The Special Operations Medical Association's Official Journal

JSOM

UNCONVENTIONAL WARFARE
UNCONVENTIONAL MEDICINE

Spring 2016
Volume 16, Edition 1

JOURNAL *of* SPECIAL OPERATIONS MEDICINE™

THE JOURNAL FOR OPERATIONAL MEDICINE AND TACTICAL CASUALTY CARE

Inside this Issue:

- Case Report: Needling Techniques for Chronic Neck Pain
- Case Report: Machine Learning and Hemodynamic Instability
- In Brief: Comparing C-A-T® Gen 6 to Prototype Gen 7
- TCCC Guidelines: XStat™ Sponge for External Hemorrhage
- Comparison of Tactical Tourniquets
- Junctional Tourniquet Testing for Groin Hemorrhage
- SOF Testing of CRoC and JETT Tourniquets
- Triage Accuracy and Reliability During OEF
- Point-of-Care Ultrasound Update
- Editorials: SOLCUS After-Action Report, USASOC Division of Science & Technology, Traumatic Brain Injury, and Power to the People
- Letters to the Editor: Needle Decompression and The Hartford Consensus
- Ongoing Series: Clinical Corner, Human Performance Optimization, Infectious Diseases, Injury Prevention, Law Enforcement & Tactical Medicine, Operational Medicine in the Austere Environment, Picture This, Prolonged Field Care, Special Talk, World of Special Operations Medicine, TCCC Updates, TacMed Updates, *and more!*

Dedicated to the Indomitable Spirit and Sacrifices of the SOF Medic

A Peer-Reviewed Journal that Brings Together the Global Interests of Special Operations' First Responders

Compensatory Reserve for Early and Accurate Prediction of Hemodynamic Compromise

Case Studies for Clinical Utility in Acute Care and Physical Performance

Camille L. Stewart, MD; Corinne D. Nawn, BS; Jane Mulligan, PhD;
Greg Grudic, PhD; Steven L. Moulton, MD; Victor A. Convertino, PhD

ABSTRACT

Background: Humans are able to compensate for significant loss of their circulating blood volume, allowing vital signs to remain relatively stable until compensatory mechanisms are overwhelmed. The authors present several clinical and performance case studies in an effort to demonstrate real-time measurements of an individual's reserve to compensate for acute changes in circulating blood volume. This measurement is referred to as the Compensatory Reserve Index (CRI). **Methods:** We identified seven clinical and two physical performance conditions relevant to military casualty and operational medicine as models of intravascular volume compromise. Retrospective analysis of photoplethysmogram (PPG) waveform features was used to calculate CRI, where 1 represents supine normovolemia and 0 represents hemodynamic decompensation. **Results:** All cases had CRI values suggestive of volume compromise (<0.6) not otherwise evident by heart rate and systolic blood pressure. CRI decreased with reduced central blood volume and increased with restored volume (e.g., fluid resuscitation). **Conclusion:** The results from these case studies demonstrate that machine-learning techniques can be used to (1) identify a clinical or physiologic status of individuals through real-time measures of changes in PPG waveform features that result from compromise to circulating blood volume and (2) signal progression toward hemodynamic instability, with opportunity for early and effective intervention, well in advance of changes in traditional vital signs.

Keywords: *Compensatory Reserve Index; machine learning; photoplethysmography; shock; testing, orthostatic; physical exercise*

Introduction

Continuous assessment of clinical or performance consequences related to reduced circulatory blood volume is one of the most difficult tasks in civilian medicine, as well as military clinical and operational medicine.[1] This assessment is usually made by physical examination and a review of traditional vital signs, especially some combination of heart rate (HR), blood pressure (BP), respiratory rate, oxygen saturation, and mental status. These vital signs can prove to be unreliable.[2–6] This is especially true for young healthy people (e.g., children, athletes, military personnel), who are able to compensate for comparatively larger volume losses without evidence of compromise.[7] When individuals do decompensate, the process can be sudden and unpredictable.[4,7]

Technology to detect and track compensated hemorrhage that is more sensitive and specific than "legacy" vital signs remains a capability gap in military emergency medicine. In an effort to address this gap, photoplethysmogram (PPG) waveform signals were recorded from a large cohort of healthy volunteers by investigators at the US Army Institute of Surgical Research (USAISR) to study individual responses to hemorrhage-like reductions in central blood volume.[8,9] Advanced signal processing and machine-learning techniques were used by researchers at the University of Colorado to analyze the entirety of millions of PPG waveforms generated during the USAISR experiments. This work led to the discovery of multiple, previously unidentified waveform features, which represent the integration of all mechanisms that enable a human to compensate for acute reductions in central blood volume (e.g., hemorrhage, dehydration). This physiologic phenomenon is described as the compensatory reserve,[8] and the algorithm used to calculate this reserve capacity is called the Compensatory Reserve Index (CRI).[5,8,10] The CRI acts like a "fuel gauge," indicating the proportion of additional circulating blood volume loss a patient can tolerate before the onset of hemodynamic decompensation. CRI values range from 1 to 0 and correspond with the body's ability to compensate for acute changes in intravascular volume.[8,10] When a patient loses intravascular volume due to bleeding or dehydration, the "fuel tank" begins to empty and CRI goes down. We thus hypothesized that CRI values would parallel changes in central blood volume status over time specific to individuals whose physiologic reserve to compensate had been compromised. As an initial interrogation of our hypothesis, we present several case studies to demonstrate the potential clinical and operational utility of the CRI in a variety of emergency medical and human performance settings that are relevant to military medicine.

Materials and Methods

For clinical cases 1–6, consent or waiver of consent was obtained from each patient after study approval was obtained from the Colorado Multiple Institution Review Board (IRB) or the Brooke Army Medical Center IRB. CRI data were obtained from small pulse oximetry-based DataOx or CipherOx devices (Flashback Technologies; http://www.flashbacktechnologies.com) and vital sign data were recorded on a BedMasterEx system (Excel Medical; http://excel-medical.com). These devices were applied in the emergency department (ED) and used to record data as a patient traveled from the ED to radiology and the operating room or intensive care unit (ICU). Deidentified PPG waveform data from select patients of interest were analyzed independently without any reference to clinical scenarios or therapeutic interventions. Clinical information from the patient medical records was then correlated with CRI results.

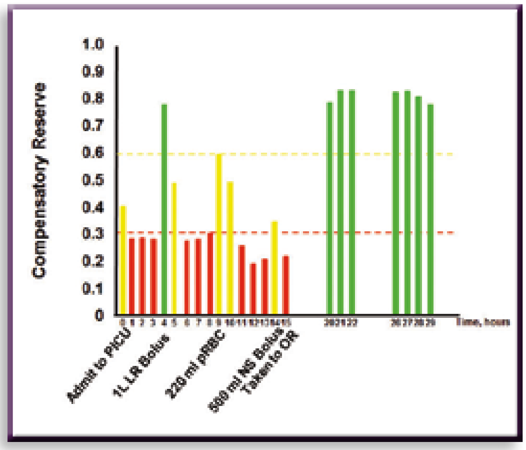
For experimental cases 7 and 9, written consent to use collected data was obtained from each subject before their participation in a laboratory demonstration. For case 8, consent was obtained after receiving study approval from the University of Texas Southwestern Medical Center IRB. For study case 8, CRI values were calculated from PPG waveforms recorded from a Finometer BP monitor (Finapres Medical Systems; http://www.finapres.com) during exposure to progressive lower-body negative pressure (LBNP) with and without exposure to a heat stress (protocol details are presented under Results). For study cases 7 and 9, CRI values were recorded directly and continuously on a CipherOx device during graded exercise (protocol details presented under Results).

Results

Case 1: Patient With Acute Blood Loss Due to Trauma Followed by Sepsis

A 15-year-old, unhelmeted, male bicyclist was struck by an automobile and dragged 250 feet. Initial evaluation noted tachycardia and hypotension, followed by 4L of intravenous (IV) crystalloid resuscitation. He arrived at a Level I trauma center ED with an HR of 146 beats per min (bpm) and BP of 99/61mmHg after a 1-hour transport. A focused abdominal sonography for trauma (FAST) examination was negative for free intra-abdominal fluid, and trace intraperitoneal free fluid was noted on an abdominal computed tomography (CT) scan. The patient was admitted to the pediatric ICU (PICU), where monitoring began (Figure 1). CRI after arrival in the PICU was initially 0.4 but quickly declined to <0.3 within 1 hour (i.e., loss of compensatory reserve). As the day progressed, the patient complained of increasing abdominal pain. Three hours after admission to the PICU, the patient received 1L of lactated Ringer's solution, which was successful in restoring his compensatory reserve to 0.8, but after 2 hours, the CRI drifted to <0.3. Subsequent infusions of packed red blood cells (PRBCs) and saline restored some reserve, but the CRI eventually fell to <0.2. The patient's HR and BP remained relatively stable throughout this period; 14 hours after admission to the PICU, the patient reached a nadir CRI of 0.12, with an HR of 148 bpm, and BP of 115/48mmHg. Shortly thereafter, he had a large emesis and rapidly decompensated, becoming unresponsive, hypotensive, and bradycardic. This prompted an emergent exploratory laparotomy, where two jejunal perforations were discovered. Significant reduction of this patient's compensatory reserve within the initial hours in the PICU was contrasted by his stable BP and adequate urine output. Successful surgery was reflected by postoperative restoration maintenance of his CRI to >0.8.

Figure 1 *The compensatory reserve measured over 29 hours in a pediatric trauma patient admitted to the PICU with acute blood loss due to trauma followed by development of sepsis.*



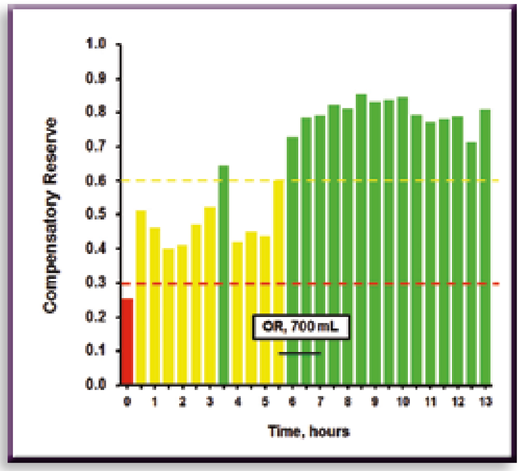
Each bar represents 1 hour. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI ≤0.3. LR, lactated Ringer's; NS, normal saline; OR, operating room; PICU, pediatric intensive care unit; pRBC, packed red blood cells.

Case 2: Patient With Acute Appendicitis

A 10-year-old boy presented to the ED following 12 hours of abdominal pain. He was febrile and normotensive (systolic BP [SBP], 118mmHg) but tachycardic with an HR of 108 bpm, and a white blood cell count of 18.6 × 10^9 L. CT scan of the abdomen showed evidence of acute appendicitis. His last oral intake was 10 hours before the initiation of monitoring, and he received antibiotics and maintenance fluids. The patient's preoperative

CRI corroborated this history, with an average value of 0.48 (Figure 2). The child underwent a laparoscopic appendectomy for acute, nonperforated appendicitis and received 700mL of crystalloid solution (14.4mL/kg). His CRI rose to normal values by the conclusion of surgery (average postoperative CRI, 0.85).

Figure 2 *The compensatory reserve measured over 13 hours in a pediatric patient with appendicitis before and after surgery.*



Each bar represents 30 minutes. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI ≤0.3. OR, operating room.

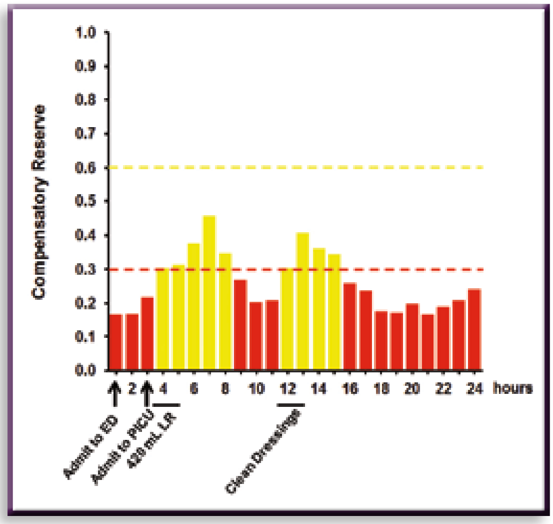
Case 3: Patient With Burn Injury

A 13-year-old girl sustained a 10% total body surface area burn injury to her face, arms, and hands from a propane explosion. She was admitted to the PICU to monitor her respiratory status. She was given 500mL of resuscitative fluids before PICU arrival and another 500mL on arrival to the PICU, where she was placed on maintenance IV fluids. Her CRI briefly increased after the second crystalloid bolus, hitting a peak of 0.6 (Figure 3). This effect was transient. For most of the day, CRI remained <0.3. The patient was tachycardic (HR, 104 ± 1 bpm; range, 80–135 bpm) but generally normotensive (systolic [SBP], 111 ± 1mmHg; range, 133–88mmHg). The patient's CRI increased transiently during a dressing change in the afternoon but then dropped again to levels <0.3.

Case 4: Patient With Massive Hematemesis

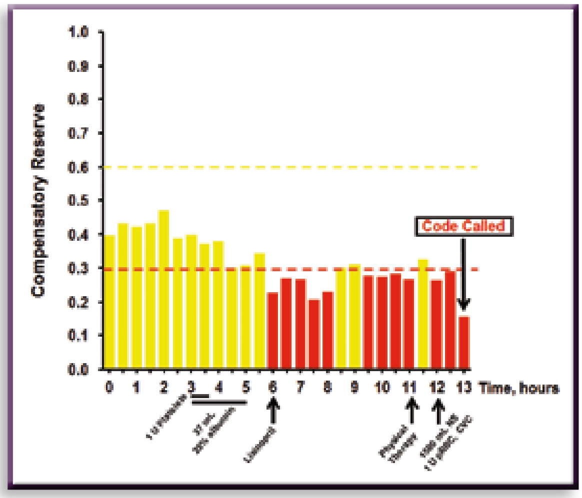
A 12-year-old girl with a past medical history significant for systemic lupus erythematosus requiring steroid immunosuppressive therapy was admitted to the PICU for bacteremia. During hospitalization, she developed hematemesis from a gastric ulcer, which was cauterized. One week after this initial hemorrhage, the patient was noted to be tachycardic (HR, 134 bpm) with a hematocrit of 30%. A chart note indicated "no evidence of acute bleeding." On her final day of care, CRI was initially recorded at 0.4–0.5 (Figure 4). At approximately 06:00, the patient's CRI began to trend downward, but her HR (range, 130–150 bpm), SBP (range, 98–122mmHg), and urine output remained stable into the afternoon. At approximately 15:30, during a physical therapy session, the patient began to vomit large volumes of blood. She rapidly became hypotensive and a code was called. She was given 1.45L of normal saline and 1 unit PRBCs. Her follow-up hematocrit was 16%. Her CRI reached a nadir of 0.17 at 16:28, immediately before the time that the patient was rushed to the operating room, where she died.

Figure 3 *The compensatory reserve measured over 24 hours in a pediatric burn patient admitted to the pediatric intensive care unit.*



Each bar represents 30 minutes. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI ≤0.3. ED, emergency department; LR, lactated Ringer's solution; PICU, pediatric intensive care unit.

Figure 4 *The compensatory reserve measured over 13 hours in a pediatric patient with life-threatening hematemesis.*

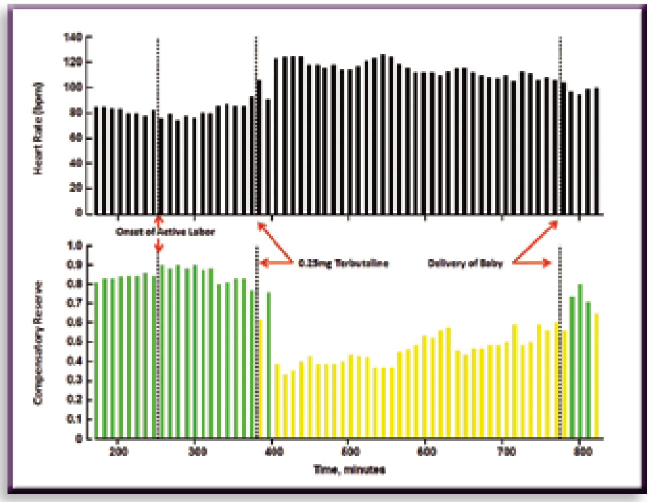


Each bar represents 30 minutes. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI ≤0.3.

Case 5: Healthy Woman During Active Labor

A healthy, normotensive (baseline BP, 115/75mmHg), 34-year-old woman (71.67kg, 157.5cm) was admitted to labor and delivery at 37.9 weeks' gestation of her first child. CRI measures were continuously recorded and averaged over approximately 10-minute periods (Figure 5). The patient's baseline average CRI was 0.83 and remained at 0.83 after she received an epidural anesthetic at around 137 minutes. She began active labor at 257 minutes. After the onset of active labor, CRI showed slight elevation as the patient experienced more frequent and intense contractions. At 365 minutes, the patient experienced a 5-minute uterine contraction associated with a reduction in CRI from 0.82 to 0.76. Immediately following IV administration of 0.25mg terbutaline (a β_2-adrenergic receptor agonist) as a tocolytic, the patient's HR increased (Figure 5, top panel); coincident BP fluctuations were between hypertensive (approximately 130/75mmHg) and baseline levels. With terbutaline administration, CRI initially decreased to 0.38 and remained low (>0.4) for the following 150 minutes. After 4 hours of active pushing, the patient delivered a viable male infant (3.38kg) via vaginal birth at 772 minutes, with an estimated blood loss of 250mL. The CRI returned to >0.7 as the patient recovered and underwent repair of a second-degree perineal laceration. There was no postpartum hemorrhage or further complications.

Figure 5 *Heart rate* **(top)** *and compensatory reserve* **(bottom)** *measured during approximately 7 hours of labor.*

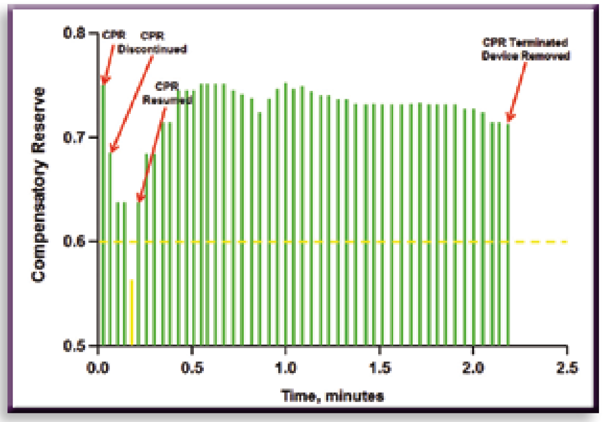


Each bar represents approximately 10 minutes. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; and yellow, CRI ≤0.6 and >0.3.

Case 6: Patient Receiving Cardiopulmonary Resuscitation

A 57-year-old man sustained a self-inflicted gunshot wound to the anterior chest. Medics arrived on scene within minutes and found the patient comatose (Glasgow Coma Scale score, 3) and asystolic. Chest compressions were initiated, and the patient was intubated and given one dose of epinephrine via the endotracheal tube. He was transported to a nearby Level I adult trauma center, where chest compressions were continued and a DataOx device was applied to the patient's index finger, revealing a CRI of 0.75 with active cardiopulmonary resuscitation (CPR). CPR was briefly halted when the patient was transferred from the medics' stretcher to a gurney in the trauma bay. Since CRI is calculated in a beat-to-beat fashion using a sliding 30-beat window, an anticipated drop of CPR to 0 during approximately 10 seconds of chest compression termination (i.e., no perfusing rhythm) was buffered by previous CRI values, resulting in a transient drop in CRI to a low of 0.55. CRI returned to approximately 0.75 with continued active compressions (Figure 6). A FAST examination confirmed no cardiac activity. The patient was pronounced dead within 5 minutes of arrival, and the DataOx device was then removed. Unfortunately, when the patient was pronounced dead and CPR stopped, the data collection device was immediately removed, preventing the demonstration of CRI to 0.

Figure 6 *Continuous Compensatory Reserve Index values during 2.25 minutes of CPR in an asystolic man with a self-inflicted gunshot wound to the chest.*

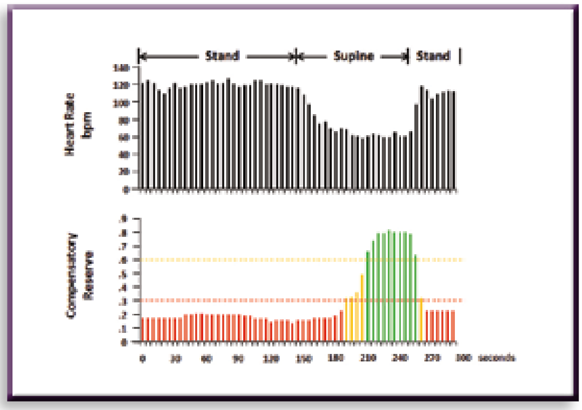


CPR, cardiopulmonary resuscitation.

Case 7: Subject With Postural Orthostatic Tachycardia Syndrome

The CRI was measured during a stand-to-supine demonstration conducted on a 16-year-old girl who had developed postural orthostatic tachycardia syndrome (POTS) 6 years earlier. Figure 7 shows her continuously recorded HR (upper panel) and CRIs (lower panel). She demonstrated a typical tachycardic response (average HR, 120–125 bpm) when she was asked to stand quietly; her average CRI was 0.17. At 3 minutes, the subject was instructed to assume a supine posture. Within 30 seconds, the subject became clinically "normal," with an HR of 60 bpm and CRI >0.8. After 2.5 minutes in the supine posture, the subject stood up, resulting in immediate tachycardia and a drop in her CRI to nearly 0.2.

Figure 7 *Heart rate* **(top)** *and compensatory reserve* **(bottom)** *measured during a 5-minute orthostatic test in a patient with postural orthostatic tachycardia syndrome.*



Each bar represents 5 seconds. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI, ≤0.3.

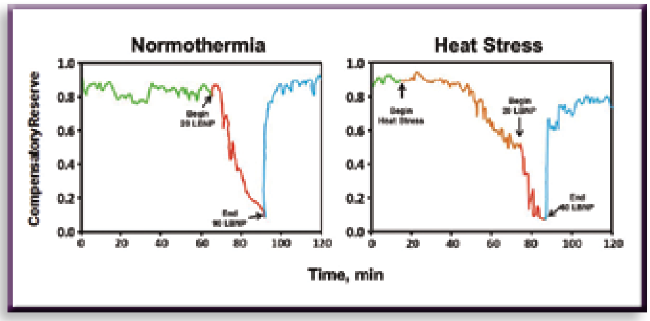
Case 8: Healthy Subject Undergoing Progressive Central Hypovolemia With and Without Heat Stress

Tolerance to central hypovolemia was evaluated in a healthy adult man following whole-body passive heat stress induced by circulating hot water through a water-perfused suit. The heat stress elicited an elevation of approximately 1°C in core (intestinal) temperature. A normothermic trial performed on a separate day was conducted as the control condition. Tolerance to central hypovolemia was quantified as the time to hemodynamic decompensation during progressive LBNP. The compensatory reserve and tolerance to reduced central blood volume under normothermic and heat stress conditions are illustrated in Figure 8. The subject's average baseline CRI was approximately 0.83 for both experimental conditions. Heat exposure before LBNP reduced his CRI to approximately 0.5. Compared with normothermia, heat stress reduced LBNP tolerance time by nearly 50% (from approximately 27 to 14 minutes) and maximal LBNP level from 90 to 60mmHg.

Case 9: Healthy Subject Performing Exercise

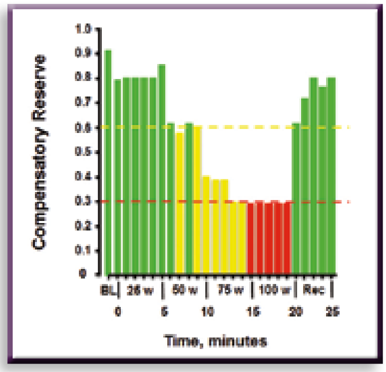
After a 5-minute baseline resting period of sitting in an environment of 100°F and 44% relative humidity, a healthy 22-year-old woman (56.8kg) performed physical exercise at a pedaling rate of 60 rpm with consecutive 5-minute work rates at 25, 50, 75, and 100W on a cycle ergometer, followed by a 5-minute recovery period. Average steady-state oxygen requirement was 653mL/min (25W), 880mL/min (50W), 1,140mL/min (75W), and 1,380mL/min (100W). CRI values recorded every minute are presented in Figure 9. CRI decreased slightly from 0.92 at baseline rest to an average of 0.80 during the 5 minutes of the 25W exercise level. Following a slight transient increase in CRI during the transition from 25W to 50W that coincided with deeper inspiration (i.e., increased tidal volume from 1.0 to 1.8 L), CRI decreased gradually to an average of 0.60 during the 50W exercise level, to approximately 0.40 during the 75W level, and to less than 0.30 during the 100W level. Although restoration of compensatory reserve occurred upon cessation of exercise, it was more gradual and did not return to baseline level.

Figure 8 *The compensatory reserve measured continuously over 2 hours in a healthy adult man during baseline rest* **(green line)**, *heat stress* **(orange line, right panel)**, *progressive reduction in central blood volume* **(red line)**, *and restoration of central blood volume* **(blue line)** *(personal communication, Dr Craig Crandall and coworkers).*



LBNP, lower-body negative pressure.

Figure 9 *The Compensatory Reserve Index measured during a 25-minute, graded-cycle ergometer exercise test performed at 100°F.*



Each bar represents 30 minutes. Bar colors: green, Compensatory Reserve Index (CRI) >0.6; yellow, CRI ≤0.6 and >0.3; red, CRI ≤0.3. BL, baseline; W, watts.

Discussion

Dependence on traditional vital signs to identify hypovolemia in military-relevant medical and operational scenarios is problematic because they do not directly reflect the compensatory response to volume loss; instead, they are outcomes of compensation that only begin to be altered near the onset of physiologic failure. Although standard vital signs are sensitive to volume loss, they are not specific and subsequently can be abnormal for a number of reasons.[11] Diagnosis and early treatment of reduced circulating blood volume associated with hemorrhage or dehydration are top priorities for combat casualty care and military operational medicine. Measurement of the reserve to compensate for relative blood volume deficit has proven to provide a medical capability to the military with the most sensitivity and specificity for blood loss compared with all standard vital signs and hemodynamic measurements.[12] For this report, we intentionally chose nine distinct case studies in an effort to demonstrate the versatility provided by measurement of compensatory reserve in different clinical and operational conditions of central hypovolemia when standard vital signs were generally dismissed as a result of clinical assessments that did not account for compensatory changes. Cases presented here reinforce that the measurement of compensatory reserve can overcome numerous limitations associated with standard vital signs and other clinical assessment techniques, because CRI provides a continuous, real-time, beat-to-beat indicator of patient status and is specific to each patient.

The development and use of technology for real-time arterial-waveform-feature analysis, presented as a green, yellow, and red fuel gauge, was specifically developed for use by Combat Medic who may not have the experience required to accurately and rapidly assess decline in the stability of a bleeding or dehydrated Soldier displaying "normal" mentation because of effective compensation for hypovolemia. Given the challenges of nonspecificity of traditional vital signs and laboratory values, our case studies corroborate that the measurement of compensatory reserve provides the capability needed for the simple, rapid, and accurate assessment of central volume status in acutely ill or traumatically injured patients.

In the cases of hemorrhage presented here, measurement of the compensatory reserve demonstrated a continuous quantitative assessment of the individual patient's reserve remaining to compensate for blood loss. It is critical for military caregivers to appreciate that the patient's status is not dictated by the magnitude of hypovolemia alone but by the capacity of the individual patient to compensate for the volume loss.[12,13] In this regard, casualties with sensitive compensatory mechanisms may not require the immediate treatment needed by those who are "poor" compensators with lower tolerance for hypovolemia.[8,9] The cases we present corroborate earlier findings that measurement of the integrated compensatory reserve based on feature changes of arterial waveforms represents the only known technology that can provide military as well as civilian medical caregivers with a simple, noninvasive capability with superior specificity[8,12,14] for early and accurate triage decision support.[9]

In addition to a clinically continuous, sensitive, and specific evaluation of circulating blood volume loss and its restoration during resuscitation, the monitoring of CRI during child delivery in case 5 demonstrates the efficacy of this technology to provide rapid assessment of pharmacologic impacts that could compromise compensatory response(s). This capability could prove critical to the use of analgesics and anesthetics during pain management on the battlefield and during surgery at higher echelons of battlefield care. In this case, a prolonged uterine contraction was used as a clinical indicator for dosing a β_2-agonist, based on the controversial premise that the use of such tocolytics might prevent perinatal morbidity and mortality.[15] Although the agonist was effective in inhibiting the uterine contraction, the resulting prolonged reduction in peripheral vascular resistance due to vasodilation caused significant blunting of the autonomically mediated vasoconstrictor response, a critical mechanism for compensation. This was reflected in the patient's reflex tachycardia and rapid decrease in compensatory reserve to less than 40% (CRI, <0.4) of the remaining reserve to compensate. Taken together, it is important to recognize that many therapeutic interventions could compromise a patient's ability to adequately respond to a severe hemorrhagic insult. Given that postpartum hemorrhage is a life-threatening event, it was fortunate that this patient experienced very little blood loss (approximately 250mL). As such, this example serves to reinforce the importance of implementing clinical decisions and interventions based on the integrated capacity of the body to maintain an adequate compensatory reserve.

In case 6, the CRI algorithm was able to interrogate CPR-generated waveforms and quantify peripheral perfusion. There was a measureable drop in compensatory reserve when CPR stopped, which returned to approximately 75% (CRI, 0.75) when compressions resumed. The ability of the CRI to interpret the waveforms generated by chest compressions suggests that measurement of compensatory reserve may serve as a useful adjunct for rescuers during resuscitation efforts, since real-time CPR-sensing and feedback technology has been shown to modestly improve the quality of CPR during in-hospital cardiac arrest.[16] As a result of findings from case 6, collection of CRI measurements during CPR are continuing in an effort to test the hypothesis that measurement of the compensatory reserve can be associated with gains in CPR quality and translate into improvements in patient survival.

In addition to clinical orthostatic intolerance affecting one-half million civilians, more than 10,000 active component Servicemembers experience approximately 21,500 cases of syncope in military operational environments annually, with women displaying nearly three times the rate of fainting events as men. Situations associated with syncope in US Armed Forces personnel include invasive medical procedures (e.g., blood donations, other venipunctures, immunizations), standing for long periods (e.g., military formations), and physically demanding training or exercises, especially in hot environments. More importantly, 4% of military syncope cases can result in serious debilitating injuries, including concussions, cerebral lacerations, skull and vertebral fractures, and/or other intracranial injuries.[17] Given these health threats, a simple diagnostic technology that could provide a predictive capability forewarning imminent collapse would prove invaluable in preventing physical collapse and potentially serious injury in military operations. Case 7, the patient with POTS, supports the usefulness of a continuous, real-time measure of compensatory reserve as a sensitive and specific assessment of orthostatic instability when vital signs measurements are neither available nor stable.

The data generated from case 8 demonstrate that measurement of the CRI can quantify in real time the compromise to compensate for blood loss during heat stress that commonly accompanies military activities. An elevation in core temperature of 1°C caused a greater than 30% reduction in the reserve to compensate for reduced central blood volume. Based on hemorrhage estimates,[18] a blood loss of only approximately 1,000mL caused this individual to decompensate in the heat, which normally would require approximately 1,500mL under normothermic conditions. Most significant is that the time to the early decompensatory phase of shock was reduced by nearly 50% in heat, dramatically limiting the time that a medic has to intervene with effective field care. The observation of case 8 has been recently corroborated by findings that the CRI accurately tracks the ability of military personnel to compensate for blood loss when exposed to heat stress and physical activity conditions.[13] As such, real-time measurement of the compensatory reserve could provide an improved decision-support tool for Combat Medics and unit commanders.

In case 9, we were able to demonstrate that measurement of the CRI provided a capability to quantitatively assess the magnitude of compromise to the body's reserve to compensate for the metabolic and thermoregulatory demands of performing progressive increases of work intensity in the heat. Such an application has significant implications for assessment of field performance and warfighter combat readiness. The CRI technology could provide a decision-assist tool for commanders to assess the risk of their units' ability to meet the demands for a successful mission. In addition, the recovery of compensatory reserve following exercise (Figure 9) suggests the potential use of CRI monitoring as a sensitive field hydration monitor that could be used for directing effective fluid replacement. With future investigations designed to study the effectiveness of the CRI in monitoring healthy individuals during activities in military relevant environments (e.g., physical work, heat, cold, altitude), we are corroborating the observations in case 9 that are consistent with a capability for providing Soldiers with real-time military goal-directed physical training and assessment of performance status.

Conclusion

There are several unique aspects of the CRI that make it ideal for clinical and performance applications. It can be easily and noninvasively determined using a PPG-based device and needs no reference baseline; it can be calculated after 30 heartbeats and continuously thereafter. It is easy to use and understand,[19] with lower numbers representing diminishing reserve and higher numbers indicating volume repletion. Importantly, the CRI algorithm can distinguish individuals who have low tolerance to central hypovolemia, thus providing the first monitoring capability, to our knowledge, for early detection of those at highest risk for shock, fainting, or physical fatigue. Last, CRI requires no reference measurement to normovolemia, with a scale that represents the same information for individual subjects.[10] Unlike other parameters, which are based on raw, uninterpreted information that requires synthesis by the caregiver, CRI provides a single new parameter that trends volume change. Results presented here from a series of nine distinctly different physiologic scenarios demonstrate that the ability of each Soldier to sustain an injury or mission-critical performance depend on the reserve to compensate for physiologic compromise. Measurement of the compensatory reserve can anticipate a trajectory of outcome (e.g., shock, fainting, heat stress) resulting from hemodynamic changes secondary to intravascular volume loss well in advance of changes in traditional vital signs. If we continue to find that measurement of the compensatory reserve anticipates hemodynamic compromise or decompensation in advance of changes in standard clinical metrics or subjective symptoms in traumatically injured patients, we hypothesize that CRI will dramatically change how patient volume status is assessed and monitored in military and civilian acute care and emergency medicine scenarios.

Acknowledgments

The authors thank Ms Mariam Calderon and Ms Jessie Fernandez for their assistance in the editorial preparation of the manuscript and Dr Craig Crandall and Dan Gagnon for their contribution of data to case 8.

Funding

This work was supported by the US Army Medical Research and Materiel Command Combat Casualty Research Program (Grants D_009_2014_USAISR, W81X

WH-09-1-0750, W81XWH-09-C-0160, W81XWH-11-2-0091, W81XWH-11-2-0085, and W81XWH-12-2-0112) and the US Army Small Business Innovative Research Program (Grant W81XWH-13-C-0121).

Disclaimers

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. This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

Disclosures

Drs Grudic and Mulligan codeveloped the CRI model used in this study. Dr Moulton is a cofounder and medical consultant to Flashback Technologies, Inc. Drs Stewart and Convertino and Ms Nawn have nothing to disclose.

References

1. **Marik P, Cavallazzi R, Vasu T, et al.** Dynamic changes in arterial wave form derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med.* 2009;37:2642–2647.
2. **Brasel KJ, Guse C, Gentilello LM, et al.** Heart rate: is it truly a vital sign? *J Trauma.* 2007;62:812–817.
3. **King RW, Plewa MC, Buderer NM, et al.** Shock index as a marker for significant injury in trauma patients. *Acad Emerg Med.* 1996;3:1041–1045.
4. **Convertino VA, Ryan KL, Rickards CA, et al.** Physiological and medical monitoring for en route care of combat casualties. *J Trauma.* 2008;64(4 Suppl):S342–S53.
5. **Convertino VA, Moulton SL, Grudic GZ, et al.** Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *J Trauma.* 2011;71(1 Suppl):S25–S32.
6. **Ryan KL, Batchinsky A, McManus JG, et al.** Changes in pulse character and mental status are late responses to central hypovolemia. *Prehosp Emerg Care.* 2008;12:192–198.
7. **Rhee P.** *Sabiston textbook of surgery*. 19th ed. Oxford, UK: Saunders Elsevier; 2012.
8. **Convertino VA, Wirt MD, Glenn JP, Lein BC.** The compensatory reserve for early and accurate prediction of hemodynamic compromise: a review of the underlying physiology. *Shock.* In press.
9. **Convertino VA, Mulligan J, Grudic G, et al.** Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. *J Applied Physiol.* 2013; 115:1196–1202.
10. **Moulton SL, Mulligan J, Grudic G, et al.** Running on empty? The compensatory reserve index. *J Trauma Acute Care Surg.* 2013;75:1053–1059.
11. **Tisherman S, Barie P, Bokhari F, et al.** Clinical practice guideline: endpoints of resuscitation. *J Trauma.* 2004;577:898–912.
12. **Convertino VA, Howard JT, Hinojosa-Laborde C, et al.** Individual-specific, beat-to-beat trending of significant human blood loss: the compensatory reserve. *Shock.* 2015;44(Suppl 1):27–32.
13. **Schlader ZJ, Gagnon D, Rivas E, et al.** Fluid restriction during exercise in the heat reduces tolerance to progressive central hypovolaemia. *Exp Physiol.* 2015;100:926–934.
14. **Janak JC, Howard JT, Goei KA, et al.** Predictors of the onset of hemodynamic decompensation during progressive central hypovolemia: comparison of the peripheral perfusion index, pulse pressure variability, and compensatory reserve index. *Shock.* 2015;44:548-553.
15. **Tsatsaris V, Cabrol D, Carbonne B.** Pharmacokinetics of tocolytic agents. *Clin Pharmacokinet.* 2004;43:833–844.
16. **Abella B, Edelson D, Kim S, et al.** CPR quality improvement during in-hospital cardiac arrest using a real-time audiovisual feedback system. *Resuscitation.* 2007;73:54–61.
17. **Armed Forces Health Surveillance Center.** Syncope, active and reserve components, U.S. Armed Forces, 1998–2012. *MSMR.* 2013;20:5–9.
18. **Hinojosa-Laborde C, Shade RE, Muniz GW, et al.** Validation of lower body negative pressure as an experimental model of hemorrhage. *J Applied Physiol.* 2014;116:406–415.
19. **Muniz GW, Wampler DA, Manifold CA, et al.** Promoting early diagnosis of hemodynamic instability during simulated hemorrhage with the use of a real-time decision-assist algorithm. *J Trauma Acute Care Surg.* 2013;75(2 Suppl 2):S184–189.

Dr Stewart is with the University of Colorado School of Medicine, Department of Surgery, and the Children's Hospital Colorado, Department of Pediatric Surgery, Aurora, Colorado.

Ms Nawn is with the US Army Institute of Surgical Research, Ft Sam Houston, Texas.

Dr Mulligan is with Flashback Technologies Inc., Boulder, Colorado.

Dr Grudic is with Flashback Technologies Inc., Boulder, Colorado.

Dr Moulton is with the University of Colorado School of Medicine, Department of Surgery, and the Children's Hospital Colorado, Department of Pediatric Surgery, Aurora, Colorado; and Flashback Technologies Inc., Boulder, Colorado.

Dr Convertino is with the US Army Institute of Surgical Research, Ft Sam Houston, Texas. E-mail: victor.a.convertino.civ@mail.mil.