The compensatory reserve: potential for accurate individualized goal-directed whole blood resuscitation

Victor A. Convertino and Natalie J. Koons

Hemorrhagic shock can be mitigated by timely and accurate resuscitation designed to restore adequate delivery of oxygen (DO_2). Current doctrine of using systolic blood pressure (SBP) as a guide for resuscitation can be associated with increased morbidity. The compensatory reserve measurement (CRM) is a novel vital sign based on the recognition that the sum of all mechanisms that contribute to the compensatory response to hemorrhage reside in features of the arterial pulse waveform. CRM can be assessed continuously and non-invasively in real time. Compared to standard vital signs, CRM provides an early, as well as more sensitive and specific, indicator of patient hemorrhagic status since the activation of compensatory mechanisms occurs immediately at the onset of blood loss. Recent data obtained from our laboratory experiments on non-human primates have demonstrated that CRM is linearly related to DO_2 during controlled progressive hemorrhage and subsequent whole blood resuscitation. We used this relationship to determine that the time of hemodynamic decompensation (i.e., CRM = 0%) is defined by a critical DO_2 at approximately 5.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. We also demonstrated that a target CRM of 35% during whole blood resuscitation only required replacement of 40% of the total blood volume loss to adequately sustain a DO_2 more than 50% (i.e., 8.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) above critical DO_2 (i.e., threshold for decompensated shock) while maintaining hypotensive resuscitation (i.e., SBP at ~90 mmHg). Consistent with our hypothesis, specific values of CRM can be used to accurately maintain DO_2 thresholds above critical DO_2, avoiding the onset of hemorrhagic shock with whole blood resuscitation.

Historically, the fields of emergency and critical care medicine have been challenged with monitoring capabilities that are limited in timely detection of hemorrhage and progression toward shock, as well as guiding accurate resuscitation. This monitoring challenge has been created by the dependence on measures of traditional vital signs that show minimal changes during the early stages of compensation. To address this limitation, we have focused research efforts over the past decade on the development of assessing a novel physiological phenomenon that has come to be known as the "compensatory reserve (CR)." The objectives of this review article are to: 1) review the concept and physiology that forms the basis for the measurement of the CR; 2) define the relationship between the CR and delivery of oxygen (DO_2); and 3) provide a new approach for the application of the compensatory reserve measurement (CRM) to guide resuscitation based on sustaining adequate DO_2.

DEFINING THE CR

The CR is defined as the sum of all integrated mechanisms of the body that together act to protect against inadequate DO_2 during conditions of low circulating blood volume and flow states.[1,2] Conceptual illustrations have been previously published that describe the relationship between lowering the CR with progressive reductions in blood volume[1,3–5] and tissue oxygenation[2]. Under healthy physiological baseline conditions defined by a state of "normovolemia," each individual has a potential of 100% CR. As circulating blood volume becomes progressively reduced during ongoing hemorrhage, various

From the Battlefield Health & Trauma Center for Human Integrative Physiology, United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Texas.

Address reprint requests to: Victor A. Convertino, PhD, US Army Institute of Surgical Research, 3698 Chambers Pass, Bldg. 3611, JBSA Fort Sam Houston, TX 78234; e-mail: victor.a.convertino.civ@mail.mil.

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physiological mechanisms (e.g., baroreflexes, neuroendocrine activation) initiate compensatory responses (e.g., tachycardia, vasoconstriction) that reduce the reserve for compensation. If the hemorrhage is not controlled, the finite reserve to compensate will be depleted (i.e., CR reaches 0%) and hemodynamic decompensation, manifested by a precipitous fall in arterial blood pressure, will ensue.

MESAURING THE CR

Algorithm development

The CRM represents a relative capacity for compensation, and is based on subtle changes in multiple features of each arterial waveform that can be obtained non-invasively from analog recordings such as the photoplethysmogram (PPG). The machine-learning algorithm for measurement of the CR was developed using analog arterial waveforms obtained from more than 260 healthy men and women ranging in age from 18 to 55 years of age during progressive reductions in central blood volume that resulted in decompensation.[6] These experiments resulted in the generation of a large data library that included more than 650,000 individual arterial waveforms. The algorithm is capable of processing 100 million data points per second, while identifying hundreds of specific features on each waveform that enable trending from various states of circulating blood volume to the time of hemodynamic decompensation. Each arterial waveform (represented in Fig. 1 as the monitored "Unknown Individual's Arterial Waveform") is the input to calculate an individual's reserve to compensate (i.e., CRM) based on comparison to the large data registry of reference waveforms from a CR of 100% to 0% (represented in Fig. 1 as the "Algorithm Waveform Library").

Comparisons with standard clinical measures

The CRM has proven to be an earlier as well as more sensitive and specific indicator of compromised physiological status under conditions of reduced central blood volume than blood pressure, SpO_2, heart rate, shock index, radial pulse character, end-tidal CO_2, respiratory rate, Glasgow Coma Score, blood pH, blood lactate, peripheral perfusion index, pulse pressure variability, and tissue oxygen, in both human experimentation and trauma patients.[1–3,5,7–12] The superior sensitivity of the CRM is reflected by earlier changes in CRM when compared to various standard vital signs while its specificity emerges from the capability that the algorithm has "learned" to distinguish individuals who compensate well to hemorrhage from those who do not.[6,13] Among other labels, these populations can be defined as "Good Compensators" who make up about two-thirds of individuals while the remaining one-third

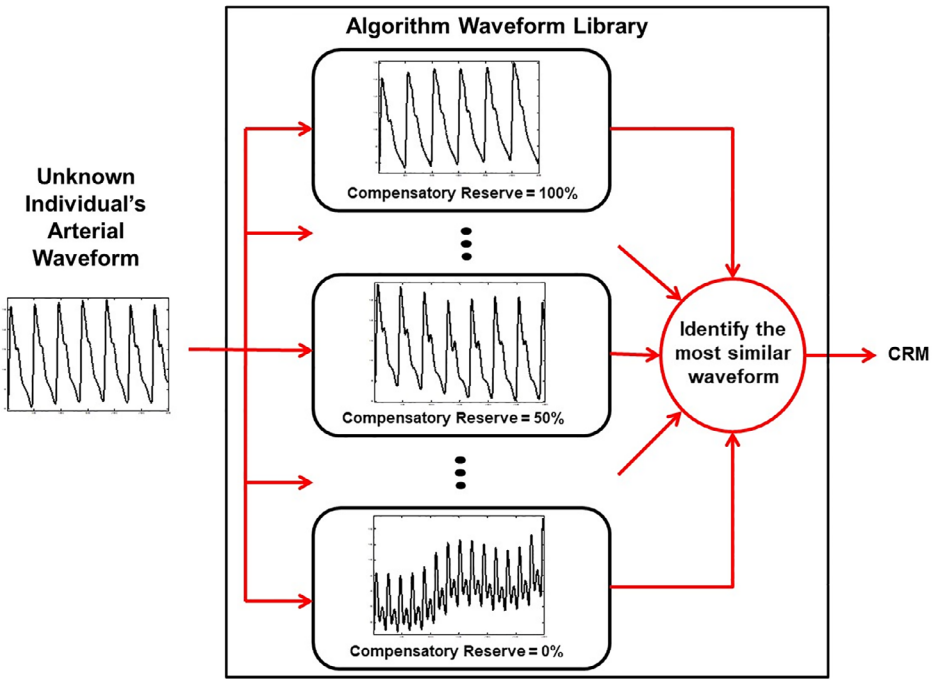

Fig. 1. Diagram illustrating the process of measuring the compensatory reserve (CR) with a machine-learning algorithm designed to assess beat-to-beat analog arterial waveform features in an individual patient unknown to the algorithm. The unknown arterial waveform is compared to a large waveform "library" collected from human subjects exposed to progressive reductions in central blood volume. The algorithm identifies the most similar waveform in the waveform library with the unknown sample to generate a CRM value. Modified from Convertino et al.[1,2,6]

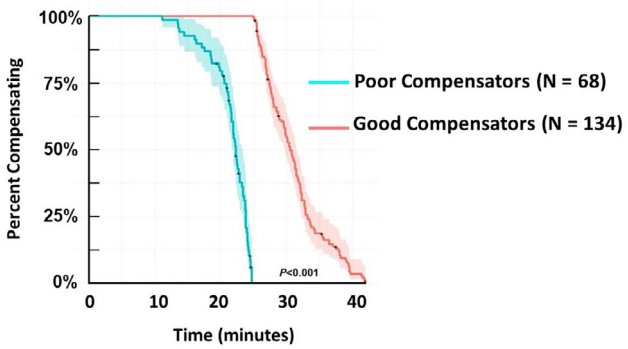

Fig. 2. Kaplan–Meier survival curve analysis of time to hemodynamic decompensation obtained from 202 healthy human subjects categorized as "Good" or "Poor" compensators. Hemodynamic decompensation was defined by a precipitous fall of systolic blood pressure (SBP) < 80 mmHg induced by progressive reductions in central blood volume. Modified from Schiller et al.[13]

comprises "Poor Compensators" (Fig. 2). As such, it is the capability of the CRM algorithm to "learn" specific features from an immense arterial waveform library that provides a monitoring technology capable of recognizing the DO_2 status of each individual patient. This characteristic defines the first monitoring capability that represents precision medicine.

Evidence for individual goal-directed resuscitation

Our initial recognition that the CRM could be used for accurate goal-directed resuscitation in individual patients emerged from a preliminary observation in our laboratory using lower body negative pressure (LBNP) on a human subject.[14] We observed that the CRM algorithm accurately tracked the reduction in central blood volume during progressive LBNP and its restoration during reversed LBNP (Fig. 3)]. Subsequently, we conducted an investigation on 20 healthy humans who underwent a controlled hemorrhage of an estimated 20% of their blood volume.[15] The results recorded from two specifically-selected subjects are presented in Fig. 4. Several characteristics of comparing CR responses became evident with this inter-subject comparison. First, the linear relationships between the reduction in CR with progressive loss of circulating blood volume in these two subjects demonstrates the ability of the algorithm to accurately track individualized real-time compensatory status. Second, the different slopes of the blood volume-CR relationships reflect the individual variability in the capacity to compensate for blood loss. In this regard, the CRM algorithm distinguished Subject 1 (Fig. 3, left panel) as a "Good Compensator" (i.e., relatively large CR) since he required use of only ~30% of CR despite losing more total blood volume (~1.4 liters) compared to Subject 2 (Fig. 3, right panel) who lost less blood volume (~1.2 liters) while using more (~70%) of his CR (i.e., "Poor Compensator"). In this comparison, the CRM was able to show greater specificity for measuring the status of circulating blood volume in individual patients than any standard vital signs that remained clinically normal during the hemorrhage.[15] Third, the comparison of these two individuals reinforces the concept that blood volume loss *per se* is not as sensitive and specific a predictor of clinical status than the measurement of the

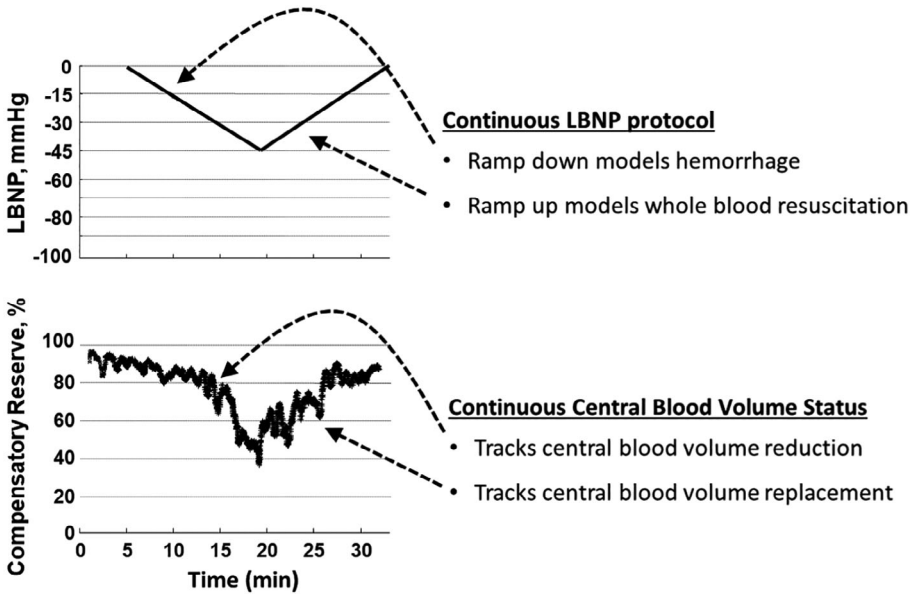

Fig. 3. Tracking reduction and replacement of central blood volume with the CRM algorithm. Top panel illustrates a ramp reduction in LBNP to simulate a continuous hemorrhage followed by an upward ramp to simulated whole blood resuscitation. Bottom panel shows the ability of the CRM to continuously track "hemorrhage" and "resuscitation profiles." Modified from Convertino.[14]

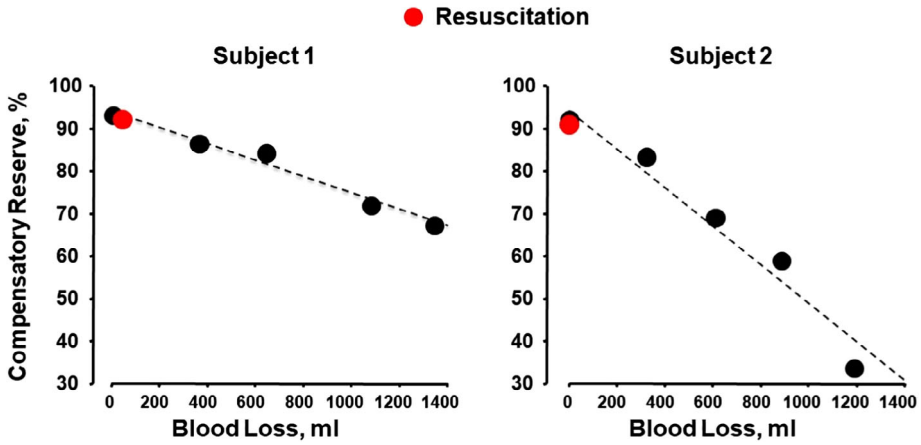

Fig. 4. Individual compensatory reserve (CR) responses of 2 subjects before and during a stepwise controlled hemorrhage of ~20% of estimated circulating blood volume (black circles) and whole blood resuscitation (red circles). Linear regression relationships are shown as dashed lines. Modified from Convertino et al.[15]

total capacity to compensate for hemorrhage. Fourth, returning the subjects' whole blood at the end of the experiment completely restored the CR (Fig. 3, red circles). This final observation, verified in animal and human clinical studies using various resuscitative methods,[14–18] supports the potential efficacy of using the CRM as a monitoring technology for accurate goal-directed fluid resuscitation.

RELATIONSHIP BETWEEN THE CR AND DO_2

Framework for a relationship between CRM and DO_2

The ability to accurately perform effective whole blood or fluid resuscitation has been limited by the absence of real-time continuous measurement of DO_2. The importance of such a capability is illustrated in Fig. 5 by the conceptual framework that describes the relationship between DO_2 and cellular requirement for oxygen utilization $(\dot{V}O_2)$ initially introduced by Ward and colleagues[19] but modified in this review to include other features. In the clinically "normal" resting state (represented by the area in the yellow box in Fig. 5), DO_2 can support virtually all of cellular energy demand at the level of baseline $(\dot{V}O_2)$ with a constant extraction of oxygen from the blood (i.e., no change in measured mixed oxygen saturation in the venous blood [SvO_2]). With the initiation of hemorrhage (red arrow moving along the continuum to the left of normal resting state), decreased total circulating red cells and blood volume translates to an immediate and progressive reduction DO_2 resulting from a combination of both lower cardiac output and oxygen carrying capacity. Despite this continuous reduction in DO_2 during the early stages of bleeding, $(\dot{V}O_2)$ (green line) can be maintained at baseline levels by "borrowing" oxygen from existing oxygen "reserves" bound to tissue myoglobin, blood hemoglobin, and dissolved in tissue and plasma as well as phosphocreatine [PCr] (depicted by the area in the pink box in Fig. 5). This O_2 "deficit" occurs immediately at the onset of hemorrhage, and is supported by the observation in humans of no change in systemic $V^{\cdot}O_2$ or blood lactate in the presence of reduced hemoglobin concentration,[20] progressive reductions in tissue oxygen,[21] and increasing oxygen extraction ratio (OER).[21] These oxygen stores have been

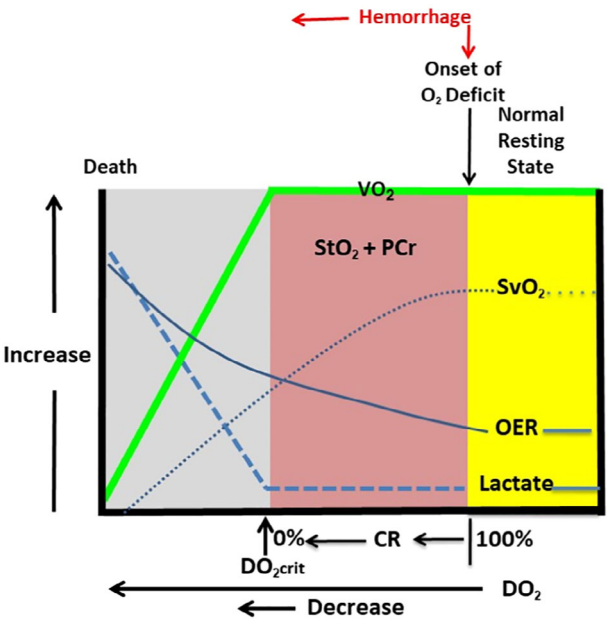

Fig. 5. Conceptual framework for continuum of metabolic relationship between oxygen delivery (DO_2), utilization (VO_2), and compensatory reserve (CR). Modified from Hooper et al.[19] and Convertino et al.[22]

referred to collectively as the "O_2 extraction reserve"[22] and constitute an important compensatory mechanism for supplementing oxygen unavailable to the cells as a result of reduced DO_2 during progressive blood loss. In this regard, we have included in the conceptual framework an indication that the O_2 extraction reserve represents a critical part of the CR. When DO_2 and O_2 extraction reserves reach their maximal capacity to maintain energy requirements of cells by aerobic metabolism (i.e., CR = 0), DO_{2crit} is reached as the initial phase of decompensated shock. Reaching DO_{2crit} is manifested by a precipitous fall in $(\dot{V}O_2)$ that requires a greater dependence on anaerobic glycolysis to maintain cellular energy production, resulting in accumulation of blood lactate (metabolic responses represented in the grey box). If this conceptual model for associating CR with DO_2 during the compensatory phase of hemorrhage is valid, we should expect a high positive correlation between CRM and DO_2 during conditions of changing blood volume.

Establishing a relationship between CRM and DO_2

We conducted an experiment using non-human primates to investigate characteristics of hemodynamic and CR responses during a progressive controlled hemorrhage,[23] in which we resuscitated the animals with their own shed whole blood at a rate of 50 mL/min.[17] During the experimental protocol, cardiac output, hemoglobin concentration, and saturation of oxygen in the arterial blood were measured, allowing for the calculation of systemic DO_2. CR was also calculated which allowed for a correlation analysis to be conducted with DO_2 (Fig. 6). Consistent with our hypothesis, we found that CR was linearly correlated with DO_2 during whole blood resuscitation. This relationship provided the unique opportunity to define critical DO_2 that might be translatable to human patient monitoring. There have been previous attempts to define critical DO_2 in humans by reducing DO_2 with acute isovolemic red blood cell reduction and infusion of a β-adrenergic antagonist.[24] The lowest level of DO_2 was found to be 7.3 ± 1.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ without changes in systemic $V^{\cdot}O_2$ and lactate, leading to the conclusion that critical DO_2 must be below this threshold in humans. With the regression equation generated from the non-human primate relationship, an average DO_2 of 13.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ was calculated for a CRM of 100%, very similar to the 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ value measured at baseline in humans.[24] Moreover, a critical DO_2 value of 5.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ calculated from the non-human primate data appears to be a reasonable value for humans since it meets the criteria of being less than 7.3 and given the striking similarity in the average response of CR between human and non-human primates during progressive stepwise reductions in central blood volume.[17] The translation of critical DO_2 to CRM in trauma patients is supported by the first clinically-available data showing the CRM becoming 0% at the point in time for four trauma patients in septic shock who went on to die.[25]

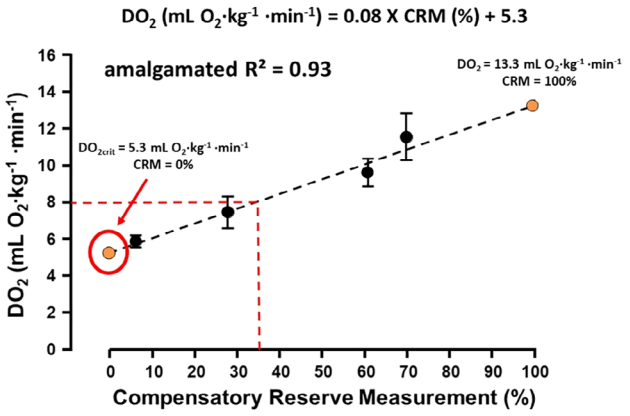

Fig. 6. Best-fit linear regression (broken line) and equation for the relationship between DO_2 and CRM during whole blood resuscitation generated from 12 baboons (DO_2 [mL $O_2 \cdot kg^{-1} \cdot min^{-1}$] = 0.08 × CRM [%] + 5.3). The plotted points correspond to CRM levels of 6% (end of hemorrhage) and 70% (end of resuscitation), with two CRM mid-points at 30% and 60%. The orange circles represent the calculated DO_2 at 100% CRM and at 0% CRM (i.e., DO_{2crit}). Data are expressed as mean ± SEM. Modified from Koons et al.[17]

Using CRM as a clinical practice guideline for whole blood resuscitation

By understanding the relationship between CRM and DO_2, resuscitation can be goal-directed based on specific thresholds (Fig. 7). For instance, a target threshold for resuscitation with CRM set at 35% would maintain a DO_2 of 8.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, well above the critical DO_2 of 5.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ required to avoid the onset of shock (Fig. 6). A CRM of 35% translated to 5 minutes of whole blood resuscitation at a transfusion rate of 50 mL/min (Fig. 7A). This 5-minute time point translated to a requirement of only about 40% replacement of the blood volume lost (200 mL of the 508 mL removed in the non-human primates; Fig. 7B) and a systolic blood pressure (SBP) of approximately 90 mmHg (Fig. 7C). Although this resuscitation strategy provides evidence to support the safety of hypotensive resuscitation, it is limited to the use of whole blood with the likelihood to be altered significantly with the use of other resuscitation fluids. Most importantly, the ability of CRM to provide the specificity to recognize inter- and intra-individual variability in DO_2 supports the notion of advancing the first individualized goal-directed resuscitation capability.

EVIDENCE FOR CRM USE IN CLINICAL SETTINGS

Although data from use in clinical settings are limited, CRM has been studied in patients when hemorrhage has contributed to compromised DO_2 with reduced circulating volume and/or loss in oxygen carrying capacity. In one study, CRM

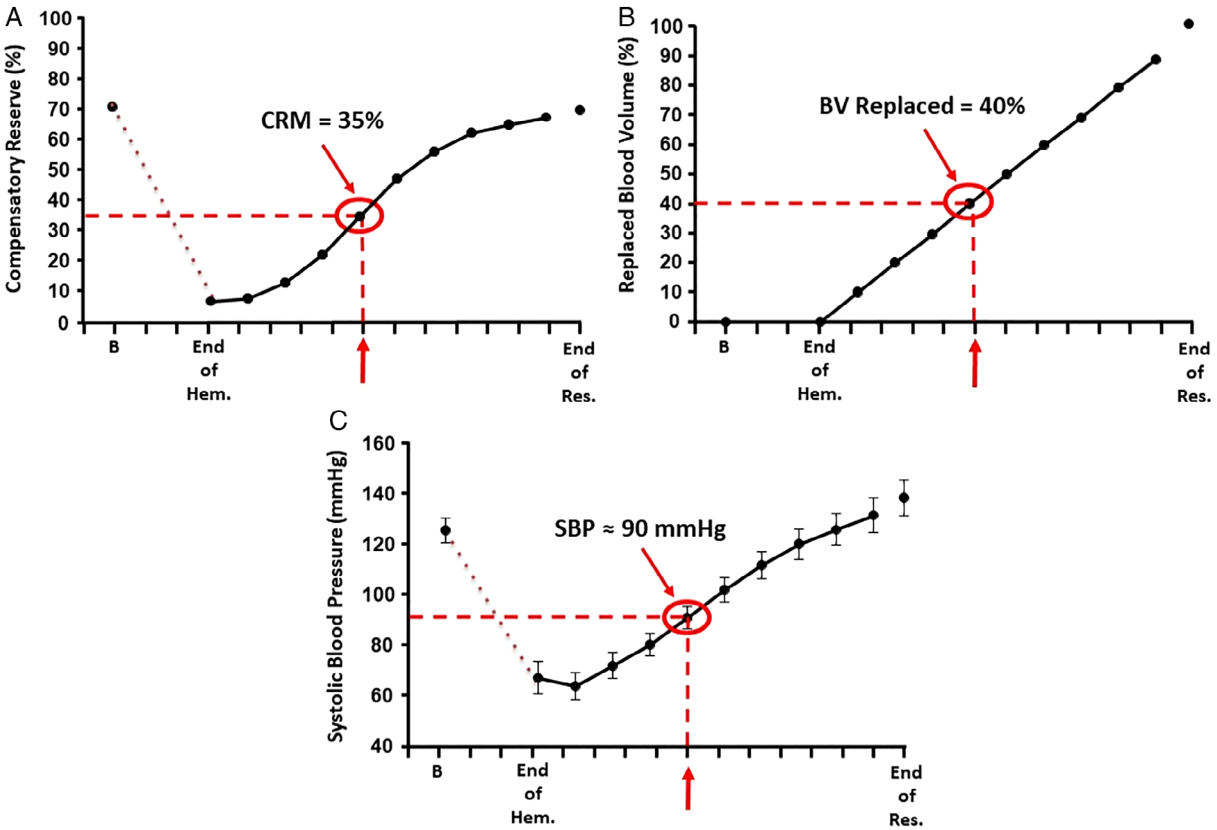

Fig. 7. Compensatory reserve (CR) measurement, replaced blood volume, and systolic blood pressure (SBP) at baseline (B), end of hemorrhage (End of Hem.), and whole blood resuscitation at a rate of 50 mL·min^{-1} (End of Res.). In this example, a target threshold for resuscitation with CRM set at 35% (Panel A) would require replacement of <40% of the lost blood volume (Panel B), and correspond to a SBP of ~90 mmHg (Panel C). Data are expressed mean ± SEM; N = 12. Modified from Koons et al.[17]

was found to be significantly lower (0.17) in patients with severe hemorrhage due to penetrating trauma resulting in relative anemia (as indicated by lower hematocrit and hemoglobin) compared with a CRM of 0.56 in patients with blunt trauma who were not actively bleeding.[26] When patients with gastrointestinal bleeding required red blood cell transfusion, a nearly 11% increase in CRM was associated with a 22% increase in hemoglobin.[11] CRM has consistently shown accuracy in assessing fluid interventions when applied during resuscitative treatment of hemorrhage in patients suffering from Dengue hemorrhagic fever,[16] blunt or penetrating trauma with significant blood loss,[18,26,27] internal bleeding,[11] and sepsis or septic shock.[25] With these clinical data taken together with the relationship between CRM and DO_2 presented in this review, the sensitivity of CRM in patients with lowered circulating red blood cells supports the notion that anemia may act as a trigger to support the need for transfusion therapy. If this hypothesis is supported by additional clinical trials, CRM technology may prove to provide practitioners with an accurate transfusion trigger for patients with severe anemia independent of their circulating volume. However, these clinical data have been obtained in a hospital setting where issues related to motion artifact have been minimized. Given that the photoplethysmogram waveform signal may be obtained optically from a finger oximeter, we cannot dismiss the possibility that accuracy and/or calibration of the CRM may be compromised by factors such as extreme environmental cold, skin color, interstitial fluid, or movement artifact. Further clinical investigations, particularly performed in pre-hospital or austere environments, will provide the opportunity to continue validation and refinement of the CRM technology.

CURRENT STATE OF THE TECHNOLOGY

The CRM technology focused on development of software amenable to being imbedded on standard pulse oximeter hardware capable of translating to a monitoring capability that can be easily and quickly applied in the pre-hospital setting by combat medics as well as in the hospital. An original algorithm for CRM received FDA clearance in 2016 with the intended use of "*continuous noninvasive monitoring. … which trends changes in intravascular volume relative to the*

individual patient's response to hypovolemia" [FDA approval DEN160020]. A second FDA clearance was obtained in 2018 for a smaller handheld device. However, in both cases, the software algorithm was cleared as part of an integrated system consisting of a pulse oximeter designed to send and display CRM measures on a hardware device. Significant challenges with mass production of these units have limited the availability of the technology for use in patient care. New algorithms are being developed with the goal of obtaining FDA clearance for the software that can ultimately be integrated onto current FDA-cleared medical monitoring devices to bring this technology capability to clinical practice in the near future.

CONCLUSION

The CRM, based on changing features of the arterial waveform, provides the first capability to measure the integrated compensatory response for individualized medical monitoring (i.e., precision medicine). Based on both experimental and clinical human investigations, it has consistently proven to have superior sensitivity and specificity for early and accurate detection of hemorrhage and prediction of hemorrhagic shock. The technology is FDA-cleared and can be used with non-invasive sensors (e.g., pulse oximeter) with "green-yellow-red" visual alarm indicators, but without the need for baseline measures. Because of a demonstrated linear relationship with DO_2, the CRM can be used to accurately guide whole blood resuscitation by defining specific levels of systemic oxygen delivery that can be easily recognized by clinicians. There is now quantifiable evidence presented in this review that using a target CRM above 0% can effectively guide accurate individualized whole blood resuscitation with hemodynamic stability while avoiding the onset of hemorrhagic shock following severe hemorrhage (i.e., keeping the critical DO_2 above 5.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$). As such, the CRM provides emergency caregivers a technology to support accurate goal-directed resuscitation that targets oxygenation to ensure optimizing end-organ perfusion in the individual trauma patient suffering with severe hemorrhage.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. 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.

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