

Use of Advanced Machine-Learning Techniques for Non-Invasive Monitoring of Hemorrhage

Victor A. Convertino, Caroline A. Rickards, Carmen Hinojosa-Laborde, Kathy L. Ryan

US Army Institute of Surgical Research
Fort Sam Houston, Texas
USA

victor.convertino@amedd.army.mil

Steven L. Moulton, Gregory Z. Grudic

²Departments of Surgery, University of Colorado, School of Medicine
Aurora, Colorado
USA

ABSTRACT

Hemorrhagic shock is a leading cause of death in both civilian and battlefield trauma. Currently available medical monitors provide the capabilities to measure standard vital signs that are often imprecise, subjective, and inconsistent. More important, the appearance of hypotension and other signs and symptoms of shock represent a point in time when it may be too late to apply effective life saving interventions. The resulting challenge is that early diagnosis is difficult because hemorrhagic shock is first recognized by late-responding vital signs and symptoms. The solution to this dilemma is to identify physiological signal(s) that provides the best early indicators of blood volume loss and impending circulatory failure. We hypothesized that state-of-the-art machine learning techniques when integrated with novel non-invasive monitoring technologies could detect subtle, physiological changes in conscious, healthy humans who underwent progressive reduction in their central blood volume.

Methods

We exposed 28 healthy humans to progressive reductions in central blood volume using lower body negative pressure (LBNP) as a model of hemorrhage until the onset of hemodynamic decompensation. Continuous, non-invasively measured hemodynamic signals (e.g., ECG, blood pressures, stroke volume) were used for the development of machine-learning algorithms. Accuracy estimates were obtained by building models using 27 subjects and testing on the 28th. This process was repeated 28 times, each time using a different subject.

Results

Our method was 96.5% accurate in predicting the amount of central blood volume reduction (i.e., level of LBNP). The correlation between predicted and actual LBNP level for hemodynamic decompensation was 0.89.

Conclusion

Machine modeling can accurately identify loss of central blood volume and predict the point at which an individual will experience hemodynamic decompensation (onset of shock). Such a capability can provide decision support for earlier identification of blood loss and need for intervention.

Report Documentation Page

Form Approved
OMB No. 0704-0188

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

1. REPORT DATE APR 2010		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Use of Advanced Machine-Learning Techniques for Non-Invasive Monitoring of Hemorrhage				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) US Army Institute of Surgical Research Fort Sam Houston, Texas USA				8. PERFORMING ORGANIZATION REPORT NUMBER	
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 See also ADA564622. Use of Advanced Technologies and New Procedures in Medical Field Operations (Utilisation de technologies avancees et de procedures nouvelles dans les operations sanitaires). RTO-MP-HFM-182					
14. ABSTRACT Hemorrhagic shock is a leading cause of death in both civilian and battlefield trauma. Currently available medical monitors provide the capabilities to measure standard vital signs that are often imprecise, subjective, and inconsistent. More important, the appearance of hypotension and other signs and symptoms of shock represent a point in time when it may be too late to apply effective life saving interventions. The resulting challenge is that early diagnosis is difficult because hemorrhagic shock is first recognized by late-responding vital signs and symptoms. The solution to this dilemma is to identify physiological signal(s) that provides the best early indicators of blood volume loss and impending circulatory failure. We hypothesized that state-of-the-art machine learning techniques when integrated with novel non-invasive monitoring technologies could detect subtle, physiological changes in conscious, healthy humans who underwent progressive reduction in their central blood volume.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT SAR	18. NUMBER OF PAGES 12	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

1.0 INTRODUCTION

Accurate, early diagnosis and application of life saving interventions for the treatment of hemorrhage prior to the development of circulatory shock is a high priority for the Army Medical Department since hemorrhage is a leading cause of death on the battlefield [3,23]. Survival rates increase when patients requiring immediate intervention are correctly identified in a mass-casualty scenario, but methods of prioritizing casualties based on current triage algorithms are severely limited. In critical trauma and combat casualty care medicine, a profound need exists for improved physiological algorithms that will provide a reliable early indication of survival outcome [21,28,43]. Despite ongoing study, mental status, pulse character, and low blood pressure (systolic < 90 mmHg) are still considered to be the best indicators of the need for life-saving interventions [1,19,26,36], even though the unreliability of arterial blood pressure as an early indicator of blood loss was recognized as early as the World War II era [20,35].

The role-I medical practitioner (including combat medics, physician assistants, and field surgeons) is currently limited to the assessment of mental status, pulse character and pulse rate measurements for diagnosis of wounded soldiers. Even in special operation forces, it is rare that standard blood pressure (BP) and pulse oximetry (SaO₂) will be available. However, compensatory mechanisms that buffer against changes in BP and SaO₂ make these measurements poor indicators for *early* detection of the severity of hemorrhage [42]. Although pulse rate is also available, there exist several confounding etiologies for tachycardia, including recent physiological exertion, hydration status, ambient temperature, and epinephrine release due to anxiety and/or fear in response to threats, which collectively serve to compromise its specificity as a sign of emerging hemorrhagic shock. Therefore, the absence or presence of hypotension as measured by changes in mental status, pulse character, and/or pulse rate can be misleading since it does not represent the underlying physiology of compensated hemorrhage that eventually leads to the development of overt shock. Subsequently, the appearance of hypotension and other signs and symptoms of shock usually represent a point in time when it may be too late to introduce effective life saving interventions [28]. The resulting challenge is to identify physiological *signals* associated with the underlying compensatory mechanisms of hemorrhage and *technologies* to track these signals so as to provide *early* diagnosis of a patient's risk for developing circulatory shock through measurements of physiological responses associated with the underlying compensatory mechanisms of hemorrhage.

An additional challenge facing battlefield medical personnel is the absence of moment-to-moment physiological measurements obtained from the wounded soldier, limiting decision-making to isolated "snapshot" data points. As a result, rapid decisions about priority of care and application of interventions are made without the benefit of observing trends and the dynamic nature of the evolving physiology of the traumatic injury (and specifically hemorrhage) physiology. Thus, the current process of combat casualty care can be greatly improved by providing specific, sensitive, and continuous physiological observations. It is therefore clear that identification of the best early markers of hemorrhage can only be accomplished by simultaneous and continuous measurement of various physiological signals (compensatory responses) associated with BP regulation that have been proven to be accurate predictors of cardiovascular collapse.

2.0 METHODS

2.1 Experimental Models of Hemorrhage

In 1733, Alexander Pope eloquently stated "Know then thyself, presume not God to scan: The proper study of Mankind is Man". Development of effective procedures to predict the magnitude of hemorrhage and the likelihood for progression to hemorrhagic shock must necessarily be based on carefully-controlled human

experimentation, but experimentally-induced severe bleeding in conscious, unanesthetized humans is not possible. The ability to experimentally study the hemodynamic effects of hemorrhage has been primarily limited to animal studies [15]. Although valuable, application of information derived from such studies to a triage algorithm meant for humans is confounded by species differences (e.g., quadruped vs. biped), particularly regarding blood pressure regulation, and the presence of anesthesia [17].

In the case of human studies in which mild blood loss is induced by voluntary blood donation, the removal of only small percentages of total blood volume is easily compensated for in most cases, so consequently fails to provide a point of hemodynamic decompensation as occurs with greater volumes of blood loss experienced in combat trauma. In order to accomplish the objective of investigating the dynamics of severe hemorrhage in humans, we designed a model to safely and noninvasively induce decompensation in human subjects for reliable prediction of tolerance (e.g., 'survival') outcomes [7,13,15]. We adopted an approach of applying negative pressure to the lower body (below the iliac crest) as a method of investigating cardiovascular mechanisms under conditions of controlled, experimentally-induced hypovolemic hypotension by the redistribution of blood away from the head and heart [7,13,15, Figure 1]. With this approach, we have demonstrated that lower body negative pressure (LBNP) mimics hemodynamic and compensatory responses in conscious healthy humans similar to those observed during the early stages of hemorrhage in anesthetized animal models without attenuating peripheral vasoconstriction [6,22]. The application of LBNP as an experimental surrogate for hemorrhage represents a basic premise for algorithm development; that is, like hemorrhage, we have demonstrated that LBNP reduces central blood volume and cardiac output [7,13,15], increases sympathetic nerve activity [9,15,16], reduces tissue oxygen content and pH [37,38,41], and eventually leads to severe hypotension and hemodynamic decompensation [7-11,13,15,25-27,30-32]. These hemodynamic similarities between the reductions in central blood volume caused by LBNP and bleeding have been recently validated by a computational model of human hemorrhage [39]. Most importantly, extensive experience with induction of hemodynamic decompensation has been demonstrated using LBNP protocols in our laboratory [4-7,10,15,24,33,40], providing the capability to develop algorithms designed to predict a clinically-meaningful target outcome. In the absence of effective resuscitative measures, compensatory reflex mechanisms eventually fail to adequately compensate as LBNP-induced loss in central blood volume gradually increases, and a subsequent collapse of blood pressure regulation ensues [7] with frank onset of hypotension, similar to that reported in humans during severe hemorrhage [2,18,34]. Therefore, application of LBNP provides a method of investigating continuous and simultaneous physiological responses and underlying compensatory mechanisms associated with hemorrhage in human subjects under conditions of controlled, experimentally-induced central hypovolemia. By defining hemodynamic decompensation as the primary outcome variable, we have successfully developed a novel database of physiological responses to progressive central blood volume reduction in more than 150 human subjects that provides the foundation for development of a machine-learning algorithm capable of accurately predicting outcome.

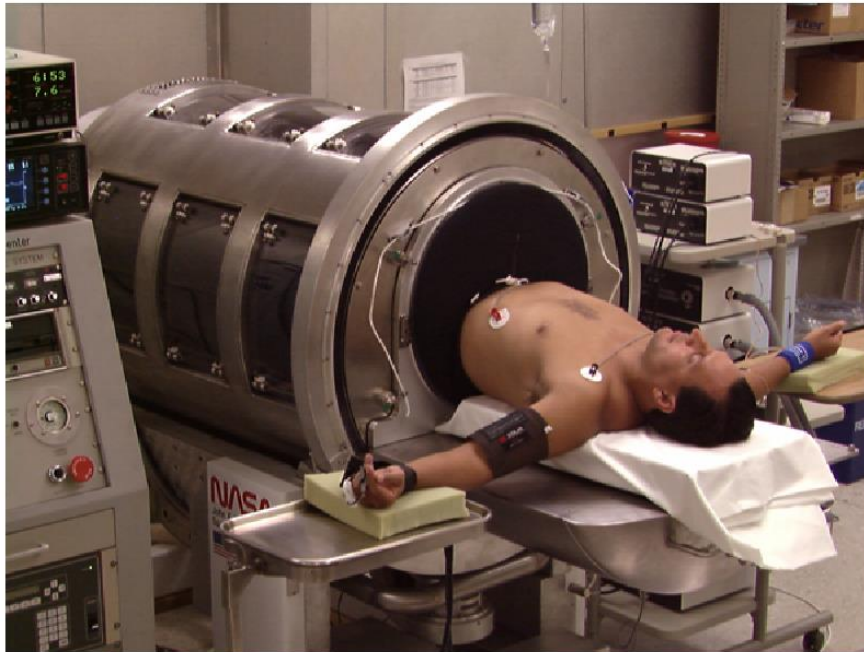


Figure 1: Human subject placed in the lower body negative pressure (LBNP) device. Subject is instrumented with standard lead II ECG, Finometer® Blood Pressure Monitor, and pulse oximeter.

In the presence of compensatory hemodynamic, autonomic and metabolic responses during LBNP, we have studied the dynamics (time course) of standard vital signs. Our experiments verified data reported in the trauma literature that during the early compensatory phase of hemorrhage, there are no clinically-meaningful alterations in mental status [31], pulse character [31], systolic and mean blood pressures [8,13,25,27,31], arterial oxygen saturation [12-14,41], end-tidal CO₂ [27], respiration rate [14], or blood pH and base deficit [41]. These responses are pictorially illustrated in Figure 2. As such, the results from our experiments suggest that humans can lose as much as 40% to 50% of their central blood volume without clinically-meaningful changes in standard vital signs. Our experiments verify that changes in current standard vital signs fail to provide *early* prediction of clinical outcomes, but correlate well with mortality and the need for intervention because they are themselves outcome responses (i.e., outcomes correlate well with outcomes). It is therefore clear that there is a requirement for a device that quickly and reliably detects and estimates the level of blood loss (red line in Figure 2) based on the real-time integration of physiological signals that represent responses of dynamically complex mechanisms during the compensatory phase of hemorrhage (green line in Figure 2). This is the true data gap that exists with current medical monitoring capabilities; i.e., normality and failure of blood pressure regulation can be defined by standard vital signs, but the physiological dynamics that lead from normality to failure cannot be defined by current monitoring technologies (Figure 3). The approach presented in this paper using our LBNP model of hemorrhage is the only one that we are aware of that provides the capability required for the development of a monitor for the early prediction of bleeding and risk for hemodynamic decompensation in humans.

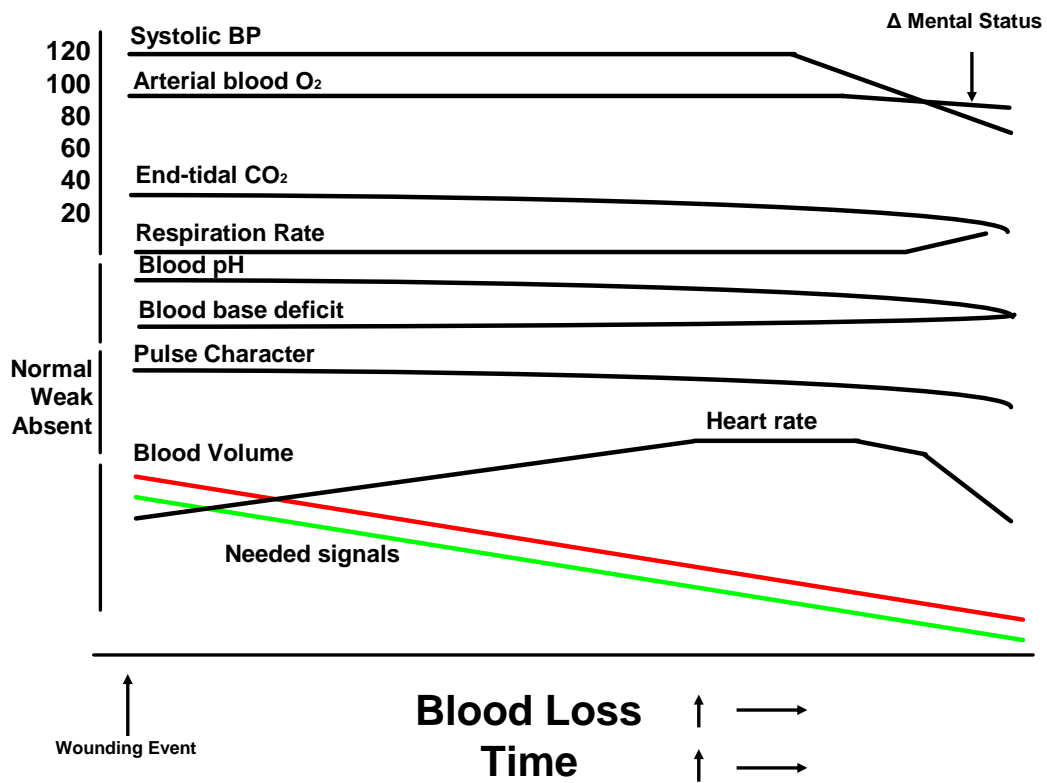


Figure 2: The time course of standard vital signs measured on current medical monitors (black lines) during the dynamic compensatory phase of progressively reduced central blood volume (red line) simulated by LBNP. Green line indicates signals required to track blood loss.

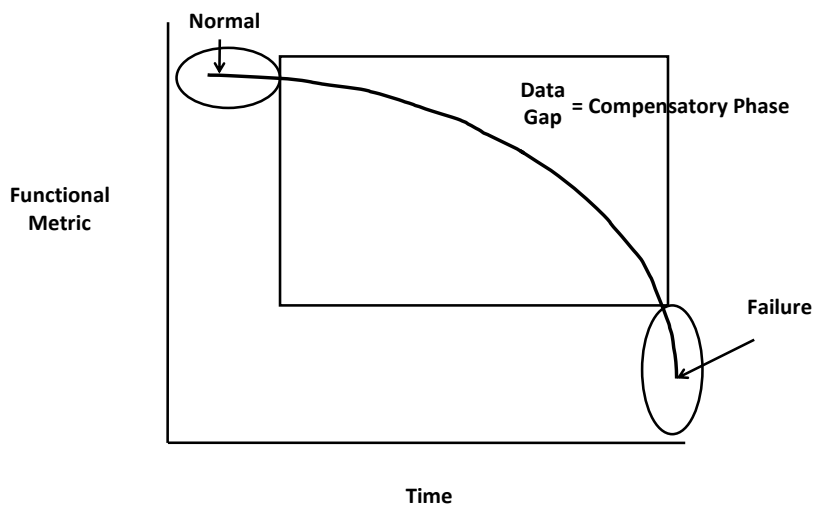


Figure 3: The time course of physiological dynamics that define the 'data gap' that leads from normality to failure of the blood pressure regulation system.

2.2 Algorithm Development

Feature extraction is a useful tool for identifying important phenomena in a noisy or confounded signal. Task or process related knowledge and classic signal processing techniques are used to interrogate large, complex datasets, in order to identify salient events and signals (features). These features are then subjected to powerful modeling methods to find important co-occurrences. For example, high dimensional nonparametric statistical modeling techniques can be applied to complex, multi-input sequences to not only recognize, but predict temporal phenomena. Machine learning is concerned with the design and development of algorithms that can be used to automatically extract information from large volumes of data.

In 2008, we began using feature extraction and machine-learning methods to analyze complex physiological waveform data collected during LBNP experiments. Our goal was to *identify* subtle changes in human physiology that are *predictive* of acute blood loss and cardiovascular collapse. We utilized an image-based, robot navigation system for our machine-learning framework. This system builds linear and nonlinear density models in real-time and is able to process > 100 million pixels or data points/second for the analysis of high frequency waveform data based on experience in building an image-based robot navigation system. This approach was used to analyze continuous, physiological waveform data from 28 healthy humans exposed to progressive central hypovolemia using LBNP until the onset of hemodynamic decompensation. Hemodynamic decompensation was identified in real time by a precipitous fall in systolic blood pressure greater than 15 mmHg concurrent with the onset of pre-syncopal symptoms such as bradycardia, grey-out (loss of color vision), tunnel vision, sweating, nausea or dizziness. The objective was to generate an initial machine-learning algorithm for the early identification of reduction in central blood volume and prediction of hemodynamic decompensation based on continuous, beat-to-beat hemodynamic measurements obtained from a pulse oximeter, transthoracic impedance plethysmography, a near-infrared tissue perfusion monitor, transcranial Doppler flow probe, and a finger infrared photoplethysmography blood pressure monitor (Finometer™, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). Continuous, non-invasively measured physiological signals were analyzed, including RR interval, heart rate, arterial blood pressures, pulse pressure, stroke volume, and cardiac output. Initial sample size was 64 heart beats, after which a new prediction was made with each new beat. Accuracy estimates were obtained by building models using 27 subjects and testing on the 28th. This process was repeated 28 times, each time using a different test subject. The resulting algorithm represented an average of these 28 experiments, giving a statistically unbiased estimate of the efficacy of the algorithm for hypovolemia predictions on future human subjects undergoing the same LBNP protocol.

4.0 RESULTS

Figure 4 demonstrates the curve fit and correlation of predicted, beat-to-beat values of LBNP (blue line) compared with the actual LBNP level (red line) in two of the 28 original subjects. Our method was 96.5% accurate in predicting the amount of central blood volume reduction (i.e., level of LBNP); correlation between predicted and actual LBNP level was 0.94; the correlation between predicted and actual LBNP level for hemodynamic decompensation is 0.89. We subsequently tested the capability of the algorithm to track central blood volume reduction (i.e., LBNP) in real time on a subject whose data were not used to develop the original algorithm (Figure 5). The algorithm tracked the LBNP profile (progressive reduction in central blood volume) and accurately predicted the level of decompensation between -70 and -80 mmHg LBNP (the subject decompensated at 3:55 min of the 5:00 min interval of the -70 mmHg LBNP level prior to reaching -80 mmHg). The algorithm also accurately predicted the level of decompensation in two subsequent subjects. These preliminary results were very encouraging. Interestingly, however, the algorithm incorrectly predicted a higher level of LBNP than the actual level of decompensation in the fourth and fifth real-time tests. We have

previously classified individuals into two distinct tolerance groups: 1) subjects with high tolerance (HT) to reductions in central blood volume because they complete at least the 4th level of LBNP (-60 mmHg); and 2) subjects with low tolerance (LT) to reductions in central blood volume because they fail to complete -60 mmHg LBNP [10,11]. In reviewing the tolerance times of the 5 subjects for whom we applied our machine-learning algorithm, the first 3 subjects were classified as HT while the last 2 subjects were classified as LT. In retrospect, we recognized that a limitation to the development of the initial algorithm was that the majority of the original 28 subjects used to develop the algorithm were HT. We therefore hypothesized that there are characteristics of physiological signals unique to HT and LT subjects that can be identified and integrated into the current algorithm to improve the precision of prediction for both subgroup classifications.

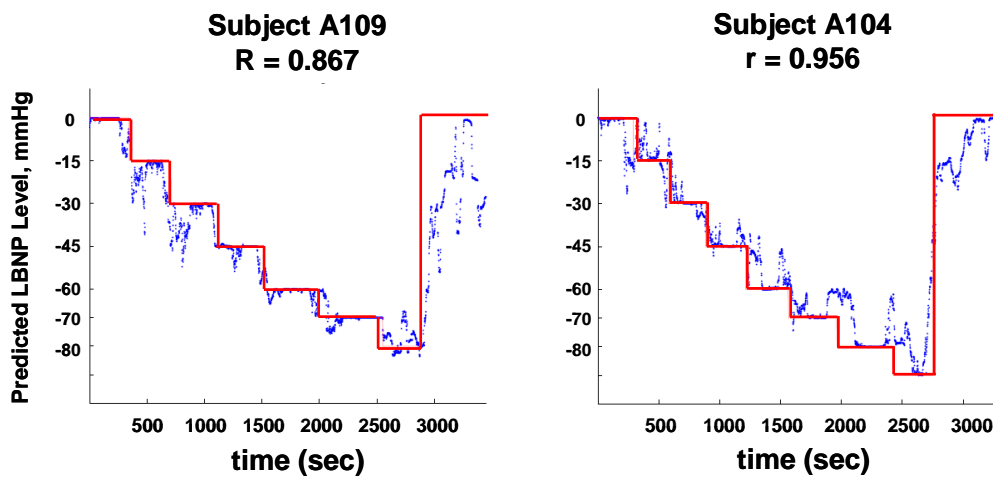


Figure 4: Curve fit and correlation of predicted, moment-to-moment values of LBNP (blue line) compared with the actual LBNP level (red line) in two subjects.

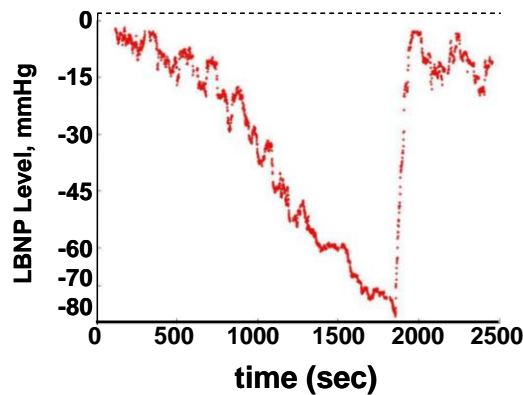


Figure 5: Tracing obtained from the first preliminary algorithm test to track central blood volume reduction in real time on a human subject undergoing progressive LBNP whose data was not used to develop the algorithm.

We subsequently expanded our data set from the original 28 subjects to 104 subjects to refine the algorithm and limited our analysis to only non-invasive blood pressure waveform data. We specifically included data

from both HT and LT subjects. Similar to the initial approach, the latter experiments involved building 104 models, each using 103 subjects and testing on the 104th different test subject each time. Preliminary results using a window size of only 30 heart beats (less than the initial 64 heart beats) revealed a correlation coefficient of 0.95 between predicted and actual LBNP level, with the correlation coefficient between the predicted and actual hemodynamic decompensation level also being 0.95. Although preliminary, the most current model built on data from 104 subjects displays increased accuracy. We subsequently tested the capability of the refined algorithm to track central blood volume reduction in real time on a subject whose data were not used to develop the algorithm (Figure 6). The algorithm now provides the capability to predict the level of blood volume reduction that will induce decompensation (blue line, Fig. 6) and track the progressive reduction in central blood volume (red line, Fig. 6). That is, the algorithm accurately predicted the level of decompensation (i.e., when the red line meets the blue line). Final error analysis for models using more subjects is ongoing; we hypothesize that this model will demonstrate this higher accuracy on future subjects gathered under the same experimental protocol.

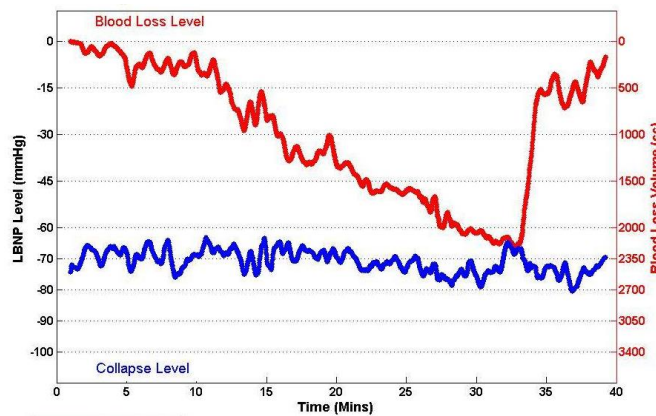


Figure 6: Tracing obtained from the revised preliminary algorithm to predict blood volume level for hemodynamic decompensation (blue line) and track central blood volume reduction (red line) in real time on a human subject undergoing progressive LBNP whose data was not used to develop the algorithm. Decompensation occurred when the red and blue lines met, at which point LBNP was released and blood was returned to the subject.

5.0 DISCUSSION

Hemorrhage is the most prevalent cause of death on the battlefield, accounting for 83% to 87% of the ‘potentially survivable’ deaths [23], and is the primary cause of death in about 30% of the injured soldiers who die from wounds [3]. Some of these deaths might be avoided if military medical personnel had monitors with the capability to assess the presence and severity of hemorrhage in its earliest stages. This point is best described by an email message sent from the 28th Combat Support Hospital in Baghdad on 20 June 2007 by the Director of the Deployed Combat Casualty Care Research Team. The email provided the following scenario: “There are 3 groups of casualties: 1) the ones who are really sick and (almost) everyone knows it; 2) the ones who have minimal injuries and will live almost regardless of what we do; and 3) those who look like they aren't too bad but then deteriorate. (We are) most interested in identifying group 3.” In this scenerio, it is possible that patients in Group 3 actually belong to Group 1, but have not yet manifested signs of overt hemodynamic decompensation at initial triage. As such, it is probable that many of the casualties in ‘group 3’ compose the population of ‘potentially survivable’ deaths in which lethal bleeding goes undiagnosed. This group represents the lives of casualties that could be saved using the approach outlined in this paper.

The Initial Capabilities Document (ICD) for Tactical Combat Casualty Care (TCCC) drafted on 31 March 2006 defines the inability to accurately assess internal injury (e.g., bleeding) as a capability gap at nearly all levels of care. Unfortunately, decision-support systems designed for determining the severity of blood loss or guiding resuscitation in combat casualties do not exist. For pre-hospital transport, the tools available to the medic for decision support are limited to the physical auscultation of the pulse character and assessment of mental status. Current medical monitoring devices used in Combat Support Hospitals provide no earlier prediction of a need to implement a life saving intervention or patient outcome than an on-site physical exam [12]. Thus, a primary objective of the US Army combat casualty care research program is to reduce mortality and morbidity on the battlefield through development of medical technologies that improve trauma triage by providing advanced casualty information continuously throughout all phases of emergency care.

The results presented in this paper demonstrate that machine modelling can quickly and accurately identify loss of central blood volume and predict the point at which individuals will experience hemodynamic decompensation (onset of shock) in advance of changes in standard vital signs. Such a capability can 'buy time' until more definitive care is available by providing timely decision support for earlier identification of blood loss and need of intervention. Since early intervention is associated with reduced morbidity and mortality [29], this machine-learning capability provides a promising approach directed at improving clinical outcomes for combat casualties and civilian trauma patients with unrecognized hemorrhage.

6.0 ACKNOWLEDGEMENTS

This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board, and in accordance with good clinical practices. 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.

7.0 REFERENCES

- [1] Asensio JA, McDuffie L, Petrone P, Roldan G, Forno W, Gambaro E, Salim A, Demetriades D, Murray J, Velmahos G, Shoemaker W, Berne TV, Ramicone E, Chan L. Reliable variables in the exsanguinated patient which indicate damage control and predict outcome. *Am J Surg* 182: 743-751, 2001.
- [2] Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer. Posthemorrhagic fainting. *Lancet* I:489-491, 1944.
- [3] Bellamy RF. The causes of death in conventional land warfare: Implications for combat casualty care research. *Mil Med* 149:55-62, 1984.
- [4] Convertino VA, Sather TM, Goldwater DJ, Alford WR. Aerobic fitness does not contribute to prediction of orthostatic intolerance. *Med Sci Sports Exerc* 18:551-556, 1986.
- [5] Convertino VA. Endurance exercise training: conditions of enhanced hemodynamic responses and tolerance to LBNP. *Med Sci Sports Exerc* 25:705-712, 1993.
- [6] Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 275:R1909-R1920, 1998.

- [7] Convertino VA. Lower body negative pressure as a tool for research in aerospace medicine and military medicine. *J Gravitat Physiol* 8:1-14, 2001.
- [8] Convertino VA, Cooke WH, Holcomb JB. Arterial pulse pressure and its association with reduced stroke volume during progressive central hypovolemia. *J Trauma* 61:629-634, 2006.
- [9] Convertino VA, Ludwig DA, Cooke WH. Stroke volume and sympathetic responses to lower-body negative pressure reveal new insight into circulatory shock in humans. *Auton Neurosci* 111:127-134, 2004.
- [10] Convertino VA, Sather TM. Vasoactive neuroendocrine responses associated with tolerance to lower body negative pressure in humans. *Clin Physiol* 20:177-184, 2000.
- [11] Convertino VA, Sather TM. Effects of cholinergic and adrenergic blockade on orthostatic tolerance in healthy subjects. *Clin Auton Res* 10:327-336, 2000.
- [12] Convertino VA, Ryan KL. Identifying physiological measurements for medical monitoring: implications for autonomous health care in austere environments. *J Gravit Physiol* 14:P39-P42, 2007.
- [13] Convertino VA, Ryan KL, Rickards CA, Salinas J, McManus JG, Cooke WH, Holcomb JB. Physiological and medical monitoring for en route of combat casualties. *J Trauma* 64:S342-353, 2008.
- [14] Convertino VA, Rickards CA, Lurie KG, Ryan KL. Hyperventilation in response to reduction in central blood volume to near syncope. *Aviat. Space Environ. Med.* 80:1012-1017, 2009.
- [15] 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* 96:1249-1261, 2004.
- [16] Cooke WH, Rickards CA, Ryan KL, Kuusela TA, Convertino VA. Muscle sympathetic nerve activity during intense lower body negative pressure to syncope in humans. *J Physiol* 587:4987-4999, 2009.
- [17] Deterling RA, Ngai SH, Laragh JH, Papper EM. The cardiovascular effects of continuous intravenous infusion of norepinephrine, epinephrine and neosynephrine during cyclopropane and ether anesthesia in the dog. *Anesthesiology* 15:11-18, 1945.
- [18] Foex BA. Systemic responses to trauma. *Brit Med Bull* 55:726-743, 1999.
- [19] Franklin GA, Boaz PW, Spain DA, Lukan JK, Carrillo EH, Richardson JD. Prehospital hypotension as a valid indicator of trauma team activation. *J Trauma* 48:1034-1039, 2000.
- [20] Grant RT, Reeve EB. Clinical observations of air-raid casualties. *Br Med J* 2:293-297, 1941.
- [21] Garner A, Lee A, Harrison K, Schultz CH. Comparative analysis of multiple-casualty incident triage algorithms. *Ann Em Med* 38:541-548, 2001.
- [22] Hannon JP. Hemorrhage and Hemorrhagic Shock in Swine: A Review. In: *Swine as Models in Biomedical Research*. Swindle MM (ed). Ames: Iowa State University Press, 1992. p. 197-245.

- [23] Kelly JF, Ritenour AE, McLaughlin DF, Bagg KA, Apodaca AN, Mallak CT, Pearse L, Lawnick MM, Champion HR, Wade CE, Holcomb JB. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J Trauma* 64:S21-S27, 2008.
- [24] Ludwig DA, Convertino VA. Predicting orthostatic intolerance: physics or physiology? *Aviat Space Environ Med* 65:404-411, 1994.
- [25] McGrath SP, Ryan KL, Wendleden SM, Rickards CA, Convertino VA. Alterations in photoplethysmogram features track reductions in central blood volume in a human model of pre-shock hemorrhage. *Anesth Analgesia* 2010 (in press).
- [26] McManus J, Yershov AL, Ludwig DA, Holcomb JB, Salinas J, Dubick MA, Convertino VA, Hinds D, David D, Flanagan T, Duke JH. Radial pulse character relationships to systolic blood pressure and trauma outcomes. *Prehosp Emerg Care* 9:423-428, 2005.
- [27] McManus JG, Ryan KL, Morton MJ, Rickards CA, Cooke WH, Convertino VA. Limitations of end-tidal CO₂ as an early indicator of central hypovolemia in humans. *Prehosp Emerg Care* 12:199-205, 2008.
- [28] Orlinsky M, Shoemaker W, Reis ED, Kerstein MD. Current controversies in shock and resuscitation. *Surg Clin North Am* 81:1217-1262, 2001.
- [29] Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. *Chest* 132:2020-2029, 2007.
- [30] Ryan KL, Cooke WH, Rickards CA, Lurie KG, and Convertino VA. Breathing through an inspiratory threshold device improves stroke volume during central hypovolemia in humans. *J Appl Physiol* 104:1402-1409, 2008.
- [31] Ryan KL, Batchinsky A, McManus JG, Rickards CA, Convertino VA. Changes in pulse character and mental status are late responses to central hypovolemia. *Prehosp Emerg Care* 12:192-198, 2008.
- [32] Ryan KL, Rickards CA, Ludwig DA, Convertino VA. Tracking central hypovolemia with heart period variability in humans: implications of group vs. individual responses for patient monitoring. *Shock* 2009 (in press).
- [33] Sather TM, Goldwater DJ, Montgomery LD, Convertino VA. Cardiovascular dynamics associated with tolerance to lower body negative pressure. *Aviat Space Environ Med* 57:413-419, 1986.
- [34] Secher NH, Jensen KS, Werner C, Warberg J, Bie P. Bradycardia during severe but reversible hypovolemic shock in man. *Circ Shock* 14:267-274, 1984.
- [35] Shenkin HA, Cheney RH, Govons SR, Hardy JD, Fletcher AG Jr, Starr I. On the diagnosis of hemorrhage in man; A study of volunteers bled large amounts. *Am J Med Sci* 209:421-436, 1944.
- [36] Shoemaker WC, Wo CCJ, Chan L, Ramicone E, Kamel ES, Velmahos GC, Belzberg H. Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. *Chest* 120: 528-537, 2001.
- [37] Soller BR, Soyemi OO, Yang Y, Ryan KL, Rickards CA, Walz JM, Heard SO, Cooke WH, Crookes BA, Convertino VA. Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans. *Crit Care Med* 36:176-182, 2008.

- [38] Soller BR, Soyemi OO, Yang Y, Ryan KL, Rickards CA, Walz JM, Heard SO, Convertino VA. Noninvasively measured muscle oxygen saturation is an early indicator of central hypovolemia in humans. *J Appl Physiol* 104:475-481, 2008.
- [39] Summers RL, Ward K, 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* 80:1405-1410, 2009.
- [40] Tatro DL, Dudley GA, Convertino VA. Carotid-cardiac baroreflex response and LBNP tolerance following resistance training. *Med Sci Sports Exerc* 24:789-796, 1992.
- [41] Ward KR, Tiba MH, Ryan KL, Torres I, Rickards CA, Witten T, Soller BR, Ludwig DA, Convertino VA. Oxygen transport characteristics of a human model of progressive hemorrhage. *Shock* 2010 (in press)
- [42] Wo CJ, Shoemaker WC, Appel PL, et al. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med* 21:218-223, 1993.
- [43] Zajtchuk R, Sullivan GR. Battlefield trauma care: focus on advanced technology. *Mil Med* 160:1-7, 1995.