as it was reduced to lower levels in those individuals with higher tolerance to reduced central blood volume. Our results suggest that a mechanism for individuals who tolerate blood loss appears to be an ability to compensate by tolerating lower StO_2. This greater capacity to utilize tissue oxygen stores can act as a mechanism to delay reaching physiological threshold of critical delivery of oxygen and subsequently the onset of overt hemorrhagic shock.[28]

In this investigation, we used measures of compensatory reserve as a physiologically equivalent marker across humans to control for individual variations so that we could compare the tissue oxygen response and its association with different tolerances to progressive reductions in central blood volume similar to those created by hemorrhage. Small 95% confidence intervals around CRM values (Fig. 1) demonstrates the robust nature of this experimental approach. Consequently, we demonstrated that CRM was able to distinguish between "good" compensators (HT) and "poor" compensators (LT) earlier in the time course of progressive hypovolemia with greater sensitivity and specificity. Our results suggest that the greater ROC AUC observed using CRM rather than StO_2 can be explained by a greater specificity[15,16] created with the ability of the CRM to differentiate HT from LT participants.

In the present investigation, the majority (13/17) of females displayed LT to progressive central hypovolemia while the majority of males (20/34) were classified as having HT. These results are consistent with previous findings that showed females generally have less tolerance and lower StO_2 to progressive central hypovolemia compared to males.[29] One factor that may contribute to lower tolerance to reduced central

blood volume in women might be the potentially confounding impact of timing relative to menses. In this regard, we have previously shown that tolerance in females is not different across menstrual cycle phases nor naturally menstruating women.[30] We cannot dismiss the possibility that differences in sex influenced our observation that CRM provided greater prediction of lower tolerance to central hypovolemia compared to StO_2. In order to test the hypothesis that observed differences in sensitivity and specificity between CRM and StO_2 were not due to differences between sexes, we conducted separate ROC AUC analyses for the female and male groups. We found that the ROC AUC for CRM in males (0.90) and females (0.91) were greater than the ROC AUC for StO_2 in males (0.69) and females (0.71). These nearly identical results in males and females support the notion that sex differences cannot explain sensitivity and specificity differences between CRM and StO_2 for predicting tolerance to progressive reductions in central blood similar to hemorrhage. As such, a physiological characteristic consistent across several investigations including the present study is that LT to reductions in central blood volume is associated with lower tolerable levels of tissue oxygenation as well as less elevation in heart rate, less arterial vasoconstriction and systemic vascular resistance.[1,7,18,31–33]

A novel aspect of this study was the application of NIRS to examine microvascular metabolic variations during progressive reductions in central blood volume in groups of human participants defined by their tolerance to LBNP. Since vessel constriction alters the volume of blood in the NIRS sensor's optical path, changes in HbT reflect the magnitude of change in vasoconstriction.[23] Previous investigations conducted in humans undergoing LBNP-induced reductions in central blood volume have demonstrated reduced forearm muscle blood flow as a result of sympathetically-mediated arteriolar vasoconstriction[16,34] that mimic reductions in forearm HbT.[35] Consistent with our previous observations,[19,29] the greater HbT reduction in HT compared to LT participants in the present study suggests that "good" compensators are characterized by a greater compensatory capacity for arteriolar vasoconstriction than "poor" compensators despite having a lower StO_2. Greater maximal vasoconstriction may be explained at least in part by greater elevations in sympathetic nerve activity reported in HT compared to LT individuals.[32]

The present study may be limited in translation of results from a controlled laboratory setting to clinical practice. Valid application of the CRM algorithm to critically ill patients requires incorporation of data that represents potential individual confounding variables that could impact tolerance to reduced central blood volume such as that experienced by bleeding trauma patients. Such confounding variables include sex, age, relative anemia and physical fitness as well as hydration and prandial status.[36] In this regard, we strategically included for algorithm development human subjects that represented both sexes across a wide range of age, race, ethnicity and fitness in normal states of hydration and nutrition. The use of healthy participants exposed to a progressive reduction in central blood volume using a model of simulated hemorrhage fails to include the factor of tissue injury in a trauma patient with actual blood loss. Paradoxically, this same experimental limitation is a strength in that the entire compensatory phase associated with the physiology of ongoing hemorrhage can be examined without the confounding impact of trauma. More importantly, our protocol provided a direct head-to-head comparison of StO_2 and CRMs that is unlikely to be accomplished during the early compensatory phase of hemorrhage in trauma patients. However, confidence of translating the results of the present investigation to bleeding trauma patients can be gained by the similarity of the ROC AUC (0.90) for CRM in our participants when compared to 0.90 in humans with a controlled hemorrhage of 20% estimated blood volume[11] and 0.97 reported in trauma patients without and with hemorrhage.[37]

CONCLUSION

"Good" compensators with HT to progressive reductions in central blood volume similar to hemorrhage are characterized by a greater capacity to utilize tissue oxygen (i.e., significantly lower StO_2) compared to "poor" compensators. Greater utilization of oxygen stored in the tissue can increase the threshold of critical DO_2 and consequently delay the onset of shock. In addition, "good" compensators have a greater capacity to sustain adequate perfusion pressure with higher heart rates and greater vasoconstrictor reserve. These and other compensatory mechanisms are collectively measured as the compensatory reserve. As such, the CRM can provide earlier prediction of hemodynamic decompensation during progressive hypovolemia and distinguish between "good" compensators and "poor" compensators with greater sensitivity and specificity. Significant to clinical application, our results demonstrate that lower tissue oxygen during low flow states can be a misleading signal for predicting those at greatest risk for the onset of hemorrhagic shock since lower StO_2 does not necessarily translate to a more compromised physiological state. We therefore conclude that measures of StO_2 could be misleading for triage and resuscitation decision support in patients who have suffered a hemorrhagic injury.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest. The opinions or assertions contained herein are the private views of the authors and are

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REFERENCES

1. Schiller AM, Howard JT, Convertino VA. The physiology of blood loss and shock: new insights from a human laboratory model of hemorrhage. Exp Biol Med (Maywood) 2017;242:874-83.
2. Hinojosa-Laborde C, Shade RE, Muniz GW, et al. Validation of lower body negative pressure as an experimental model of hemorrhage. J Appl Physiol (1985) 2014;116:406-15.
3. Hinojosa-Laborde C, Howard JT, Mulligan J, et al. Comparison of compensatory reserve during lower-body negative pressure and hemorrhage in nonhuman primates. Am J Physiol Regul Integr Comp Physiol 2016;310:R1154-9.
4. Soller BR, Yang Y, Soyemi OO, et al. Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. J Appl Physiol 2008;104:475-81.
5. Ward KR, Tiba MH, Ryan KL, et al. Oxygen transport characterization of a human model of progressive hemorrhage. Resuscitation 2010;81:987-93.
6. Gutierrez G, Reines HD, Wolf-Gutierrez ME. Clinical review: hemorrhagic shock. Crit Care 2004;8:373-81.
7. Schiller AM, Howard JT, Lye KR, et al. Comparisons of traditional metabolic markers and compensatory reserve as early predictors of tolerance to central hypovolemia in humans. Shock 2018;50:71-7.
8. Butler FK, Holcomb JB, Schreiber MA, et al. Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC Guidelines Change 14-01-2 June 2014. J Spec Oper Med 2014; 14:13-38.
9. Convertino VA, Sawka MN. Wearable compensatory reserve measurement for hypovolemia sensing. J Appl Physiol 2018; 124:442-51.
10. Convertino VA, Wirt MD, Glenn JF, et al. The compensatory reserve for early and accurate prediction of hemodynamic compromise: a review of the underlying physiology. Shock 2016;45:580-90.
11. Convertino VA, Howard JT, Hinojosa-Laborde C, et al. Individual-specific, beat-to-beat trending of significant human blood loss: the compensatory reserve. Shock 2015;44(Suppl 1):27-32.
12. Convertino VA, Schiller AM. Measuring the compensatory reserve to identify shock. J Trauma Acute Care Surg 2017;82(6S Suppl 1):S57-65.
13. Moulton S, Mulligan J, Grudic G, et al. Running on empty? The compensatory reserve index. J Trauma Acute Care Surg 2013; 75:1053-9.
14. Convertino VA, Hinojosa-Laborde C, Muniz GW, et al. Integrated compensatory responses in a human model of hemorrhage. J Vis Exp 2016;117:e54737.
15. Convertino VA, Grudic GZ, Mulligan J, et al. Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. J Appl Physiol 2013;115: 1196-202.
16. Howard JT, Janak JC, Hinojosa-Laborde C, et al. Specificity of compensatory reserve and tissue oxygenation as early predictors of tolerance to progressive reductions in central blood volume. Shock 2016;46(3S):68-73.
17. Janak JC, Howard JT, Goei KA, et al. Predictors of the onset of hemodynamic decompensation during progressive central hypovolemia: comparison of the peripheral perfusion index, pulse pressure variability, and compensatory reserve index. Shock 2015;44:548-53.
18. Convertino VA, Rickards CA, Ryan KL. Autonomic mechanisms associated with heart rate and vasoconstrictor reserves. Clin Auton Res 2012;22:123-30.
19. Koons NJ, Nguyen B, Suresh M, et al. Tracking DO2 with compensatory reserve during whole blood resuscitation following controlled hemorrhage in baboons. Shock 2020 (In Press).
20. Convertino VA, Moulton SL, Grudic GZ, et al. Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. J Trauma 2011;71:S25-32.
21. Martina JR, Westerhof BE, van Goudoever J, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin®. Anesthesiology 2012;116:1092-103.
22. Yang Y, Soyemi OO, Scott PJ, et al. Quantitative measurement of muscle oxygen saturation without influence from skin and fat using continuous-wavenear infrard spectroscopy. Opt Express 2007;15:13715-30.
23. Zou F, jin C, Ross RR, et al. Investigation of spectral interferences on the accuracy of broadband CW-NIRS tissue SO2 determination. Biomed Opt Express 2010;1:748-61.
24. Stratonnikov AA, Loschenov VB. Evaluation of blood oxygen saturation in vivo from diffuse reflectance spectra. J Biomed Opt 2001;6:457-67.
25. Soyemi OO, Landry M, Yang Y, et al. Standardization method for correcting spectral differences across multiple units of a portable near infrared-based medical monitor. Proc SPIE 2005;5702:135-42.
26. Convertino VA, Cardin S, Batchelder P, et al. A novel measurement for accurate assessment of clinical status in patients with significant blood loss: the compensatory reserve. Shock 2015; 44(Suppl 1):27-32.
27. Wampler MR, Johnson MC, Alarhayem AQ, et al. Establishing threshold variables for the dashboard view of the compensatory reserve measurement. J Am Coll Surg 2018;227:S263.
28. Convertino VA, Koons NJ. The compensatory reserve: potential for accurate individualized goal-directed whole blood resuscitation. Transfusion 2020. [In press].
29. Schlotman TE, Akers KS, Nessen SC, et al. Differentiating compensatory mechanisms associated to low tolerance to central hypovolemia in females. Am J Physiol Heart Circ Physiol 2019; 316:H609-16.
30. Convertino VA, Schlotman TE, Stacey W, et al. Tolerance to central hypovolemia is not affected by menstrual cycle phases. Aerosp Med Hum Perform 2019;90:378-83.
31. Schafer K, Van Sickle C, Hinojosa-Laborde C. Physiological mechanism underlying the failure of the "Shock Index" as a tool for accurate assessment of patient status during progressive simualted hemorrhage. J Trauma Acute Care Surg 2013;75:S197-202.

32. Convertino VA. Neurohumoral mechanisms associated with orthostasis: reaffirmation of the significant contribution of the heart rate response. Front Physiol 2014;5:1-8.
33. Xiang L, Hinojosa-Laborde C, Ryan KL, et al. Time course of compensatory physiological responses to central hypovolemia in high and low tolerant subjects. Am J Physiol 2018;315: R408-16.
34. Joyner MJ, Shepherd JT, Seals DR. Sustained increases in sympathetic outflow during prolonged lower body negative pressure in humans. J Appl Physiol 1990;68:1004-9.
35. Hachiya T, Blaber AP, Saito M. Near Infrared spectroscopy provides an index of blood flow and vasoconstriction in calf skeletal muscle during lower body negative pressure. Acta Physiol (Oxf) 2008;193:117-27.
36. Goswami N, Blaber A, Hinghofer-Szalkay H, et al. Lower body negative pressure: physiological effects, applications and implementations. Physiol Rev 2019;99:807-51.
37. Stewart CL, Mulligan J, Grudic GZ, et al. The compensatory reserve index following injury: results of a prospective clinical trial. Shock 2016;46(3 Suppl 1):61-7.