SHOCK, Vol. 37, No. 6, pp. 586 591, 2012

PROGRESSIVE REDUCTION IN CENTRAL BLOOD VOLUME IS NOT DETECTED BY SUBLINGUAL CAPNOGRAPHY

Kevin K. Chung,* Kathy L. Ryan,* Caroline A. Rickards,† Carmen Hinojosa-Laborde,* Jeremy C. Pamplin,‡ Shimul S. Patel,‡ Thomas S. Herold,* and Victor A. Convertino*

**US Army Institute of Surgical Research, Fort Sam Houston; †Department of Health and Kinesiology, University of Texas at San Antonio, San Antonio, and ‡San Antonio Military Medical Center, Fort Sam Houston, Texas*

Received 26 Jan 2012; first review completed 14 Feb 2012; accepted in final form 27 Feb 2012

ABSTRACT Early detection and management of shock are important in optimizing clinical outcomes. One regional marker, sublingual capnography ($SLCO_2$), is particularly appealing as redistribution of blood flow away from the sublingual mucosa can happen very early in the compensatory phase of hypovolemic shock. Our objective was to test the hypothesis that $SLCO_2$ would detect early hypovolemia in a human laboratory model of hemorrhage: progressive lower body negative pressure until onset of cardiovascular collapse. Eighteen healthy nonsmoking subjects (10 males, 8 females) with mean age of 28 (SD, 8) years, body weight of 72 (SD, 13) kg, and height of 172 (SD, 9) cm were recruited to participate, of whom 17 completed the experiment. Average time to presyncope was 1,579 ± 72 s (mean ± SE). At the time of cardiovascular collapse, lower body negative pressure altered ($P < 0.001$) systolic blood pressure (mean ± SE: 130 ± 3 vs. 98 ± 2 mm Hg), pulse pressure (mean ± SE: 58 ± 2 vs. 33 ± 2 mm Hg), and heart rate (mean ± SE: 63 ± 3 vs. 102 ± 6 beats/min) when compared with baseline, whereas $SLCO_2$ did not change (49.1 ± 1.0 vs. 48.6 ± 1.5 mm Hg, P 0.624). In a model of progressive central hypovolemia in humans, we did not detect metabolic derangements in the sublingual mucosa as measured by $SLCO_2$.

KEYWORDS Shock, hypovolemia, monitoring, near-infrared spectroscopy, hemodynamics

INTRODUCTION

Early detection and management of shock, defined as inadequate delivery of oxygen to the end-organs in relation to tissue oxygen consumption, are important in optimizing clinical outcomes after severe trauma (1). Traditional markers of hypoperfusion such as mental status, heart rate (HR), blood pressure, and urine output may not be sufficient in detecting early hemorrhage because evidence of inadequate tissue perfusion (i.e., base deficit, lactate, and venous saturation) may exist despite normal values of these traditional indices (1–3). To some degree, global markers of hypoperfusion, such as blood lactate and base deficit, are also problematic, especially early in the subclinical or compensated shock state (4). Elevations of these markers are seen only when an imbalance exists between their production, under anaerobic conditions, and elimination via the kidney and the liver. Other global indices, such as central or mixed venous saturation, fall in the same category and may not be helpful in the early compensated state because only a global mismatch between oxygen delivery and consumption would result in an abnormally low value. On the other hand, regional markers of hypoperfusion are particularly appealing because blood flow is redistributed away from "nonvital" organs, such as the gut and the skin, to maintain cerebral and coronary flow throughout the compensatory phase of hemorrhage (5–9).

One such regional marker is gut mucosal tissue carbon dioxide (CO_2) and, by derivation, pH assessed via gastric tonometry. In a small randomized controlled trial involving trauma patients, Ivatury et al. (10) reported that a number of patients (n = 13) had evidence of gastric tissue dysoxia (by gastric mucosal pH), although global indices (lactate and base deficit) remained normal. This subgroup of patients had a significantly higher mortality (54%) than those with no evidence of gastric hypoperfusion (7%) (10). Thus, gastric tonometry was able to uncover a subset of patients, missed by global indices, who were indeed in compensated shock. Others have demonstrated similar findings in other clinical populations (11–13).

Despite some promising early clinical findings, however, gastric tonometry has not been widely adopted because of logistical challenges that make measurements cumbersome and impractical (14). Recently, more proximal areas of the gastrointestinal tract, such as the esophagus, sublingual tissue, and buccal mucosa, have been determined to be appropriate surrogates for assessing regional perfusion and dysoxia of the gut in animal models of hemorrhage (15–17). Baron et al. (18) recently reported that partial pressure of sublingual CO_2 ($SLCO_2$) predicted survival in hypotensive trauma patients and had equivalent diagnostic ability to lactate and base deficit. Alterations in the sublingual tissue also appear to correlate with alterations seen in the gastric mucosa during hemorrhagic shock (15). Thus, it is likely that alterations in $SLCO_2$, which signal the presence of tissue dysoxia in the sublingual tissue bed, would be present before global indices become elevated.

Address reprint requests to Kevin K. Chung, MD, FCCM, US Army Institute of Surgical Research, 3638 Chambers Pass, Fort Sam Houston, TX 78234. E-mail: Kevin.chung@amedd.army.mil.

This study was funded by the Advanced Capabilities for Emergency Medical Monitoring Task Area.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

DOI: 10.1097/SHK.0b013e318252da82

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUN 2012	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Progressive Reduction in Central Blood Volume is not Detected by Sublingual Capnography	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Chung K. K., Ryan K. L., Rickards C. A., Hinojosa-Laborde C., Pamplin J. C., Patel S. S., Herold T. S., Convertino V. A.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United Stataes Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**6**	

Lower body negative pressure (LBNP) is utilized in healthy human subjects as an experimental model of progressive hypovolemia taken to the point of hemodynamic collapse (19). Prior work using this model has demonstrated that certain regional markers of tissue perfusion are altered (20–26), whereas global indices remain within clinically normal limits (4). Microcirculation of the sublingual mucosa is clearly decreased with progressive hypovolemia using this model (4). It is not clear, however, whether a reduction in regional perfusion to this tissue bed translates to metabolic alterations, as measured by $SLCO_2$. This group recently demonstrated that tissue dysoxia as measured by forearm muscle oxygen saturation (SmO_2) also occurs early in this model of hypovolemia (21). Utilizing the same LBNP model, we performed the current study to compare the metabolic alterations in the sublingual tissue, as measured by $SLCO_2$, to SmO_2. We hypothesized that measurements of $SLCO_2$ would reflect early tissue dysoxia during progressive central hypovolemia.

MATERIALS AND METHODS

Subjects

Eighteen healthy nonsmoking subjects (10 males, 8 females) with a mean age of 28 (SD, 8) years, body weight of 72 (SD, 13) kg, and height of 172 (SD, 9) cm were recruited to participate. A complete medical history and physical examination were obtained on each of the potential subjects. Subjects were instructed to maintain their normal sleep pattern, refrain from exercise, and abstain from caffeine and other autonomic stimulants such as selected prescription or nonprescription drugs for at least 24 h before each experimental protocol. In addition, female subjects underwent an initial urine test immediately before experimentation to ensure that they were not pregnant.

During an orientation session that preceded each experiment, all subjects received a verbal briefing and a written description of all procedures and risks associated with the experiments and were made familiar with the laboratory, the protocol, and the experimental procedures. Each subject gave written informed voluntary consent to participate in the experiment. This study was conducted under a protocol reviewed and approved by the institutional review board of the Brooke Army Medical Center, Fort Sam Houston, Tex, and was performed in accordance with the approved protocol.

Model of central hypovolemia

LBNP was used in the present investigation as an experimental tool to simulate loss of central blood volume (e.g., hemorrhage) in humans (19). With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of LBNP (below the iliac crest) with the subject in a supine position results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen (Fig. 1A). Thus, this model provides a unique method of investigating the conditions of controlled, progressive, experimentally induced hypovolemic hypotension. Absolute equivalence between the magnitude of negative pressure applied and the magnitude of actual blood loss cannot, at this time, be determined, but review of both human and animal data reveals ranges of effective blood loss (or fluid displacement) caused by LBNP (19). Based on the magnitude of central hypovolemia, we have previously proposed that negative pressure 10 to 20 mm Hg induces hemodynamic responses equivalent to those resulting from blood loss ranging from 400 to 550 mL; negative pressure 20 to 40 mm Hg equates to blood loss ranging from 550 to 1,000 mL; and negative pressure greater than 40 mm Hg induces hemodynamic responses equivalent to those resulting from blood loss approximating 1,000 mL or more (19, 27).

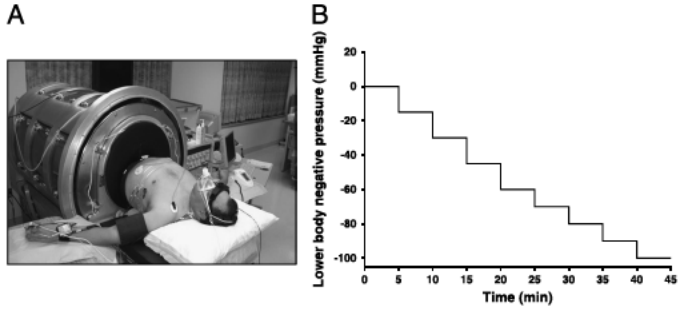

FIG. 1. **Subject in the LBNP device (A) and the LBNP protocol (B).**

Experimental protocol

All subjects were instrumented with an infrared finger photoplethysmograph (Finometer Blood Pressure Monitor; TNO TPD Biomedical Instrumentation, Amsterdam, the Netherlands) and an electrocardiogram to record beat by beat arterial pressures and HR. 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 physiological maneuvers have been demonstrated with this device (28 30). End tidal CO_2 ($ETCO_2$) was monitored on a breath by breath basis as subjects exhaled into a face mask (BCI Capnocheck Plus; Smiths Medical Inc, Waukesha, Wis) and was also used to calculate respiratory rate. A probe was placed under the tongue for continuous measurement of $SLCO_2$ using a modification of the MicroStat system (ExoStat Medical, Prior Lake, Minn). SmO_2 and muscle pH (pHm) were determined noninvasively by using near infrared spectroscopy, with the sensor placed over the flexor digitorum profundus muscle in the right forearm as described previously (21, 31).

All subjects underwent exposure to an LBNP protocol designed to test their tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a 5 min rest period (0 mm Hg) followed by 5 min of chamber decompression to 15, 30, 45, and 60 mm Hg and additional increments of 10 mm Hg every 5 min until the onset of cardiovascular collapse or the completion of 5 min at 100 mm Hg (Fig. 1B). Cardiovascular collapse was identified in real time by the attending investigator by a precipitous fall in systolic arterial pressure (SAP) greater than 15 mm Hg concurrent with the onset of presyncopal symptoms such as bradycardia, gray out (loss of color vision), tunnel vision, sweating, nausea, or dizziness.

Data analysis

Data from one of the 18 original subjects were not used because of widely varying $SLCO_2$ readings resulting because the subject did not maintain the probe in a stationary position under the tongue. The final sample size for all $SLCO_2$ and hemodynamic data analysis was thus 17. Hemodynamic data were sampled at 500 Hz, digitized to computer (WinDAQ; Dataq Instruments, Akron, Ohio) and then imported into commercially available data analysis software (WinCPRS; Absolute Aliens Oy, Turku, Finland). Individual R waves from the electrocardiogram were marked at their occurrence in time and used for subsequent identification of SAP and diastolic arterial pressure (DAP) generated from the Finometer. R R intervals were used to calculate HR. Mean arterial pressure (MAP) was calculated by dividing the sum of SAP and twice DAP by 3. Pulse pressure was calculated by subtracting DAP from SAP. Using the arterial pressure waveform as input, we estimated stroke volume (SV) on a beat to beat basis using the pulse contour method (32). $SLCO_2$ and SmO_2 data were collected independently at 0.2 and 0.05 Hz, via software specific to each sensor, and subsequently downloaded for analysis.

Statistical analysis

Subjects reached cardiovascular collapse (i.e., maximal LBNP tolerance) at different absolute LBNP levels based on their individual physiological responses. As such, we chose to normalize each individual's data by reapportioning their responses to equal fractions between 0% LBNP tolerance (baseline) and 100% LBNP tolerance, the level at which the LBNP protocol was terminated as a result of impending cardiovascular collapse (presyncope). This approach has been used previously (4, 31) because it allows the consideration of data from all subjects relative to their maximum capacity for LBNP tolerance.

Baseline values were calculated by averaging each variable over the last 3 min of the pre LBNP baseline period. Similarly, values for all variables were averaged over the last 3 min of each LBNP level and for 1 min before presyncope. Paired Student *t* tests were used for comparing baseline values with those at 100% LBNP tolerance. A one way (LBNP level) randomized block (subjects) analysis of variance for repeated measures was used for comparing outcome variables over time. If there was a low probability that a difference occurred by chance alone, Bonferroni corrected comparisons with baseline measurements were performed to determine the first level of LBNP that could be distinguished statistically from the baseline. Linear regression analysis was used to correlate changes between variables of interest. All data are presented as mean ± SE except where otherwise noted, and exact *P* values are presented for all comparisons.

RESULTS

Average values for all variables of interest at baseline and 100% LBNP tolerance are presented in Table 1. All variables

Table 1. **Absolute values of measured variables at baseline and at 100% LBNP tolerance**

Variable	Baseline	100% LBNP tolerance	P
Systolic blood pressure, mm Hg	130 ± 3	98 ± 2	<0.001
Diastolic blood pressure, mm Hg	73 ± 1	66 ± 1	<0.001
Pulse pressure, mm Hg	58 ± 2	33 ± 2	<0.001
Stroke volume, mL	103 ± 6	49 ± 5	<0.001
Heart rate, beats/min	63 ± 3	102 ± 6	<0.001
Respiratory rate, breaths/min	16 ± 1	14 ± 1	0.003
End-tidal CO_2, mm Hg	42.7 ± 0.8	32.2 ± 1.5	<0.001
Muscle oxygen saturation, %	61.6 ± 1.8	50.3 ± 2.1	<0.001
Muscle pH	7.40 ± 0.01	7.36 ± 0.02	<0.001
Sublingual P_{CO_2}, mm Hg	49.1 ± 1.0	48.6 ± 1.5	0.624

were statistically distinguishable between these time points, with the exception of $SLCO_2$. Average time to presyncope was 1,579 ± 72 s; subjects reached presyncope at different levels of LBNP (−45 mm Hg [1], −60 mm Hg [6], −70 mm Hg [7], −80 mm Hg [1], −90 mm Hg [2]). Time to presyncope above includes 300 s of baseline; thus, LBNP was applied for an average of 1,279 s (approximately 21 min).

Group mean trends for MAP, SV, SmO_2, pHm, $SLCO_2$, and $ETCO_2$ during LBNP are graphically depicted in Figure 2. Compared with baseline, MAP did not begin to decrease until 80% LBNP tolerance. SV was lower than baseline at 40% of maximal LBNP, whereas SmO_2, pHm, and $ETCO_2$ were lower than baseline at 60% of maximal LBNP. In contrast, $SLCO_2$ did not change from baseline throughout the experiment.

Amalgamated linear regressions (R^2) describing relationships between SV and $SLCO_2$, SmO_2, and pHm were 0.20, 0.95, and 0.87, respectively (Fig. 3).

DISCUSSION

Jin et al. (33) first reported an increase in CO_2 in the sublingual tissue in animals subjected to profound and sustained hemorrhagic shock. Since then, $SLCO_2$ has been evaluated in a number of clinical studies involving critically ill patients in various states of shock (34–36), including hemorrhage (18, 37), with consistently positive findings. Using a preshock model of simulated hemorrhage in humans, we sought to determine whether $SLCO_2$ would change early in the course of central hypovolemia, before the onset of frank shock as indicated by hypotension and alterations in systemic metabolic indices.

The most interesting finding of the current study is that metabolic alteration in the sublingual tissue estimated by continuous $SLCO_2$ was not detected, despite the fact that previous studies have demonstrated that mesenteric and sublingual perfusion is altered in this model (4, 20, 22–24, 26, 38). This finding was particularly surprising because $ETCO_2$, SV, and MAP decreased at various levels of LBNP. Most importantly, SO_2 decreased in the musculature of the forearm with progressive decreases in SV, reflecting the early peripheral vasoconstriction that occurs in this model (19). This observation suggests that $SLCO_2$ is not a sensitive, early indicator of the development of central hypovolemia compared with SmO_2.

There are several potential explanations for the lack of $SLCO_2$ change in our LBNP experiment. It is possible that the degree of hypoperfusion was insufficient to result in an alteration in $SLCO_2$ production. Steiner et al. (25) reported that among 13 healthy volunteers in their LBNP model, gastric P_{CO_2} levels remained unchanged despite a decrease in mesenteric flow of approximately 30% (measured by duplex Doppler). LBNP was limited at −40 mm Hg in their experiment, and only two of their 13 subjects developed presyncopal symptoms. By contrast, we applied nearly double the negative pressure (on average) with significant reductions seen in muscle O_2 and pH

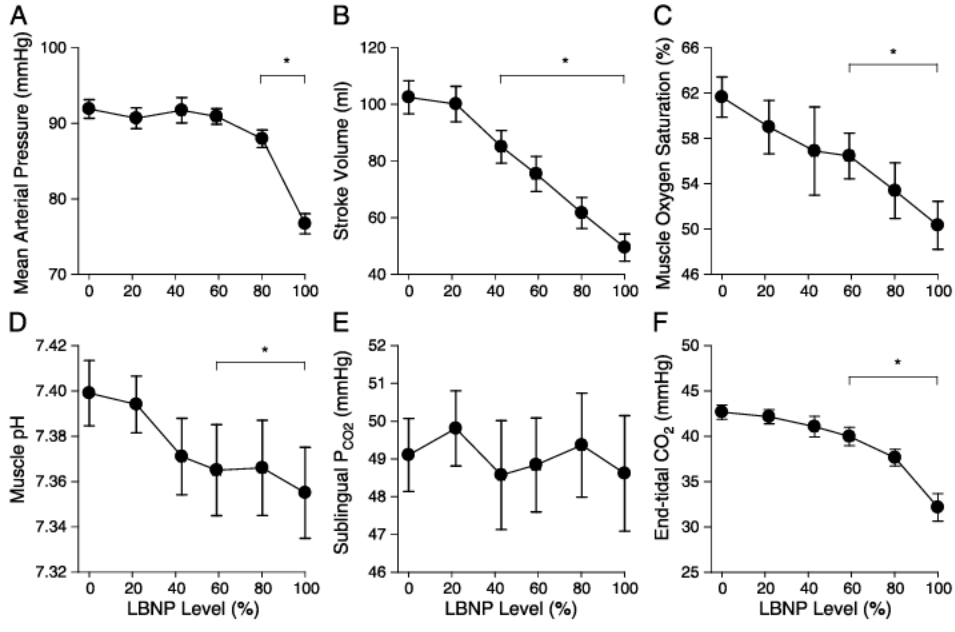

Fig. 2. **Hemodynamic and metabolic variables during the LBNP protocol.** Data are mean ± SE; n = 17 except for muscle oxygen saturation and pH, where n = 16. *$P \leq 0.017$ compared with the baseline value.

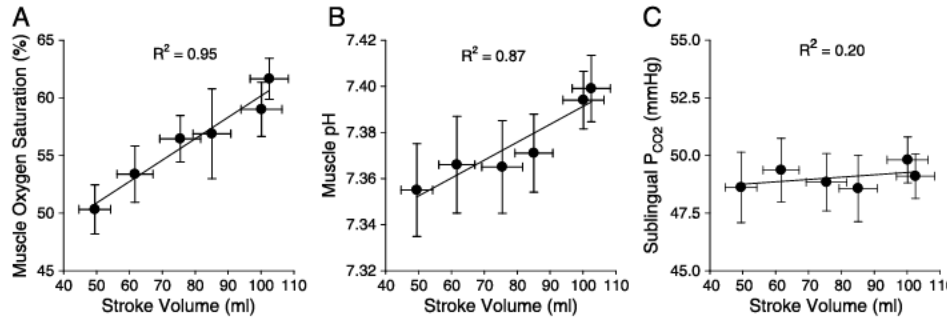

FIG. 3. **Relationship between SV and muscle oxygen saturation (A), muscle pH (B), and sublingual Pco_2 (C).** Data are mean ± SE; n = 16 for muscle oxygen saturation and pH, and n = 17 for sublingual P_{CO_2}.

(Fig. 2), and all of our subjects reached hemodynamic collapse and near-syncope (4, 39). Thus, we can surmise that the degree of hypoperfusion was not likely the reason for the lack of change in $SLCO_2$. In fact, our group recently reported an alteration in sublingual perfusion, via video microscopy, as early as at 20% maximal LBNP, with a maximum decrease of microcirculatory perfusion of 25% at hemodynamic collapse (4). It would seem logical that $SLCO_2$ would follow suit and be elevated shortly thereafter.

A second possibility is that the duration of hypoperfusion was not long enough to result in significant accumulation of CO_2 in the sublingual tissue. Tissue CO_2 can rise via two proposed mechanisms in the setting of low perfusion. First, a low-flow state leads to CO_2 "stagnation" because CO_2 is not able to clear adequately even under conditions in which CO_2 production is normal (40). Second, decreased tissue perfusion leads to a subsequent decrease in oxygen delivery. As tissue perfusion becomes increasingly reduced because of progressive vasoconstriction in the peripheral tissue, oxygen supply to the tissue fails to meet oxygen demand required to maintain the metabolic rate of the cells. At this critical threshold of low oxygen, the cells become dependent on anaerobic metabolism (glycolysis) to provide the energy demands of the tissue that can no longer be met by aerobic metabolism alone (39). The subsequent production of lactic acid results in hydrogen ion production (decreasing pH), which, in combination with bicarbonate buffers, produces water and CO_2 (41). A sufficient duration of tissue hypoperfusion may be necessary for the critical conversion to anaerobic metabolism and significant tissue CO_2 production. In essence, this condition would categorically be defined as true "shock." Our group has previously reported that LBNP provides a unique model for the study of events that occur before the accumulation of blood lactate and base deficit (i.e., preshock) (4). We may need to view $SLCO_2$ in the same light. It is possible that $SLCO_2$ rises only after the accumulation of intracellular lactate and formation of a hydrogen ion gradient that promotes diffusion across the cell membrane. This cascade of events likely takes time to develop. In essence, this could be viewed as a major limitation as we tested a marker of ischemia in a nonischemic model. In our model of progressive LBNP, the average total duration of simulated hypovolemia was 21 min. In the experiment of Steiner et al. (25), where elevations in gastric Pco_2 were also not detected, LBNP was held at 30 mm Hg for 45 min and 40 mm Hg for an additional 30 min (75 min total). Although more than triple the duration, it represents a degree of simulated hypovolemia that is approximately half that induced in our protocol, as indicated by much greater hemodynamic changes (HR increased by 62% vs. 14%; SV decreased by 52% vs. 38%), and the presence of hemodynamic collapse and presyncopal symptoms in our subjects. Perhaps a combination of both a relatively high degree of simulated hypovolemia and a longer duration may be needed to induce tissue ischemia, resultant shock, and subsequent elevations in $SLCO_2$. If this supposition is true, and $SLCO_2$ changes only with a higher degree and duration of hypovolemia, however, the question of "added value" becomes important. That is, if alterations in $SLCO_2$ occur only during severe levels of tissue dysoxia associated with profound hypotension and frank metabolic alterations (e.g., increases in base deficit and lactate), what new information does measurement of $SLCO_2$ provide to the clinician over measurement of these standard clinical values?

A third possibility is that there may be a difference between the induction of gastric mucosal tissue acidosis and CO_2 production during actual hemorrhage and hemorrhage simulated by LBNP. In a human study, Hamilton-Davies et al. (12) induced hemorrhage (via phlebotomy of up to 25% blood volume) in six healthy volunteers and measured various clinical indicators as well as gastric tonometry. They reported increases in gastrointestinal intramucosal CO_2:arterial CO_2 gap and decreases in intramucosal pH that began 30 min after initiation of bleeding (12). Compared with the hemodynamic and gastric pH data reported by Hamilton-Davies et al. (12), however, the physiological stress induced by LBNP to a point of cardiovascular collapse in our experiment was equal to, or greater than, that produced by their 25% bleed in healthy human subjects. Whereas the subjects of Hamilton-Davies et al. (12) displayed only modest reductions in SAP (~13%) and SV (~16%) with little elevation in HR from a baseline of 65 beats/min, our subjects demonstrated hypotension at cardiovascular collapse (presyncope) coincident with a 52% reduction in SV and tachycardia of 102 beats/min. Furthermore, the average change in intestinal pH from baseline to maximum bleed (7.39 to 7.32) in the subjects with actual blood loss (12) was similar to that in muscle pH in the subjects of the present investigation (7.40 to 7.35; Fig. 2). Given this comparison and the pronounced reductions in splanchnic blood flow associated with LBNP (22–24), it seems unlikely that the absence of a change in $SLCO_2$ in our subjects could be explained by the inadequacy of our LBNP protocol to induce regional hypoperfusion any less than that caused by actual bleeding.

In contrast, tissue hypoperfusion appears to result in almost immediate forearm muscle dysoxia as detected by a steady and reproducible decrease in SmO_2 with each progressive LBNP level (Fig. 2). Our current observation of reduced SmO_2 in this experiment reproduced the exact same pattern observed and reported in a prior experiment (21). For the purpose of early detection of hypovolemia, SmO_2 appears highly sensitive and, therefore, very promising for clinical application. Clinical trials are clearly needed to further investigate whether this method of detecting subclinical hypovolemic shock can be helpful to bedside providers.

Some limitations exist for our study. Mesenteric flow, sublingual perfusion, gastric P_{CO_2}, lactate, and base deficit were not directly measured in this experiment. Various assumptions and comparisons made throughout this article are based on observations we reported previously in the same model and corroborated by others (4, 25, 42). However, reproducibility of our LBNP model has been well established (4, 21, 39, 43), and no significant demographic differences exist in terms of sex, age, height, and weight between our current experiment and others we have performed. Thus, we can reasonably assume that measurements and observations seen and reported in prior experiments using the same model hold true for our current experiment. In addition, it is important to note that this model does not take into consideration tissue injury, pain, or anesthetic agents encountered in clinical scenarios. Thus, we are careful to avoid suggesting that identical measurements would be obtained in the complex clinical environment. On the other hand, use of this "clean" laboratory model may also be seen as a benefit, as we were able to assess the relationship between $SLCO_2$ and reduced central volume without confounding factors such as tissue injury and painful stimuli that might affect autonomic nervous system activity. Therefore, our results may be the first to strictly demonstrate the poor relationship between reduced SV and $SLCO_2$ in human subjects. Our model is a preclinical test bed designed to generate and test various hypotheses that should optimize the design and conduct of future definitive clinical trials.

CONCLUSIONS

Although we were able to reproduce the results seen in prior experiments with decreases observed in SmO_2, $ETCO_2$, SV, and MAP with progressive LBNP, we did not detect metabolic derangements in the sublingual mucosa as measured by $SLCO_2$. Thus, $SLCO_2$ may not be a sensitive marker of early hypoperfusion before the onset of clinical shock. Animal studies with more prolonged degrees and duration of ischemia to the point of true physiologic shock may better characterize the exact time point in which $SLCO_2$ may be detected in the continuum of hypovolemic shock. Importantly, early markers of tissue hypoperfusion and dysoxia such as SmO_2, which are abnormal long before true shock, may have utility and require clinical study.

ACKNOWLEDGMENTS

The authors thank their subjects for their participation and cooperation. They acknowledge Mr. Gary Muniz for his outstanding technical assistance. In addition, they are grateful for the technical assistance provided by ExoStat Medical Inc, as well as the near-infrared spectroscopy equipment and data analysis provided by Dr. Babs Soller for muscle O_2 and pH. Finally, they thank Ms. Otilia Sánchez for her assistance in proofreading and editing the manuscript.

REFERENCES

1. Tisherman SA, Barie P, Bokhari F, Bonadies J, Daley B, Diebel L, Eachempati S, Kurek S, Luchette F, Carlos Puyana J, et al: Clinical practice guideline: endpoints of resuscitation. *J Trauma* 57(4):898 912, 2004.
2. Abou-Khalil B, Scalea TM, Trooskin SZ, Henry SM, Hitchcock R: Hemodynamic responses to shock in young trauma patients: need for invasive monitoring. *Crit Care Med* 22(4):633 639, 1994.
3. Scalea TM, Hartnett RW, Duncan AO, Atweh NA, Phillips TF, Sclafani SJ, Fuortes M, Shaftan GW: Central venous oxygen saturation: a useful clinical tool in trauma patients. *J Trauma* 30(12):1539 1543, 1990.
4. Ward KR, Tiba MH, Ryan KL, Torres Filho IP, Rickards CA, Witten T, Soller BR, Ludwig DA, Convertino VA: Oxygen transport characterization of a human model of progressive hemorrhage. *Resuscitation* 81(8):987 993, 2010.
5. Kivilaakso E, Ahonen J, Aronsen KF, Hockerstedt K, Kalima T, Lempinen M, Suoranta H, Vernerson E: Gastric blood flow, tissue gas tension and microvascular changes during hemorrhage-induced stress ulceration in the pig. *Am J Surg* 143(3):322 330, 1982.
6. Vallet B, Lund N, Curtis SE, Kelly D, Cain SM: Gut and muscle tissue P_{O_2} in endotoxemic dogs during shock and resuscitation. *J Appl Physiol* 76(2):793 800, 1994.
7. McKinley BA, Butler BD: Comparison of skeletal muscle P_{O_2}, P_{CO_2}, and pH with gastric tonometric $P(CO_2)$ and pH in hemorrhagic shock. *Crit Care Med* 27(9):1869 1877, 1999.
8. Clavijo-Alvarez JA, Sims CA, Pinsky MR, Puyana JC: Monitoring skeletal muscle and subcutaneous tissue acid-base status and oxygenation during hemorrhagic shock and resuscitation. *Shock* 24(3):270 275, 2005.
9. Chen R, Fan F, Schuessler G, Simchon S, Kim S, Chien S: Regional cerebral blood flow and oxygen consumption of the canine brain during hemorrhagic hypotension. *Stroke* 15(2):343 350, 1984.
10. Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM: A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH. *J Am Coll Surg* 183(2):145 154, 1996.
11. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, et al: Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 339(8787):195 199, 1992.
12. Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR: Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 23(3):276 281, 1997.
13. Santoso JT, Wisner DH, Battistella FD, Owings JT: Comparison of gastric mucosal pH and clinical judgement in critically ill patients. *Eur J Surg* 164(7): 521 526, 1998.
14. Fink MP: Tissue capnometry as a monitoring strategy for critically ill patients: just about ready for prime time. *Chest* 114(3):667 670, 1998.
15. Povoas HP, Weil MH, Tang W, Moran B, Kamohara T, Bisera J: Comparisons between sublingual and gastric tonometry during hemorrhagic shock. *Chest* 118(4):1127 1132, 2000.
16. Pellis T, Weil MH, Tang W, Sun S, Csapozi P, Castillo C: Increases in both buccal and sublingual partial pressure of carbon dioxide reflect decreases of tissue blood flows in a porcine model during hemorrhagic shock. *J Trauma* 58(4):817 824, 2005.
17. Totapally BR, Fakioglu H, Torbati D, Wolfsdorf J: Esophageal capnometry during hemorrhagic shock and after resuscitation in rats. *Crit Care (London, England)* 7(1):79 84, 2003.
18. Baron BJ, Dutton RP, Zehtabchi S, Spanfelner J, Stavile KL, Khodorkovsky B, Nagdev A, Hahn B, Scalea TM: Sublingual capnometry for rapid determination of the severity of hemorrhagic shock. *J Trauma* 62(1):120 124, 2007.
19. Cooke WH, Ryan KL, Convertino VA: Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J Appl Physiol* 96(4):1249 1261, 2004.
20. Arbeille P, Kerbeci P, Mattar L, Shoemaker JK, Hughson R: Insufficient flow reduction during LBNP in both splanchnic and lower limb areas is associated with orthostatic intolerance after bedrest. *Am J Physiol Heart Circ Physiol* 295(5):H1846 H1854, 2008.
21. Soller BR, Ryan KL, Rickards CA, Cooke WH, Yang Y, Soyemi OO, Crookes BA, Heard SO, Convertino VA: Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans. *Crit Care Med* 36(1):176 182, 2008.
22. Hinghofer-Szalkay HG, Goswami N, Rossler A, Grasser E, Schneditz D: Reactive hyperemia in the human liver. *Am J Physiol Gastrointest Liver Physiol* 295(2):G332 G337, 2008.

23. Fischer D, Arbeille P, Shoemaker JK, O'Leary DD, Hughson RL: Altered hormonal regulation and blood flow distribution with cardiovascular deconditioning after short-duration head down bed rest. *J Appl Physiol* 103(6):2018 2025, 2007.
24. Hughson RL, Shoemaker JK, Arbeille P, O'Leary DD, Pizzolitto KS, Hughes MD: Splanchnic and peripheral vascular resistance during lower body negative pressure (LBNP) and tilt. *J Gravit Physiol* 11(2):P95 P96, 2004.
25. Steiner LA, Staender S, Sieber CC, Skarvan K: Effects of simulated hypovolaemia on haemodynamics, left ventricular function, mesenteric blood flow and gastric Pco2. *Acta Anaesthesiol Scand* 51(2):143 150, 2007.
26. Hirsch AT, Levenson DJ, Cutler SS, Dzau VJ, Creager MA: Regional vascular responses to prolonged lower body negative pressure in normal subjects. *Am J Physiol* 257(1 Pt 2):H219 H225, 1989.
27. Summers RL, Ward KR, Witten T, Convertino VA, Ryan KL, Coleman TG, Hester RL: Validation of a computational platform for the analysis of the physiologic mechanisms of a human experimental model of hemorrhage. *Resuscitation* 80(12):1405 1410, 2009.
28. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH: Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc Res* 38(3):605 616, 1998.
29. Parati G, Casadei R, Groppelli A, Di Rienzo M, Mancia G: Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. *Hypertension* 13(6 Pt 1):647 655, 1989.
30. Dorlas JC, Nijboer JA, Butijn WT, van der Hoeven GM, Settels JJ, Wesseling KH: Effects of peripheral vasoconstriction on the blood pressure in the finger, measured continuously by a new noninvasive method (the Finapres). *Anesthesiol* 62(3):342 345, 1985.
31. Soller BR, Yang Y, Soyemi OO, Ryan KL, Rickards CA, Walz JM, Heard SO, Convertino VA: Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. *J Appl Physiol* 104(2):475 481, 2008.
32. Jansen JR, Wesseling KH, Settels JJ, Schreuder JJ: Continuous cardiac output monitoring by pulse contour during cardiac surgery. *Eur Heart J* 11(Suppl I): 26 32, 1990.
33. Jin X, Weil MH, Sun S, Tang W, Bisera J, Mason EJ: Decreases in organ blood flows associated with increases in sublingual P_{CO_2} during hemorrhagic shock. *J Appl Physiol* 85(6):2360 2364, 1998.
34. Weil MH, Nakagawa Y, Tang W, Sato Y, Ercoli F, Finegan R, Grayman G, Bisera J: Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. *Crit Care Med* 27(7):1225 1229, 1999.
35. Marik PE: Sublingual capnography: a clinical validation study. *Chest* 120(3): 923 927, 2001.
36. Creteur J, De Backer D, Sakr Y, Koch M, Vencent JL: Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 32(4): 516 523, 2006.
37. Baron BJ, Sinert R, Zehtabchi S, Stavile KL, Scalea TM: Diagnostic utility of sublingual P_{CO_2} for detecting hemorrhage in penetrating trauma patients. *J Trauma* 57(1):69 74, 2004.
38. Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K: Heterogeneous regional vascular responses to simulated transient hypovolemia in man. *Intensive Care Med* 20(6):414 420, 1994.
39. Convertino VA, Ryan KL, Rickards CA, Salinas J, McManus JG, Cooke WH, Holcomb JB: Physiological and medical monitoring for en route care of combat casualties. *J Trauma* 64(Suppl 4):S342 S353, 2008.
40. Knuesel R, Jakob SM, Brander L, Bracht H, Siegenthaler A, Takala J: Changes in regional blood flow and Pco(2) gradients during isolated abdominal aortic blood flow reduction. *Intensive Care Med* 29(12):2255 2265, 2003.
41. Heard SO, Heard SO: Gastric tonometry: the hemodynamic monitor of choice (Pro). *Chest* 123(Suppl 5):469S 474S, 2003.
42. Taneja I, Moran C, Medow MS, Glover JL, Montgomery LD, Stewart JM: Differential effects of lower body negative pressure and upright tilt on splanchnic blood volume. *Am J Physiol Heart Circ Physiol* 292(3):H1420 H1426, 2007.
43. McManus JG, Ryan KL, Morton MJ, Rickards CA, Cooke WH, Convertino VA: Limitations of end-tidal CO_2 as an early indicator of central hypovolemia in humans. *Prehosp Emerg Care* 12(2):199 205, 2008.