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Oxygen transport characterization of a human model of progressive hemorrhage☆,☆☆

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ABSTRACT

Background: Hemorrhage continues to be a leading cause of death from trauma sustained both in combat and in the civilian setting. New models of hemorrhage may add value in both improving our understanding of the physiologic responses to severe bleeding and as platforms to develop and test new monitoring and therapeutic techniques. We examined changes in oxygen transport produced by central volume redistribution in humans using lower body negative pressure (LBNP) as a potential mimetic of hemorrhage.
Methods and results: In 20 healthy volunteers, systemic oxygen delivery and oxygen consumption, skeletal muscle oxygenation and oral mucosa perfusion were measured over increasing levels of LBNP to the point of hemodynamic decompensation. With sequential reductions in central blood volume, progressive reductions in oxygen delivery and tissue oxygenation and perfusion parameters were noted, while no changes were observed in systemic oxygen uptake or markers of anaerobic metabolism in the blood (e.g., lactate, base excess). While blood pressure decreased and heart rate increased during LBNP, these changes occurred later than the reductions in tissue oxygenation and perfusion.
Conclusions: These findings indicate that LBNP induces changes in oxygen transport consistent with the compensatory phase of hemorrhage, but that a frank state of shock (delivery-dependent oxygen consumption) does not occur. LBNP may therefore serve as a model to better understand a variety of compensatory physiological changes that occur during the pre-shock phase of hemorrhage in conscious humans. As such, LBNP may be a useful platform from which to develop and test new monitoring capabilities for identifying the need for intervention during the early phases of hemorrhage to prevent a patient's progression to overt shock.

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1. Introduction

Hemorrhage remains the greatest threat to survival in the first 24 h after traumatic injury, accounting for approximately 50% of combat and 40% of civilian trauma mortality.[1,2] In 2000, the Post-Resuscitative and Initial Utility in Life Saving Efforts (PULSE) workshop was sponsored by the National Institutes of Health in conjunction with the U.S. Department of Defense in recognition of the >1000 lives lost per day in the United States as a result of cardiac arrest and trauma.[3,4] This workshop developed a basic and clinical science needs inventory with the goal of improving outcomes following cardiopulmonary or traumatic injury resuscitation. Twenty-two topics were identified as deserving high priority research. Two of these included developing better experimental models, and biosensors to identify critical limitations of blood flow.

In hemorrhage research, experimental models have been almost exclusively limited to animals. Limitations of animal models include anesthesia, physiologic and metabolic variations, and the potential for unknown differences from the cellular to organ

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level compared to humans (e.g., skin thickness, limb length and temperature regulation).[5] These differences make development of monitoring systems (especially noninvasive ones) challenging. Development of experimental models of hemorrhage using humans that are void of anesthesia could assist in understanding the human physiologic responses to hemorrhage and in developing better monitoring.

The United States Army Institute of Surgical Research (USAISR), along with others, has pioneered lower body negative pressure (LBNP) as a model to study the effects of central hypovolemia in conscious humans.[6–9] To date, this work has focused on central and systemic hemodynamics and autonomic responses produced by LBNP, with comparisons made to hemorrhage in animals or mild to moderate blood removal in humans.[8,10–12] While findings such as changes in cardiac output and mean arterial pressure are similar to hemorrhage, oxygen transport physiology has not been characterized in the model, especially as it relates to tissue oxygenation and microvascular perfusion.[7,8] This study sought to characterize the metabolic response to progressive LBNP to understand its utility as a model of human hemorrhage and platform to develop new monitoring technologies that may assist in triage and treatment of hemorrhaging patients.

2. Methods

2.1. Study design, setting, and population

This was a prospective study performed at the USAISR in San Antonio, TX. Data analysis took place at the USAISR, the Virginia Commonwealth University (Richmond, VA), and the University of Massachusetts Medical School (Worcester, MA). The Institutional Review Boards of all three institutions approved the protocol.

A total of 20 healthy, normotensive, nonsmoking subjects (9 males, 11 females) volunteered to participate in this study (age, 23 ± 4 years; height, 171 ± 11 cm; weight, 69 ± 11 kg; mean $\pm$ SD). A medical history and physical examination were obtained on each subject prior to study. Female subjects underwent urine testing to exclude pregnancy. Subjects were asked to refrain from alcohol, exercise, stimulants and other non-prescription drugs 24 h prior to testing and gave written informed consent.

2.2. Study protocol

Subjects were supine with lower extremities (from below the iliac crest) placed within the LBNP chamber (Fig. 1). A neoprene skirt provided an airtight seal between the subject and the chamber. The protocol consisted of a 5-min rest period (0 mmHg) followed by 5 min of chamber decompression to −15, −30, −45, and −60 mmHg and additional increments of −10 mmHg every 5 min until the onset of hemodynamic decompensation. Hemodynamic decompensation was identified in real time by the attending investigator as a precipitous decrease in systolic blood pressure (SBP) (>15 mmHg), or progressive diminution of SBP <70 mmHg, and/or the presence of pre-syncopal symptoms expressed by the subject such as gray-out, sweating, nausea, or dizziness.

2.3. Instrumentation

Continuous heart rate (HR) was measured from a standard electrocardiogram (ECG). Continuous, beat-by-beat blood pressure was 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 laid at heart level. Excellent estimates of directly measured intra-arterial pressures have been demonstrated with this device.[13] Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice diastolic blood pressure by three. Beat-to-beat stroke volume (SV) was calculated from the blood pressure waveform as described previously.[14] Cardiac output (Q) was calculated as the product of HR and SV. Peripheral arterial hemoglobin oxygen saturation (SpO_2) was measured using a finger pulse oximeter (BCI Capnocheck Plus, Smiths Medical Inc., Waukesha, WI). The blood pressure waveform and ECG were sampled at 500 Hz and recorded directly to data acquisition software (WINDAQ, Dataq Instruments, Akron, OH), then imported into data analysis software (WinCPRS, Absolute Aliens, Turku, Finland).

2.4. Blood gasses

A 19-gauge catheter was inserted into an antecubital vein of the right arm for collection of blood samples during pre-LBNP baseline, and during the last 30 s of each LBNP level. The catheter was flushed with saline after each blood draw, with the first 1 ml of blood drawn discarded. Each sample (~3 ml), was immediately transferred to a chilled tube containing heparin and subsequently used for measures of venous pH, hemoglobin oxygen saturation (SO_2), hematocrit (Hct), hemoglobin concentration ([Hb]), lactate and base excess with a blood gas analyzer (AVL Omni Blood Gas Analyzer, AVL Scientific, Roswell, GA).

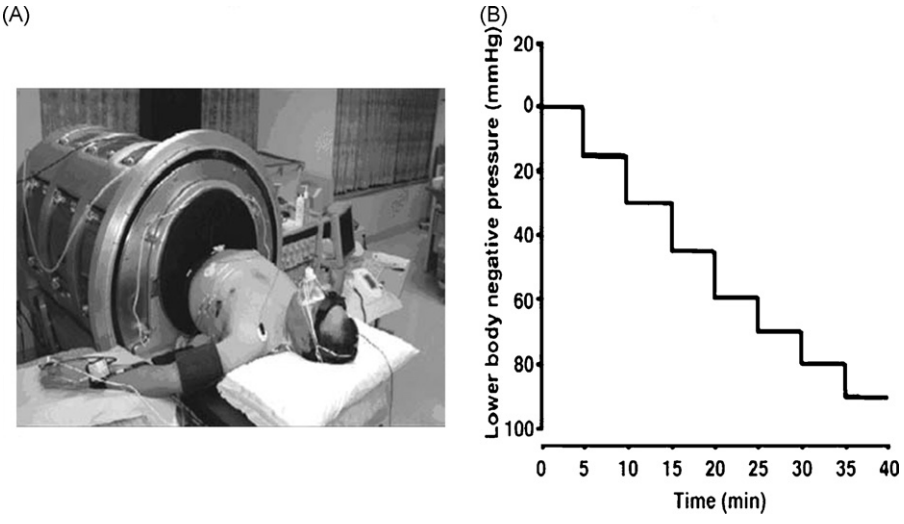

Fig. 1. Subject in the LBNP device (A) and the LBNP protocol (B).

2.5. Oxygen consumption (VO_2)

Subjects breathed through a face mask attached to a metabolic cart (Vmax-29 Metabolic Cart, SensorMedics Corp., Yorba Linda, CA, USA) for calculation of oxygen consumption (VO_2) from measurements of fractional inspired and expired oxygen and ventilation volume corrected for temperature and pressure. Measurements were taken for 2 min during each LBNP level, and 1-min averages were calculated for subsequent analysis.

2.6. Oxygen delivery (DO_2)

DO_2 was determined by the following equation: $DO_2 = Q \times CaO_2$ where $CaO_2 = [Hgb]\ (g/dl) \times 1.36 \times SaO_2$. SpO_2 was used as a surrogate of SaO_2. The partial pressure of arterial oxygen was not considered in the calculation since its contribution is small, it was not measured, and subjects were breathing room air.[15]

2.7. Tissue oxygenation measurements

Muscle tissue SO_2 was measured using a near infrared spectroscopy (NIRS) monitor developed by personnel at the University of Massachusetts Medical School and assembled by Luxtec Corporation (West Boylston, MA, USA). The device sensor was placed over the right forearm flexor digitorum profundus muscle. NIRS utilizes differential absorption spectroscopy to determine proportions of oxy- and deoxyhemoglobin within a volume of tissue based on the compartmentalization of blood in tissues, where 70–80% exists in venules, with the remaining 10–20% existing in arterioles and capillaries.[16] Thus NIRS signals emanate mainly from the post-extraction (venous) compartment of tissues. NIRS has been demonstrated to be capable of detecting tissue oxygenation changes due to hemorrhage.[17]

Acquired tissue spectra were corrected for interference from skin pigment and fat. Muscle SO_2 and pH were calculated from the corrected spectra using previously determined algorithms.[18,19] Data were collected continuously with the last 3 min of data at each LBNP level used to report the values of muscle SO_2 (as percent hemoglobin saturated with oxygen) and pH.

2.8. Oxygen extraction ratio (OER)

Both systemic and tissue OER were examined to determine the degree to which tissues extract available oxygen in order to meet utilization demands. We determined OER based on the formula: $SaO_2 - SvO_2/SaO_2$.[15] SpO_2 was used in place of SaO_2. Venous hemoglobin oxygen saturation (SvO_2) from the antecubital vein was used to determine OER for the forearm since it was considered a major source of venous effluent. It was also used as a reflection of systemic OER. NIRS muscle SO_2 values were used when determining muscle OER.

2.9. Microcirculation analysis

Side stream dark field microscopy was used to measure functional capillary density (FCD) of the sublingual mucosa,[20] as FCD reflects changes in microvascular perfusion.[21,22] This assessment was performed using video microscopy (MicroScan™ Microvision Medical, Inc., Wallingford, PA) providing 5× magnification, with probe placement in the sublingual fossa. The 500–600 nm light used allows visualization of mucosal vasculature. The device was connected to a DV player (JVC BR-DV3000: JVC, Whitlock Group, Richmond, VA) recording at 30 frames/s.

To calculate FCD, video was imported into the manufacturer's software (MAS/SDF, MicroVision Medical, Inc., Amsterdam, The Netherlands). After filtering and rejecting large vessels (over 25 μm in diameter), the software calculates the ratio of the total length of the remaining vessels over the total field area. This ratio represents FCD. Technicians performing FCD analysis were blinded to the sequence of the clips and LBNP level.

2.10. Statistical analysis

Subjects reached hemodynamic decompensation (i.e., maximal LBNP tolerance) at different LBNP levels, based on their individual physiological responses. Because these responses are the same at hemodynamic decompensation independent of the LBNP level at which an individual subject reaches this point, we chose to normalize each individual's data by re-apportioning their responses to six equal fractions, between 0% LBNP tolerance (baseline) and 100% LBNP tolerance, the level at which the LBNP protocol was terminated.[23] This approach avoids attrition of sample size as the individual absolute levels of LBNP progressed and considers the data from all subjects relative to their maximum capacity for LBNP tolerance.

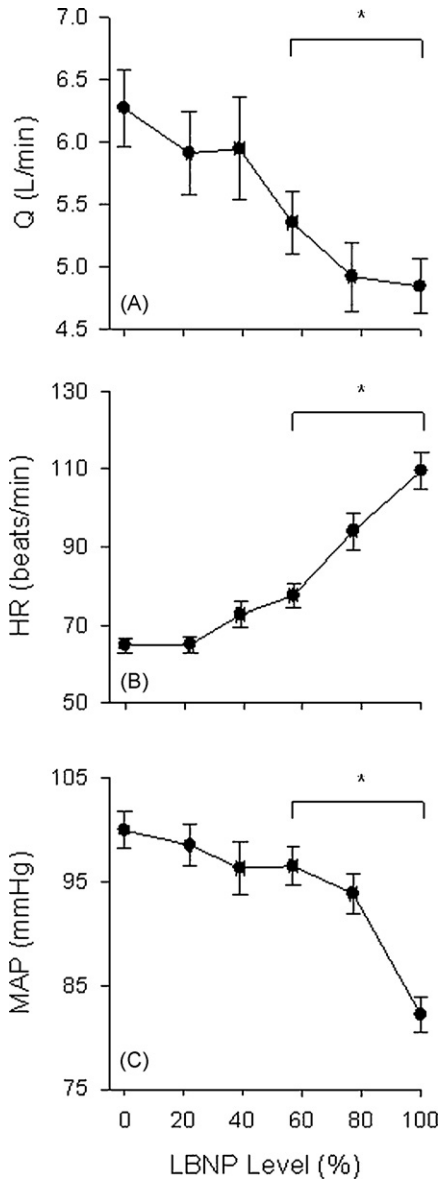

Fig. 2. Cardiovascular responses during progressive LBNP. *Q*, cardiac output; HR, heart rate; MAP: mean arterial pressure. Data are means ± SE; $n = 20$, $^*P \leq 0.013$ compared to baseline.

Table 1
Venous blood values during lower body negative pressure (LBNP).

Parameter	% of maximal LBNP					
	0	20	40	60	80	100
Hematocrit (%)	40.3 ± 0.8	39.2 ± 1.0	38.9 ± 1.2	39.9 ± 0.8	40.6 ± 1.0	42.2 ± 0.8*
Hemoglobin (g/dL)	13.5 ± 0.3	13.6 ± 0.4	12.8 ± 0.4	13.6 ± 0.3	13.6 ± 0.4	14.5 ± 0.4*
SO_2 (%)	73.7 ± 2.8	66.4 ± 3.4	64.1 ± 4.6	65.4 ± 3.7	60.7 ± 4.9*	50.8 ± 3.8*
pH	7.37 ± 0.00	7.37 ± 0.00	7.37 ± 0.01	7.37 ± 0.00	7.37 ± 0.01	7.37 ± 0.06
Lactate (mmol/L)	0.96 ± 0.06	0.95 ± 0.07	0.97 ± 0.09	1.10 ± 0.06*	1.00 ± 0.08	0.95 ± 0.06
Base excess (mmol/L)	−0.06 ± 0.37	−0.18 ± 0.45	−0.81 ± 0.83	−0.37 ± 0.41	−0.46 ± 0.48	0.19 ± 0.40

Means ± SEM.
* $P \leq 0.029$ compared to baseline values.

The experimental design was a single group repeated measures design in which the six LBNP stages were applied to each subject over time. The statistical model was therefore mixed with the autocorrelation structure of the repeated measurement modeled under the most conservative conditions. Exact *P* values were calculated and reflected the probability of variation in the LBNP means given only experimental noise. Although the experiment-wise distribution of the *F* statistics generated from the statistical tests performed on the metabolic dependent variables was evaluated and considered, no formal adjustment to the *P* values was made at the test-wise level. Bonferroni post hoc tests were performed when the overall test for mean time differences resulted in *P* values <0.05. Results of statistical tests (i.e., *P* values) reported in the text are associated with overall differences across the six time periods of LBNP. When appropriate, follow-up pairwise testing comparing baseline values to each of the subsequent five LBNP stages are presented in tables and figures. Standard errors present in figures and tables are unadjusted for between subject differences.

3. Results

Table 1 contains blood values obtained during LBNP. SvO_2 decreased ($P \leq 0.0049$) across LBNP levels. Venous hematocrit and hemoglobin both increased during the final LBNP stage (*P*'s < 0.0079) while pH, lactate, and base excess showed no trend in their mean responses to LBNP (*P*'s ≥ 0.27). There was a small but statistically significant increase in lactate found to occur at the 60% LBNP level. However, this was not sustained at higher LBNP levels and was not considered a clinically significant elevation.

Cardiac output progressively decreased ($P < 0.004$) as LBNP increased, despite a progressive increase ($P = 0.0001$) in HR (Fig. 2A and B). Although MAP decreased progressively across all levels of LBNP ($P = 0.0001$), it remained within clinically normal limits until the 100% maximal LBNP level when pronounced hypotension occurred (Fig. 2C). SpO_2 was maintained at levels greater than or equal to 97% (data not shown).

Fig. 3 shows representative FCD images of a single subject that depict progressive decreases in tissue perfusion. The average FCD for all subjects decreased ($P = 0.0021$) progressively with the decrease in DO_2 (Fig. 4A and E). At the local tissue level, muscle pH and SO_2 progressively decreased (Fig. 4B and C), while muscle OER (Fig. 4D) increased (*P*'s ≤ 0.0118). On the systemic level (Fig. 4E and F), DO_2 decreased while OER increased (*P*'s ≤ 0.005). This resulted in maintenance of VO_2 and thus no sustained increase in systemic lactate (Fig. 4G and H). Post hoc statistical tests suggested that FCD decreased earliest (at 20% LBNP tolerance), prior to changes in muscle SO_2 and OER (60% LBNP tolerance), while muscle pH only decreased at 80 and 100% LBNP tolerance.

4. Discussion

Little is known concerning the progression of human physiologic responses to hemorrhage, mainly due to the inability to perform continuous monitoring of numerous hemodynamic, auto-

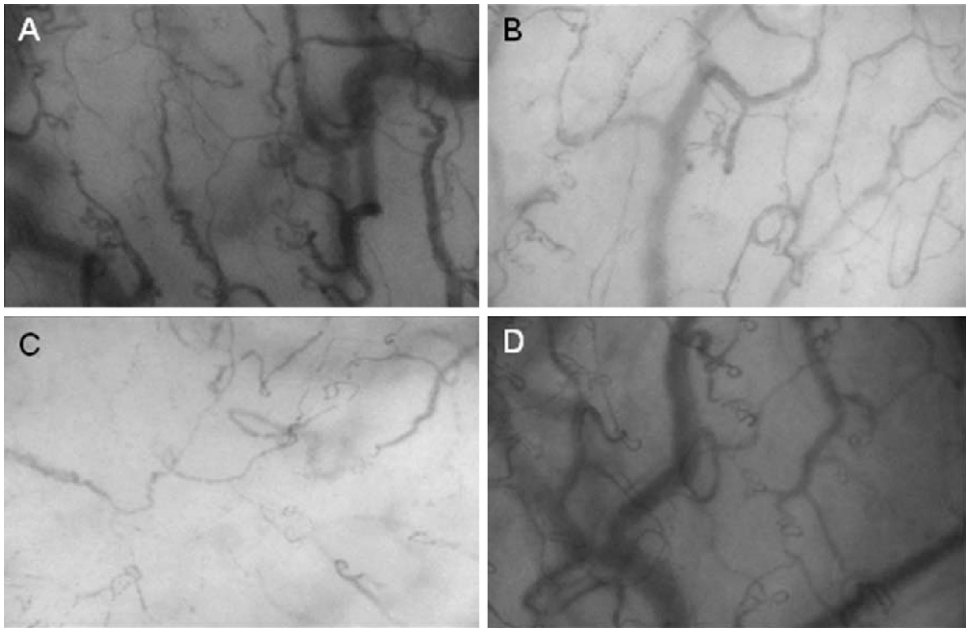

Fig. 3. Representative changes in functional capillary density (FCD) in sublingual mucosa from a single subject undergoing LBNP. (A) FCD at baseline = 13 μm^{-1}; (B) FCD at 60% LBNP tolerance = 11.2 μm^{-1}; (C) FCD at 100% LBNP tolerance = 9.82 μm^{-1}; (D) FCD at recovery = 12.3 μm^{-1}.

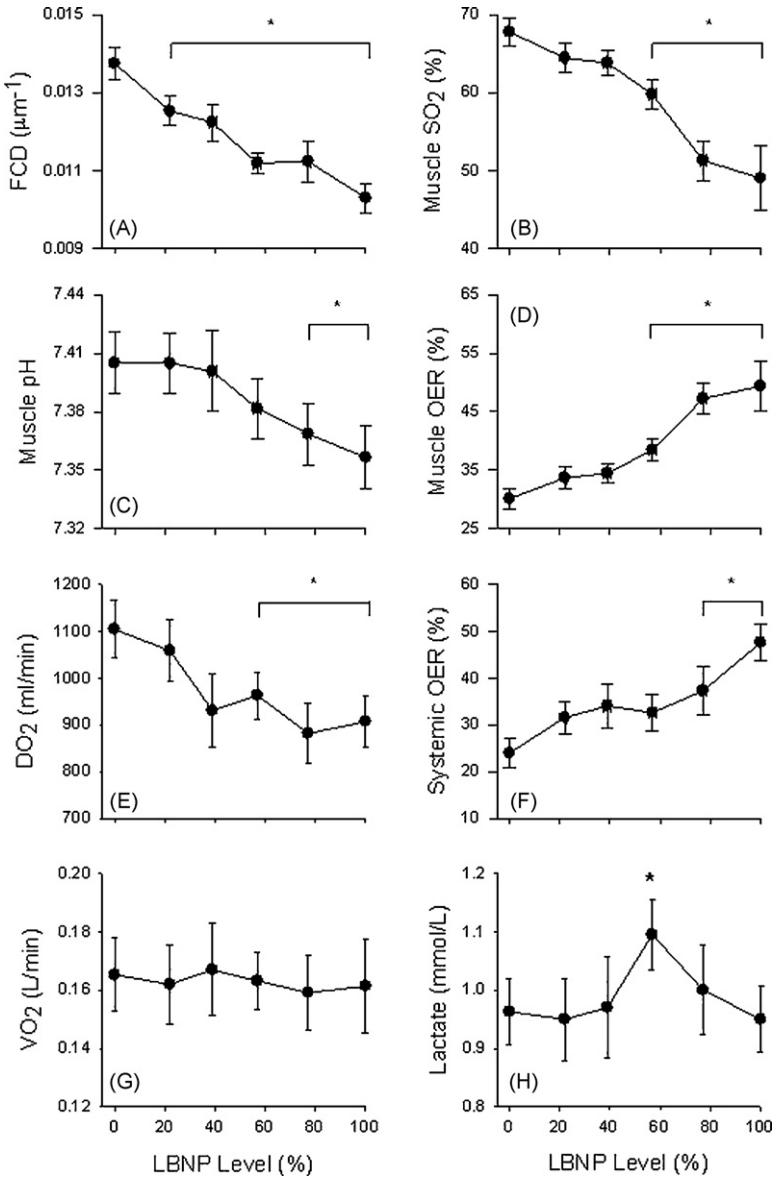

Fig. 4. Metabolic responses to progressive LBNP at the tissue level (panels A–D) and the systemic level (panels E–H). FCD, in sublingual mucosa; muscle SO_2, oxygen saturation in the flexor digitorum profundus muscle of the right forearm; OER, oxygen extraction ratio; DO_2, systemic oxygen delivery; VO_2 systemic oxygen consumption. Data are means ± SE; $n = 20$, except for FCD where $n = 16$, VO_2 and muscle SO_2, pH and OER where $n = 18$. $^*P \leq 0.047$ compared to baseline.

nomic, and metabolic responses during traumatic hemorrhage, particularly the early pre-shock phase. In this study, we were able to comprehensively monitor simulated hemorrhage in humans by systematically reducing central blood volume in a controlled experimental setting. Our results demonstrate that LBNP produces progressive tissue vasoconstriction and concomitant increases in OER but that an overt state of shock does not occur. These responses are similar to those occurring during the early pre-shock or compensatory phase of hemorrhage.[22,24–27] The use of LBNP as an experimental model may therefore both enhance the understanding of the human physiologic response to early hemorrhage and provide a platform to conceive, test, and validate new monitoring methods.

Previous studies have attempted to estimate blood volume loss to LBNP levels by various methods including comparing parameters such as stroke volume and symptoms between LBNP and blood withdrawal. These studies indicate that blood redistribution in response to LBNP is linear and equivalent to actual blood removal at the following levels: LBNP levels 10–20 mmHg = 400–500 ml removal; LBNP levels of 20–40 mmHg = 500–1000 ml removal; LBNP levels >40 mmHg = >1000 ml removal.[10,12,28–30] Recently, data from the same 20 subjects that participated herein were used in computer simulations to support the blood loss ranges above as well as several of the metabolic responses measured in this study.[31] In a manner similar to that reported during actual hemorrhage, MAP was preserved during the early phase of central hypovolemia despite a dramatic reduction in cardiac output (Fig. 2).[8]

The classic definition of shock is one where tissue DO_2 does not meet tissue VO_2.[32,33] This is traditionally signified by reductions in VO_2 and subsequently the presence of increasing systemic levels of lactate.[33,34] The VO_2, systemic lactate, and base excess responses to LBNP in this study do not support a state of delivery-dependent VO_2 in which critical DO_2 was passed.[25,33–35] Instead, it appears that physiologic compensation involving increased oxygen extraction occurred to maintain tissue VO_2, just as in the early stages of hemorrhage.[24–27]

Indeed, a reduction in tissue DO_2 did occur as evidenced by progressive reductions in muscle tissue SO_2 and visually confirmed by

reductions in oral mucosa FCD. As a result of reduced tissue DO_2, we would expect a greater percentage of oxygen to be extracted by tissues resulting in reductions in tissue SO_2 and thus progressively increased local and global OER consistent with hemorrhage.[22,24–27] In the absence of changes in VO_2 and lactate, we conclude that the LBNP model reflects a phase of hemorrhage in which increased oxygen extraction is proportional, and subsequently compensatory, to the reduction in DO_2 (i.e., the "pre-shock" stage).

An unaltered systemic [Hb] and SpO_2 throughout LBNP indicates that the significant drop in DO_2 was due solely to reductions in cardiac output. Increased systemic hematocrit at the final stage of LBNP is consistent with hemoconcentration known to occur in animal models of hemorrhage where concomitant fluid resuscitation does not take place.[36] The early and sustained reductions in microvascular perfusion are noted by FCD analysis (e.g., Fig. 3). Taken together, these findings provide confirmation that the volume redistribution produced by LBNP occurs in a manner consistent with hemorrhage and other hypoperfusion states where end-organ flow is diminished and reflex-mediated compensatory vasoconstriction occurs.[22,37] It is important to note that the metabolic changes measured were noted in multiple tissues. These include a large portion of a limb, skeletal muscle, and oral mucosa indicating that the response produced by LBNP is "global" as would be expected with hemorrhage.[25,38]

As previously demonstrated in animal models of hemorrhage, the human physiologic response to LBNP is variable since not all subjects responded in the same way to a similar absolute magnitude of LBNP.[39] This is an important element of the model, since it may reflect a novel approach to understand the physiology of why some individuals withstand greater degrees of hemorrhage than others. Once these mechanisms are understood, it may be possible to design new therapeutic interventions to prolong tolerance, thus increasing the time until physiologic collapse and extending the therapeutic window. For example, this laboratory has shown that use of inspiratory resistance delays the onset of symptoms associated with central hypovolemia produced by LBNP by increasing venous return and maintaining cardiac output for longer periods.[40] Additionally, new opportunities exist to develop monitoring modalities that allow for ultra-early prediction of eventual collapse or the ability to determine hemorrhage severity and the adequacy of treatment. In this regard, LBNP has been used to compare new technologies to detect tissue hypoperfusion and has already uncovered significant performance differences between two NIRS monitoring technologies.[18] To date, 150 subjects have safely undergone the current LBNP protocol in this laboratory without complications.

This model is not without limitations. Although humans are used in a setting without the confounding effects of anesthesia, there is no tissue injury and pain. Since traumatic hemorrhage is usually accompanied by significant tissue injury, the presence of such factors could result in more complex variations in LBNP responses than those observed in this study.[24] Additionally hypoxemia, often present after trauma from hypoventilation or lung injury, was not incorporated into this model.

Despite these limitations, the use of LBNP in humans to model the early compensatory stages of hemorrhage should prove to be a valuable addition to animal hemorrhage models. Specifically, new understanding of individual variations to central volume loss and in the monitoring of blood loss may result in new therapeutic and diagnostic targets.

5. Conclusion

Graded LBNP in humans results in a physiologic state consistent with early hemorrhage prior to the onset of shock as evidenced by dynamic changes in a number of tissue perfusion parameters. LBNP thus may be a valuable platform for the development of new diagnostic strategies for use in the setting of hemorrhage prior to the onset of shock when it may be too late to implement effective treatments.

Conflict of interest statement

Dr. Soller is a co-founder of Reflectance Medical Inc., which has rights to the NIRS technology used in this study.

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