Measuring the compensatory reserve to identify shock

Victor A. Convertino, PhD *and* **Alicia M. Schiller, PhD**, *Fort Sam Houston, Texas*

Shock is classically defined as inadequate tissue perfusion,[1–4] and associated with clinical markers such as low systolic blood pressure (<90 mm Hg), elevated heart rate (>120 bpm), increased respiration rate (>20 breaths per minute), decreased pulse pressure, cold and clammy skin, altered mental state (e.g., disorientation, confusion), and elevated blood lactate (>2–3 mmol/L) or base deficit (< −4 mmol/L).[5,6] However, these signs do not change until the later stages of hemorrhage and thus waiting until a clinically significant change can impede early diagnosis of shock when interventions could be most effective. The tendency for measuring these traditional vital signs that are easy to obtain and understand (e.g., blood pressure) but provide information of little value during the early stages of compensatory shock, rather than using technologically more advanced but meaningful measures has been defined as "tangible bias."[7] The century-long perpetuation of this bias in monitoring patients in the prehospital emergency medical setting has enabled the inability of our emergency medical community to identify shock in its earliest compensatory stages when the application of lifesaving interventions would be most effective. The emergence of new computer technologies that are based on advanced machine-learning principles and signal processing of large amounts of data has now made it possible to escape the "tangible bias" created by currently used medical monitoring technologies by providing real-time assessments of global tissue oxygenation status in individual patients (precision medicine). Within this context, the objectives of this article are to (1) describe why current physiologic monitoring is inaccurate; (2) introduce and define a new paradigm named the compensatory reserve; (3) demonstrate the usefulness of measuring the compensatory reserve with clinical examples; and (4) identify future applications of compensatory reserve monitoring, including the prehospital phase of resuscitation.

Why Current Physiologic Monitoring Is Inaccurate

There is compelling evidence that morbidity and mortality can be improved in emergency medicine by early and accurate diagnosis and thus the application of effective lifesaving interventions.[8] The applications include damage control or goal-directed resuscitation in trauma and septic patients,[9–13] blood components in patients with severe hemorrhage,[9,14,15] placement of tourniquets in extremity injury,[16] and renal replacement therapy in burn patients.[17] Unfortunately, one of the most challenging aspects of providing effective treatment of shock is an inability to recognize its early onset. Various attempts at applying advanced computational algorithms by many of the leading clinical investigators in trauma and emergency medicine have failed to produce early and accurate assessment tools for identifying shock[18–22] because they rely on measurements of "legacy" vital signs that may change very little in the early stages of hemorrhage, and thus compensatory shock, because of the body's numerous compensatory mechanisms (e.g., tachycardia, vasoconstriction, deep inspiration) that regulate blood pressure.[23–26] The inaccuracy of using current vital signs during the early compensatory phase of shock is illustrated in Figure 1A. Blood pressures, arterial oxygen saturation (Spo_2), and heart rate measurements collected in the early prehospital setting were similar 30 to 45 minutes after traumatic injury in hemorrhaging patients who went on to die compared with those who survived.[27] These results emphasize that current physiologic monitoring can be grossly misleading, and nonpredictive of hemodynamic collapse, because of the numerous compensatory mechanisms that "protect" these vital signs from significant clinical change. In other words, current vital sign monitoring lacks sensitivity and specificity to predict impending hemodynamic collapse and shock during the early compensatory stage of hemorrhage.

It occurred to us that a measurement reflecting the integrated status of the capacity of all mechanisms to compensate for a reduction in blood flow due to hypovolemia might significantly improve the sensitivity and specificity of monitoring during early and late stages of hemorrhage. To accomplish such a novel approach to monitoring, a model of human hemorrhage needed to be developed that provided the capability to investigate the physiology of integrated compensation under controlled laboratory conditions, and be capable of demonstrating a repeatable clinical outcome observed in hemorrhage (hemodynamic decompensation). Additionally, novel computer and data processing techniques with machine-learning capabilities could be applied to our extensive data "library" of physiologic signals generated from the "hemorrhage" experiments and used to develop an algorithm to recognize an individual subject's unique and integrated total of all compensatory mechanisms in real-time. Within this context, we adopted the use of lower-body negative pressure (LBNP) that has proven to produce repeatable tolerance times to hypovolemia[29,30] and accurately mimic the hemodynamic,[31–34] metabolic,[4,35] coagulation,[36] respiratory,[37] neuroendocrine,[33,35] and mental status[38] responses of hemorrhage. The value of using this experimental model is reflected in Table 1

Submitted: October 18, 2016, Revised: March 6, 2017, Accepted: March 13, 2017, Published online: March 22, 2017.

From the Battlefield Health & Trauma Center for Human Integrative Physiology, U. S. Army Institute of Surgical Research (V.A.C., A.M.S.), JBSA Fort Sam Houston, TX.

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

Presented at the 6th Annual Remote Damage Control Resuscitation Symposium of the Trauma Hemostasis and Oxygenation Research Network, June 20–22, 2016, in Os, Norway.

Address for reprints: Victor A. Convertino, PhD, U.S. Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234; email: victor.a.convertino.civ@mail.mil.

DOI: 10.1097/TA.0000000000001430

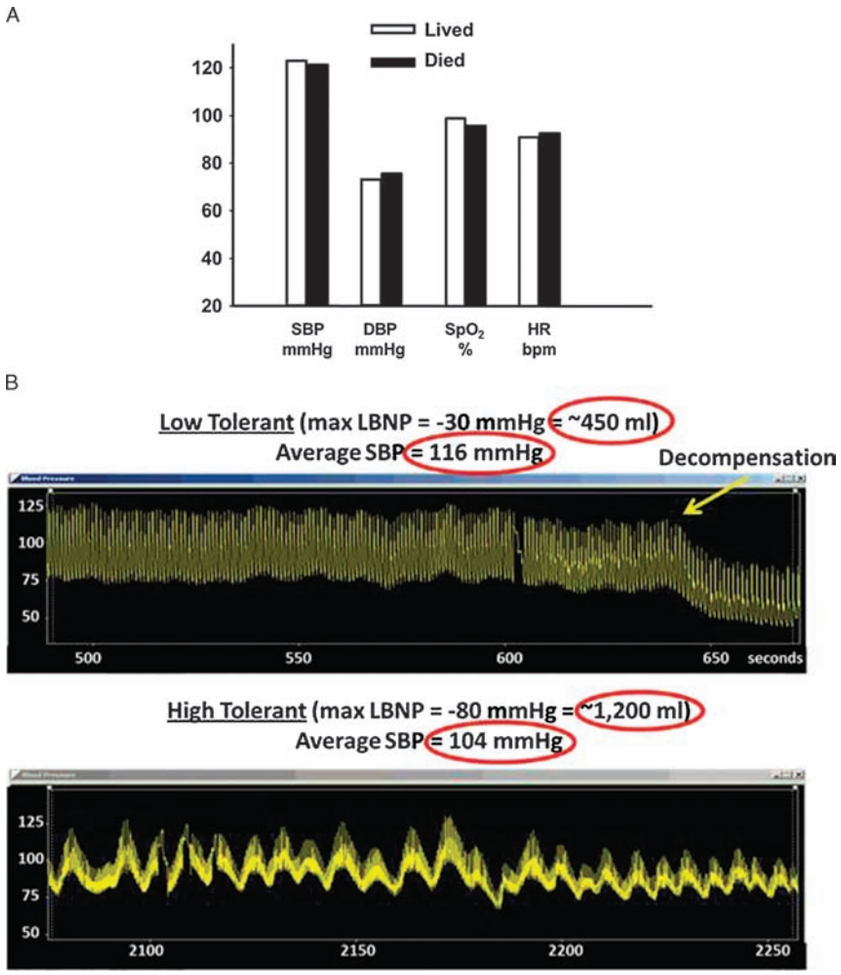

Figure 1. (*A*) Trauma patients with severe hemorrhage who lived (*open bars*) and died (*closed bars*) could not be differentiated by standard vital signs obtained 30 to 45 minutes after injury. Modified from Cooke et al.[27] (*B*) Arterial waveform recordings demonstrate pronounced oscillatory patterns in individuals with high tolerance to a progressive reduction in central blood volume (*bottom recording*) compared to low tolerance individuals (*top recording*). Modified from Convertino et al.[28]

with the reaffirmation that most standard vital signs are maintained with minimal change due to the body's ability to compensate for blood loss during the initial phase of hemorrhage. Of note is the gradual and relatively late elevation in heart rate.[27,39,40,45]

Therefore, to improve the efficacy of decision-support tools, we need technology that can measure compromise to integrated blood pressure compensation mechanisms[50] and "individualize" the assessment of a patient's progression toward "shock" well in advance of clinically relevant changes in traditional vital signs.[51] This approach requires the capability to measure the integrated total of all mechanisms that compose the reserve to compensate for blood loss. We call this physiologic measurement the "compensatory reserve."

What Is the Compensatory Reserve?

Any physiologic compensatory mechanism (e.g., tachycardia, vasoconstriction) has a finite maximal response to any specific physiologic stressor (e.g., hemorrhage). Thus, the "reserve" to compensate is defined by the difference between the maximal response and the baseline state. For example, an individual's reserve for tachycardia during blood loss is represented by the difference between the resting baseline heart rate and the maximal heart rate response. Within this context, the compensatory reserve represents a new paradigm for measuring the total of all compensatory mechanisms (e.g., tachycardia, vasoconstriction, breathing) that together contribute to "protect" against inadequate tissue oxygenation during blood loss and other low circulating blood volume states[41,49,52–54] by maintaining tissue perfusion. Since shock is the result of inadequate tissue perfusion, the compensatory reserve provides the most accurate real-time measure for identifying shock.

A unique feature of the LBNP model to mimic the human response to hemorrhage is the ability to induce the maximal compensatory response(s) necessary to define the compensatory reserve by inducing central hypovolemia to the point of hemodynamic collapse, or presyncopal symptoms. In this regard, we have used a protocol of progressive central hypovolemia to induce the clinical endpoint of decompensation in more than 270 human subjects. Consistent with clinical observations,[55,56] our experiments revealed that two thirds of the subjects display a

TABLE 1. Times Course, Sensitivity and Specificity of Changes in Traditional Vital Signs and Hemodynamic Responses During Progressive Central Hypovolemia

Vital Sign	Change During Progressive Central Hypovolemia	Sensitivity	Specificity	Reference(s)
Systolic BP	Late	0.80	0.17	5,27,39–44
Diastolic BP	Late	0.40	0.53	40–44
Mean BP	Late	0.60	0.33	40–45
Heart rate	Not specific	0.80	0.02	27,39,40,45
Shock Index	Late	—	—	39,42
SpO_2	Late	0.60	0.00	40–43,45
Stroke volume	Early	0.60	0.33	31,41,42,44
Cardiac output	Late	0.80	0.02	41
Radial pulse character	Late	—	—	38
$EtCO_2$	Late			46
Respiratory rate	Late	—	—	37,46
GCS	Late	—	—	38
Blood pH	Late	—	—	4,40
Blood lactate	Late		0.03	4,40
Blood base excess	Late		0.02	4,40
Perfusion index	Late	0.71	0.29	47
Pulse pressure variability	Late	0.78	0.69	47
SmO_2	Early, but low specificity	0.65	0.63	48
Compensatory reserve	Early and specific	0.84–0.87	0.78–0.86	28,39–43,45,47–49

BP, blood pressure.

relatively high tolerance to reduced central blood volume and can tolerate central hypovolemia well without exhibiting presyncopal symptoms until high levels of pressure are experienced, whereas the remaining one third display low tolerance to do so.[29,49,52,57,58] This physiologic dichotomy has provided a model to investigate and define the compensatory reserve of individual physiology more completely.

Low and High Tolerance to Central Hypovolemia

Traditional standard vital signs either change very late in the process of reduced central blood volume (Table 1), display low specificity for predicting decompensation (Table 1), or fail to distinguish individual tolerances.[49,58] These limitations reflect the similarity of "legacy" vital sign responses to central hypovolemia observed in individuals with high and low tolerance (e.g., elevations in heart rate, systemic vascular resistance, sympathetic nerve activity in response to lowered venous return, cardiac filling, stroke volume, cardiac output). The primary difference between high- and low-tolerant individuals is that those with high tolerance have larger absolute reserves to compensate (i.e., greater maximum responses in tachycardia, vasoconstriction, sympathetic nerve activity, cardiac vagal activity, etc.).[59] Our LBNP experiments led to the observation that specific patterns and features of arterial pressure waveforms were the most sensitive and specific physiologic measures for identifying individuals with high and low tolerance to reductions in central blood volume.[28,52,58] This relationship is best illustrated in the two tracings of arterial waveform dynamics presented in Figure 1B. Each panel represents a different individual undergoing a separate LBNP experiment. The top panel of Figure 1B depicts an individual with low tolerance to reduced central blood volume who displayed sudden decompensation with symptoms after losing less ~450 mL of the blood volume despite maintaining a clinically "normal" average systolic blood pressure of 116 mm Hg. In contrast, the bottom panel of Figure 5 depicts an arterial blood pressure tracing of an individual with high tolerance who is well compensated without symptoms despite having a relative hypotension (systolic blood pressure = 104 mm Hg) and a blood volume loss estimated at approximately 1200 mL. Oscillatory arterial waveform patterns that represent sympathetically mediated reflex compensation are pronounced in "high"-tolerant individuals.[53] The top panel (low-tolerant individual) has a pattern of arterial blood flow that visually has low variability and consistent frequency distribution. In opposition to this, the bottom panel (high-tolerant individual), exhibits a visually inconsistent arterial waveform with high variability and alteration in frequency distribution. In other words, subjects with arterial waveform features that include these visible oscillations can tolerate central hypovolemia to a much greater extent than individuals that do not exhibit

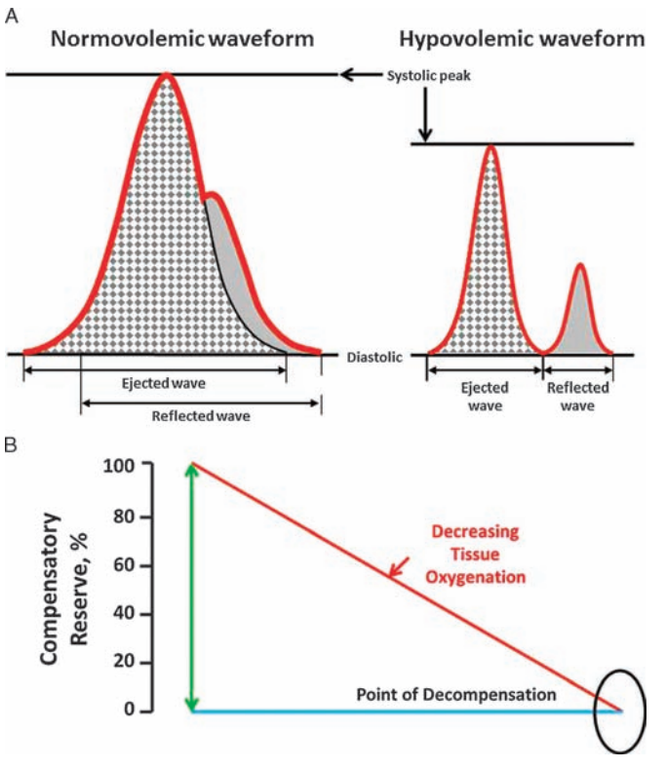

Figure 2. (*A*) Characteristic features of the arterial ejected and reflected waveforms change when progressing from a normovolemic state (*left figure*) to central hypovolemia (*right figure*). The *red line* indicates the integrated waveform that would be seen and recorded by an observer.[28] (*B*) A conceptual model is illustrating a reduction in compensatory reserve (*green line*) from 100% (*full capacity*) to decompensation (*blue line* at 0% reserve) as a result of a progressive reduction in tissue oxygenation (*red line*). Modified from Moulton et al.[54]

these waveform features. If oscillatory pressure patterns cannot be generated, adequate perfusion and oxygenation of tissue to all organs cannot be maintained, and the system decompensates.[28]

Measuring the Compensatory Reserve

The waveform comparisons presented in Figure 2 demonstrate significant information about the compensatory status of an individual patient that current monitoring technologies fail to provide. Within this context, it is now recognized that advanced computer processing that enables real-time assessment of the features of arterial waveform patterns (i.e., morphology, oscillations) combined with machine learning can provide a new clinical tool for early identification of shock.[28] Since all compensatory mechanisms that impact cardiac output and tissue perfusion are contained within features of the ejected and reflected waves, algorithms for measuring the compensatory reserve can be developed that "learn" how to identify the impending compromise of tissue oxygenation as indicated by distinct changes in arterial waveform features occurring during the progression of hypovolemic states (Figure 2A). As such, the measurement of the compensatory reserve has provided the first clinical tool for predicting hemodynamic collapse and distinguishing weak (i.e., patients at highest risk for shock) from strong compensators.

In Figure 2B, a conceptual model of the compensatory reserve is presented that demonstrates a potential capacity of 100% reserve available to compensate for compromised tissue oxygenation in low volume states (green vertical arrow). When tissue perfusion becomes compromised as a result of progressive blood loss over time (*x*-axis), the use of compensatory mechanisms (e.g., tachycardia, vasoconstriction, respiration) needed to maintain adequate oxygen to vital organs reduces the reserve to compensate. If tissue oxygenation continues to a state where maximum compensation is reached (i.e., the circle in Figure 2B where the tissue oxygenation deficit "red" line intersects with the "zero" compensatory reserve "blue" line), decompensatory shock will occur. Our research has revealed that the compensatory reserve is reduced from the onset of blood loss as compensation is initiated. Thus, the earliest and most accurate indication of hemorrhage can be reflected by measuring the compensatory reserve.[41,54]

Figure 3A illustrates the components and flow of a machine-learning model capable of measuring the compensatory reserve of an individual subject. The machine-learning algorithm was developed using an extensive reference database

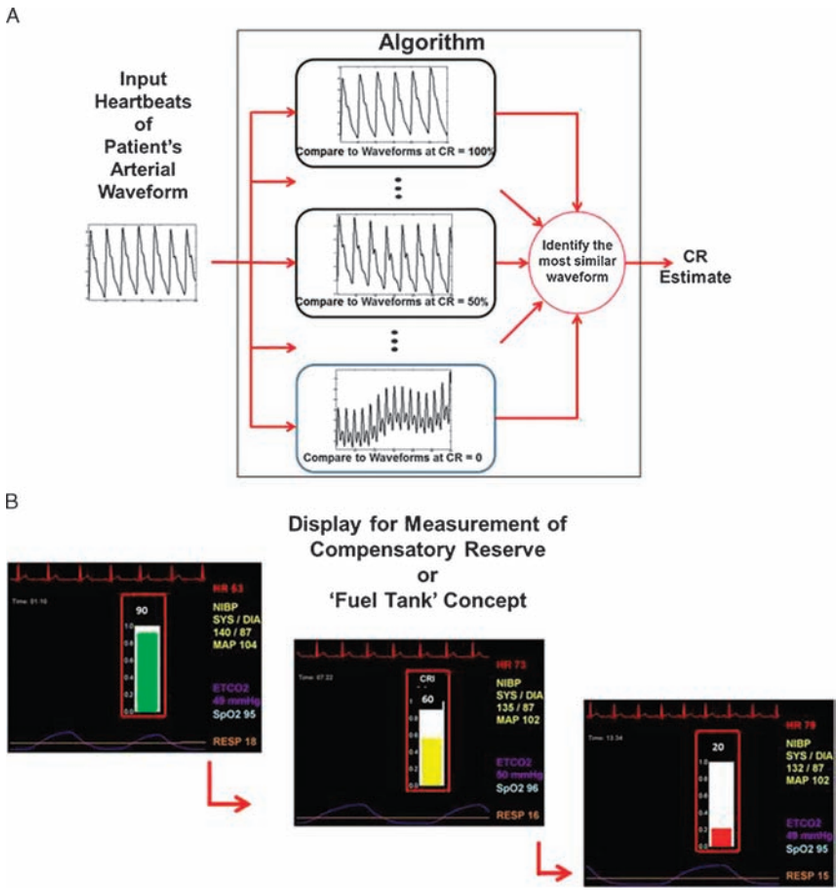

Figure 3. (*A*) Diagram illustrating the processing of beat-to-beat arterial waveform tracings obtained from a patient for comparison to a "library" of waveforms collected from human subjects exposed to progressive reductions in central blood volume for generation of an estimated measure of CR. Modified from Convertino et al.[49] (*B*) A monitor screen is illustrating the progression in the compensatory reserve "Fuel Gauge" from "green" (1.0 to 0.6—top left panel) to "amber" (0.6 to 0.3—middle panel) to "red" (0.3 to 0.0—bottom right panel). Modified from Van Sickle et al.[39] CR, compensatory reserve.

of arterial waveforms that has been generated from carefully controlled LBNP protocols conducted on more than 250 healthy men and women ranging from 18 to 55 years in age while in a supine position during a progressive reduction in central blood volume over the past 12 years.[28] The algorithm compares features of the arterial waveform from the monitored patient (input) with features of the hundreds of thousands of arterial waveforms in the reference library and calculates an estimate of the patient's compensatory reserve based on the most similar waveform identified in the "library" of reference waveforms. Each individual's compensatory reserve is estimated in real time because the machine-learning capability of the algorithm accounts for compromised tissue oxygenation as it identifies the totality of compensatory mechanisms based on the individual's arterial waveform features.

A conceptual monitor screen for displaying measurement of the compensatory reserve is presented in Figure 3B.[39] The compensatory reserve is visually shown as a "bar" similar to a fuel gauge of an automobile that indicates the amount of fuel left in the gas tank. As the reserve in the tank (i.e., compensatory reserve) is used to compensate for reduced tissue oxygenation, the gauge will change colors to correspond to the patient's status of adequate reserve (green), moderately reserve (amber), and severely limited reserve (red). A video demonstrating the responses of a subject undergoing a progressive reduction in central blood volume similar to hemorrhage can be observed in the Journal of Visual Experimentation.[61] Accuracy analysis shows a correlation of 0.95 or greater for estimating compensatory reserve at any point in time using this approach.[49,52,54]

Measuring the Compensatory Reserve: Clinical Examples

Laboratory-conducted experiments using LBNP as a model of hemorrhage[49,54] and actual blood withdrawal[41–43] in human volunteers have demonstrated the superior specificity of predicting decompensation when measuring the compensatory reserve compared with standard vital signs and other hemodynamic measurements (Table 1). Perhaps, the most clinically relevant are the data collected from various patient populations that have corroborated the usefulness of measuring the compensatory reserve as an early indicator for improved triage. In a recent study reported in trauma patients in the emergency room,[62] measurement of the compensatory reserve was able to distinguish the clinical status of a group of 30 patients with blunt trauma and negligible bleeding from 12 patients with penetrating trauma and severe hemorrhage (Fig. 4). Consistent with our laboratory experiments using LBNP, the investigators reported a high-classification accuracy between bleeding and nonbleeding patients of 93% with a sensitivity of 0.933, specificity of 0.917, and area under the receiver operating characteristic curve of 0.975.

In a recently published case report,[60] photoplethysmographic (PPG) waveforms were recorded from a 15-year-old male bicyclist who was struck by an automobile during his care in the pediatric intensive care unit (PICU) and used for retrospective analysis of the compensatory reserve using the machine-learning algorithm. An initial focused abdominal sonography for trauma and abdominal computed tomography scan were both negative. The results of sequential compensatory reserve measurements are presented in Figure 6. The compensatory

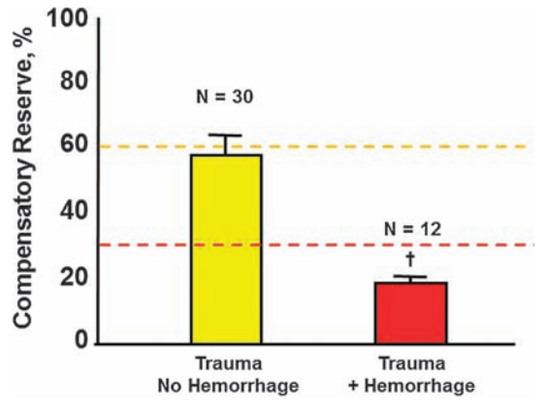

Figure 4. Measurement of compensatory reserve distinguished patients with blunt trauma (*yellow bar*) from those with penetrating trauma (*red bar*). Values are mean ± 95% CI. Graph generated from data reported by Stewart et al.[62]
CI, confidence interval.

reserve was at 40% (shown in yellow) upon arrival to the PICU, but decreased to less than 30% (shown in red) within 1 hour and remained low for 3 hours before vital signs indicated a need for intervention. After receiving 1 L of lactated Ringer's solution, the compensatory reserve was restored to 80% only to return to less than 30% within 2 hours. Subsequent infusions of red blood cells and saline temporarily restored compensatory reserve, but the reserve eventually fell below 20% before the patient underwent emergent exploratory surgery that revealed two jejunal perforations. If real-time monitoring of compensatory reserve were available, it could have revealed the need for surgery, or indication of an unknown underlying complication, 12 to 13 hours earlier. Also, postoperative restoration of the compensatory reserve to greater than 80% (shown in green) demonstrates its usefulness for continuous assessment of intervention effectiveness (Fig. 5).

Measurements of compensatory reserve obtained from retrospective analyses of PPG have proven to be consistently accurate in assessing case studies of patient status[60] under clinical conditions of an orthostatic challenge, childbirth, appendicitis, burn injury, sepsis, and cardiopulmonary resuscitation as well as dengue hemorrhagic fever[63] and blood donation.[41,42]

Future Applications of Compensatory Reserve Monitoring

Although the initial development of the measurement for compensatory reserve focused on a monitoring capability for assessing states of low vascular volume, recent experimental and clinical investigations have revealed an important future application for goal-directed resuscitation. Measurement of the compensatory reserve has been specifically listed by the Committee on Tactical Combat Casualty Care for future research and development as one technology "for continued development and expedited fielding that…(can) enable combat medical personnel to better evaluate the need for and the adequacy of fluid resuscitation."[64] Results from a recent case series study on three pediatric patients admitted to the hospital with secondary dengue virus infections[63] demonstrate a potential future application for real-time assessment of resuscitative measures. Retrospective

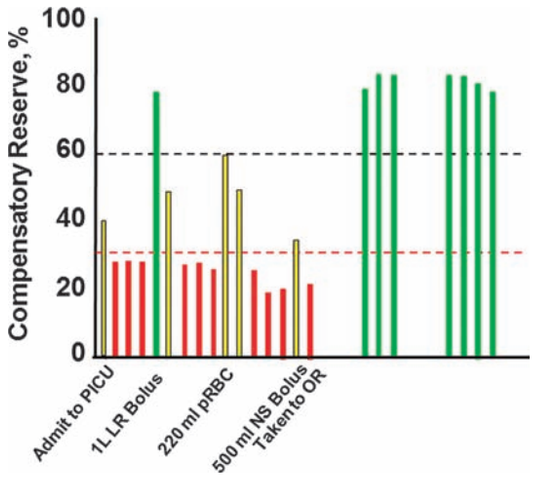

Figure 5. Measurement of the compensatory reserve obtained noninvasively over 29 hours was able to track the reductions and restorations of reserve during internal bleeding and resuscitation in a pediatric patient admitted to the PICU with severe trauma followed by the development of sepsis. Modified from Stewart et al.[60]

analyses of PPG recordings are presented in Figure 6. At the time of hospital admission, the compensatory reserve registered between 10% and 20% (shown as red), indicating that the patients were near decompensatory shock. Over a period of 5 days, resuscitative therapy was effective in restoring the compensatory reserve to greater than 70% (shown as green) without any indication of overresuscitation.

The future application for using measurements of the compensatory reserve as a guide to resuscitation is further

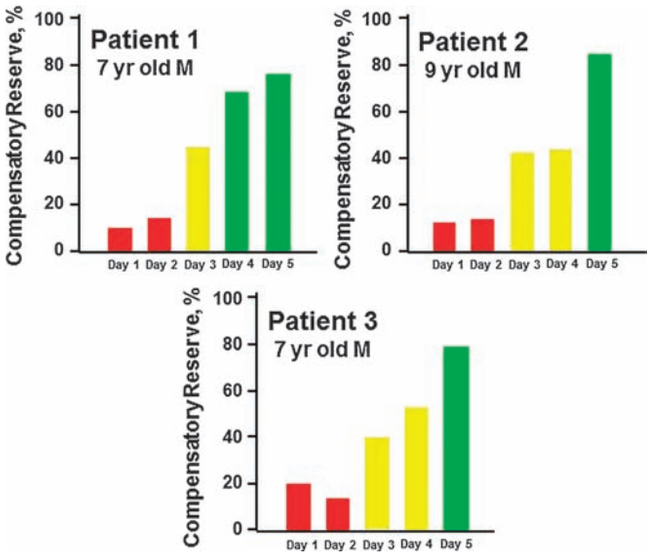

Figure 6. Measurement of the compensatory reserve obtained noninvasively in three pediatric patients with blood loss from Dengue hemorrhagic fever was able to track effective intervention from admission to the hospital with symptoms of shock (Day 1) through completion of care with fluid resuscitation therapy (Day 5). Modified from Moulton et al.[63]

supported by a recent investigation in which 20 humans underwent a controlled hemorrhage of 20% of their blood volume followed by the resuscitation of the shed blood.[41] The blood was subsequently returned by transfusion. The results recorded from two subjects are presented in Figure 7A. Several significant outcomes of measuring the compensatory reserve were revealed by the results obtained from this investigation. First, correlation coefficients (R^2) greater than 0.9 for the relationship between reduced compensatory reserve blood loss were observed in all subjects, indicating the ability of the algorithm to provide an individualized assessment of compensatory status. Second, the difference in slopes of the relationship between blood volume and compensatory reserve represents the variability in the reserve of each to compensate for bleeding. In other words, the compensatory reserve was able to distinguish subject 1 (Fig. 7, *left panel*) as the most compromised individual requiring use of approximately 70% of his reserve after losing 1.2 L of blood compared with subject 2 (Fig. 6, *right panel*) who lost more blood (~1.4 L) but only required use of approximately 30% of his reserve. In this regard, measurement of the compensatory reserve displayed significantly greater specificity for measuring the status of circulating blood volume in individual patients compared with any standard vital sign, including stroke volume and cardiac output.[41] Third, since subject 1 required more of his reserve to compensate for less

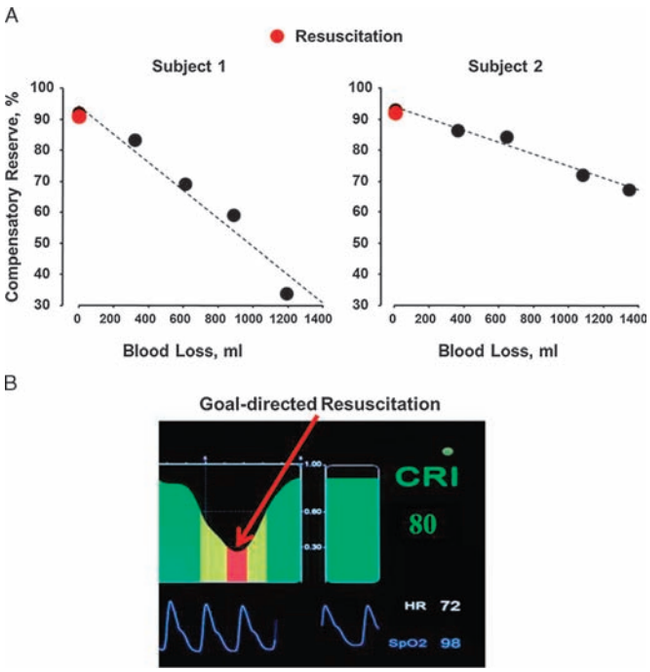

Figure 7. (*A*) The effect of controlled hemorrhage at ~20% of estimated circulating blood volume in two individual patients with a minimal change in standard vital signs was accurately tracked and differentiated by measuring the compensatory reserve. The difference in slopes indicates individual diversity in compensatory response. Modified from Convertino et al.[41] (*B*) Real-time compensatory reserve monitoring was successfully used to guide and assess the effectiveness of fluid resuscitation in a human volunteer after progressive hemorrhage simulated by application of LBNP.

blood loss than subject 2, the comparison of results in Figure 7 reinforces the notion that measurement of the compensatory response to hemorrhage is a more sensitive and specific predictor of shock than blood volume loss. Future application for accurate goal-directed fluid resuscitation is supported by the complete restoration of compensatory reserve after replacement of whole blood in these individuals (Fig. 7A, *red circles*). To provide evidence for application in guiding resuscitation, we are currently conducting experiments using the LBNP model that demonstrate the real-time prospective use of measuring compensatory reserve to guide replacement of whole blood (Fig. 7B).

Finally, an important consideration for future use is the ability of the clinician to translate changes in compensatory reserve in clinical situations. The opportunity to assess the ability of clinicians to easily understand or interpret information provided by the measurement of the compensatory reserve is limited since FDA clearance of the technology has only recently been granted. However, we previously demonstrated in a training simulation study that civilian paramedics were able to easily learn to interpret the need to act from changes in the compensatory reserve as indicated by reducing their time to recognize an unstable bleeding patient by more than 40%.[65]

CONCLUSION

Continued execution of clinical trials will prove critical to the continued development and acceptance of the medical community of the measurement of the compensatory reserve as a standard of care in patients. After FDA clearance, perhaps the most significant future application of compensatory reserve monitoring will be realized with the placement of the technology in military and civilian prehospital settings where the potential exists to reduce preventable deaths with an early diagnosis of impending shock and triage decision support. Such application has been demonstrated by the Israeli Defense Force's current use of real-time compensatory reserve monitoring in a prospective study of patients with hemorrhage admitted to the ED in which a superior capability to detect hemorrhage and accurately assess the effectiveness of RBC transfusion was demonstrated with measures of the compensatory reserve when compared with conventional vital signs.[66] Additionally, Israeli Defense Force clinicians are using compensatory reserve monitoring to assist triage decision support during helicopter transports of trauma patients (unpublished). However, waiting for further clinical data does not detract from the compelling evidence that continuous, real-time measurement of arterial waveform features represents the most sensitive and specific metric of patient status during hemorrhage and resuscitation in states of compromised tissue oxygenation. The capability of medical monitoring that provides continuous measures of compensatory reserve for early identification of shock and guidance for accurate resuscitation without requiring a baseline reference while learning the status of each patient is unprecedented in emergency medical care.

AUTHORSHIP

V.A.C. and A.M.S. interpreted results of studies, prepared figures, and drafted and approved the final version of manuscript.

ACKNOWLEDGMENTS

We thank the scientists and engineers who were instrumental in conducting the laboratory experiments, clinical studies, and technology development that allowed for measurement of the compensatory reserve.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Aslar AK, Kuzu MA, Elhan AH, Tanik A, Hengirmen S. Admission lactate level and the APACHE II score are the most useful predictors of prognosis following torso trauma. *Injury*. 2004;35(8):746–752.
2. Cestero RF, Dent DL. Endpoints of resuscitation. *Surg Clin North Am*. 2015; 95(2):319–336.
3. Rixen D, Siegel JH. Bench-to-bedside review: Oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. *Crit Care*. 2005;9(5):441.
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*. 2010;81(8): 987–993.
5. Burgess FW, Sborov MJ, Calcagni DR. Hemorrhage, shock, and fluid resuscitation. In: *Anesthesia and Perioperative Care of the Combat Casualty*. Washington, DC: Office of The Surgeon General at TMM Publications; 1995:95–97.
6. Wilson RF. *Handbook of Trauma: Pitfalls and Pearls*. Lippincott Williams & Wilkins; 1999.
7. Thiele RH, Nemergut EC, Lynch C. The physiologic implications of isolated alpha(1) adrenergic stimulation. *Anesth Analg*. 2011;113(2):284–296.
8. Gerhardt RT, Berry JA, Blackbourne LH. Analysis of life-saving interventions performed by out-of-hospital combat medical personnel. *J Trauma*. 2011;71(Suppl 1):S109–S113.
9. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev*. 2009;23(6):231–240.
10. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. *Chest*. 2007;132(6):2020–2029.
11. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–1377.
12. Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R, Childs EW. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock*. *Crit Care Med*. 2007;35(9): 2016–2024.
13. Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Curr Opin Anaesthesiol*. 2008;21(2):128–140.
14. Cap AP, Spinella PC, Borgman MA, Blackbourne LH, Perkins JG. Timing and location of blood product transfusion and outcomes in massively transfused combat casualties. *J Trauma Acute Care Surg*. 2012;73(2 Suppl 1): S89–S94.
15. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma*. 2009; 66(4):S69–S76.
16. Kragh JF, Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, Holcomb JB. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg*. 2009;249(1):1–7.
17. Chung KK, Juncos LA, Wolf SE, Mann EE, Renz EM, White CE, Barillo DJ, Clark RA, Jones JA, Edgecombe HP, et al. Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. *J Trauma*. 2008;64(Suppl 2):S179–S187.
18. Holder AL, Clermont G. Using what you get: dynamic physiologic signatures of critical illness. *Crit Care Clin*. 2015;31(1):133–164.
19. Liu J, Khitrov MY, Gates JD, Odom SR, Havens JM, de Moya MA, Wilkins K, Wedel SK, Kittell EO, Reifman J, et al. Automated analysis of vital signs to identify patients with substantial bleeding before hospital arrival: a feasibility study. *Shock*. 2015;43(5):429–436.

20. Mackenzie CF, Wang Y, Hu PF, Chen S-Y, Chen HH, Hagegeorge G, Stansbury LG, Shackelford S. Automated prediction of early blood transfusion and mortality in trauma patients. *J Trauma Acute Care Surg*. 2014;76(6): 1379–1385.
21. Liu NT, Kramer GC, Khan MN, Kinsky MP, Salinas J. Is heart-rate complexity a surrogate measure of cardiac output before, during, and after hemorrhage in a conscious sheep model of multiple hemorrhages and resuscitation? *J Trauma Acute Care Surg*. 2015;79:S93–S100.
22. Liu NT, Kramer GC, Khan MN, Kinsky MP, Salinas J. Blood pressure and heart rate from the arterial blood pressure waveform can reliably estimate cardiac output in a conscious sheep model of multiple hemorrhages and resuscitation using computer machine learning approaches. *J Trauma Acute Care Surg*. 2015;79:S85–S92.
23. Orlinsky M, Shoemaker W, Reis ED, Kerstein MD. Current controversies in shock and resuscitation. *Surg Clin North Am*. 2001;81(6):1217–1262.
24. Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med*. 1993;21(2):218–223.
25. Bruijns SR, Guly HR, Bouamra O, Lecky F, Lee WA. The value of traditional vital signs, shock index, and age-based markers in predicting trauma mortality. *J Trauma Acute Care Surg*. 2013;74(6):1432–1437.
26. Parks JK, Elliott AC, Gentilello LM, Shafi S. Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. *Am J Surg*. 2006;192(6): 727–731.
27. Cooke WH, Salinas J, Convertino VA, Ludwig DA, Hinds D, Duke JH, Moore FA, Holcomb JB. Heart rate variability and its association with mortality in prehospital trauma patients. *J Trauma*. 2006;60(2):363–370.
28. Convertino VA, Wirt MD, Glenn JF, Lein BC. The compensatory reserve for early and accurate prediction of hemodynamic compromise: a review of the underlying physiology. *Shock*. 2016;45(6):580–590.
29. Convertino VA, Sather TM. Effects of cholinergic and beta-adrenergic blockade on orthostatic tolerance in healthy subjects. *Clin Auton Res*. 2000;10(6): 327–336.
30. Convertino VA. Lower body negative pressure as a tool for research in aerospace physiology and military medicine. *J Gravit Physiol*. 2001;8(2):1–14.
31. 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*. 2004;96(4):1249–1261.
32. Johnson BD, Van Helmond N, Curry TB, Van Buskirk CM, Convertino VA, Joyner MJ. Reductions in central venous pressure by lower body negative pressure or blood loss elicit similar hemodynamic responses. *J Appl Physiol*. 2014;117(2):131–141.
33. Hinojosa-Laborde C, Shade RE, Muniz GW, Bauer C, Goei KA, Pidcoke HF, Chung KK, Cap AP, Convertino VA. Validation of lower body negative pressure as an experimental model of hemorrhage. *J Appl Physiol*. 2014; 116(4):406–415.
34. Hinojosa-Laborde C, Mulligan J, Grudic G, Convertino V. Comparison of compensatory reserve index during lower body negative pressure and hemorrhage. *FASEB J*. 2015;29(Suppl 1):800.8.
35. Hinojosa-Laborde C, Howard JT, Mulligan J, Grudic GZ, Convertino VA. Comparison of compensatory reserve during lower-body negative pressure and hemorrhage in nonhuman primates. *Am J Physiol—Regul Integr Comp Physiol*. 2016;310(11):R1154–R1159.
36. van Helmond N, Johnson BD, Curry TB, Cap AP, Convertino VA, Joyner MJ. Coagulation changes during lower body negative pressure and blood loss in humans. *Am J Physiol Circ Physiol*. 2015;309(9):H1591–H1597.
37. Convertino VA, Rickards CA, Lurie KG, Ryan KL. Hyperventilation in response to progressive reduction in central blood volume to near syncope. *Aviat Space Environ Med*. 2009;80(12):1012–1017.
38. 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*. 2008;12(2):192–198.
39. Van Sickle C, Schafer K, Grudic GZ, Mulligan J, Moulton SL, Convertino VA. A sensitive shock index for real-time patient assessment during simulated hemorrhage. *Aviat Space Environ Med*. 2013;84:907–912.
40. 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*. 2008;64(4):S342–S353.
41. Convertino VA, Howard JT, Hinojosa-Laborde C, Cardin S, Batchelder P, Mulligan J, Grudic GZ, Moulton SL, MacLeod DB. Individual-specific, beat-to-beat trending of significant human blood loss: the compensatory reserve. *Shock*. 2015;44:27–32.
42. Nadler R, Convertino VA, Gendler S, Lending G, Lipsky AM, Cardin S, Lowenthal A, Glassberg E. The value of noninvasive measurement of the compensatory reserve index in monitoring and triage of patients experiencing minimal blood loss. *Shock*. 2014;42(2):93–98.
43. Stewart CL, Mulligan J, Grudic GZ, Convertino VA, Moulton SL. Detection of low-volume blood loss: compensatory reserve versus traditional vital signs. *J Trauma Acute Care Surg*. 2014;77(6):892–898.
44. Convertino VA, Cooke WH, Holcomb JB. Arterial pulse pressure and its association with reduced stroke volume during progressive central hypovolemia. *J Trauma*. 2006;61(3):629–634.
45. 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*. 2008;104(2):475–481.
46. 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*. 2008;12(2):199–205.
47. Janak JC, Howard JT, Goei KA, Weber R, Muniz GW, Hinojosa-Laborde C, Convertino VA. 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(6):548–553.
48. Howard JT, Janak JC, Hinojosa-Laborde C, Convertino VA. Specificity of compensatory reserve and tissue oxygenation as early predictors of tolerance to progressive reductions in central blood volume. *Shock*. 2016;46(3 Suppl 1):68–73.
49. Convertino VA, Grudic G, Mulligan J, Moulton S. Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. *J Appl Physiol*. 2013;115(8):1196–1202.
50. Xiang L, Clemmer JS, Lu S, Mittwede PN. Impaired blood pressure compensation following hemorrhage in conscious obese Zucker rats. *Life Sci*. 2013; 93(5):214–219.
51. Saugel B, Trepte CJ, Heckel K, Wagner JY, Reuter DA. Hemodynamic management of septic shock: is it time for "individualized goal-directed hemodynamic therapy" and for specifically targeting the microcirculation? *Shock*. 2015;43(6):522–529.
52. Convertino VA, Moulton SL, Grudic GZ, Rickards CA, Hinojosa-Laborde C, Gerhardt RT, Blackbourne LH, Ryan KL. Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *J Trauma*. 2011;71(Suppl 1):S25–S32.
53. Convertino VA. Blood pressure measurement for accurate assessment of patient status in emergency medical settings. *Aviat Space Environ Med*. 2012; 83(6):614–619.
54. Moulton SL, Mulligan J, Grudic GZ, Convertino VA. Running on empty? The compensatory reserve index. *J Trauma Acute Care Surg*. 2013;75(6): 1053–1059.
55. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg*. 1973;106(5):630–636.
56. Shoemaker WC, Wo CC, Chan L, Ramicone E, Kamel ES, Velmahos GC, Belzberg H. Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. *Chest*. 2001;120(2):528–537.
57. Convertino VA, Rickards CA, Ryan KL. Autonomic mechanisms associated with heart rate and vasoconstrictor reserves. *Clin Auton Res*. 2012;22(3): 123–130.
58. Rickards CA, Ryan KL, Cooke WH, Convertino VA. Tolerance to central hypovolemia: the influence of oscillations in arterial pressure and cerebral blood velocity. *J Appl Physiol*. 2011;111(4):1048–1058.
59. Schiller AM, Howard JT, Convertino VA. The physiology of blood loss and shock: New insights from a human laboratory model of hemorrhage. *Exp Biol Med*. 2017;153537021769409.
60. Stewart CL, Nawn CD, Mulligan J, Grudic G, Moulton SL, Convertino VA. Compensatory reserve for early and accurate prediction of hemodynamic compromise: case studies for clinical utility in acute care and physical performance. *J Spec Oper Med*. 2015;16(1):6–13.

61. Convertino VA, Hinojosa-Laborde C, Muniz GW. Integrated compensatory responses in a human model of hemorrhage. *J Vis Exp*. 2016; In Press.
62. Stewart C, Mulligan J, Grudic G, Talley M, Jurkovich G, Convertino V, Moulton SL. Noninvasive detection of acute volume loss and fluid resuscitation in trauma patients: results of a prospective clinical trial. *Shock*. 2015;43: 72–73.
63. Moulton SL, Srikiatkhachorn A, Kalayanarooj S, Grudic GZ, Green S, Gibbons RV, Muniz GW, Hinojosa-Laborde C, Rothman AL, Thomas SJ. State-of-the-art monitoring in treatment of dengue shock syndrome: a case series. *J Med Case Rep*. 2016;10:233.
64. Butler FK, Holcomb JB, Schreiber MA, Kotwal RS, Jenkins DA, Champion HR, Bowling F, Cap AP, Dubose JJ, Dorlac WC, et al. Fluid Resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC Guidelines Change 14-01—2 June 2014. *J Spec Oper Med*. 2014;14(3): 13–38.
65. Muniz GW, Wampler DA, Manifold CA, Grudic GZ, Mulligan J, Moulton S, Gerhardt RT, Convertino VA. 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–S189.
66. Benov AO, Yaslowitz T, Hakim R, Amir-Keret R, Nadler A, Brand E, Glassberg A, Yitzhak VA, Convertino and HP. The effect of blood transfusion on compensatory reserve: a prospective clinical trial. *J Trauma Acute Care Surg*. 2017.

