Running on empty? The compensatory reserve index

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BACKGROUND: Hemorrhage is a leading cause of traumatic death. We hypothesized that state-of-the-art feature extraction and machine learning techniques could be used to discover, detect, and continuously trend beat-to-beat changes in arterial pulse waveforms associated with the progression to hemodynamic decompensation.

METHODS: We exposed 184 healthy humans to progressive central hypovolemia using lower-body negative pressure to the point of hemodynamic decompensation (systolic blood pressure > 80 mm Hg with or without bradycardia). Initial models were developed using continuous noninvasive blood pressure waveform data. The resulting algorithm calculates a compensatory reserve index (CRI), where 1 represents supine normovolemia and 0 represents the circulatory volume at which hemodynamic decompensation occurs (i.e., "running on empty"). Values between 1 and 0 indicate the proportion of reserve remaining before hemodynamic decompensation—much like the fuel gauge of a car indicates the amount of fuel remaining in the tank. A CRI estimate is produced after the first 30 heart beats, followed by a new CRI estimate after each subsequent beat.

RESULTS: The CRI model with a 30-beat window has an absolute difference between actual and expected time to decompensation of 0.1, with a SD of 0.09. The model distinguishes individuals with low tolerance to reduced central blood volume (i.e., those most likely to develop early shock) from those with high tolerance and are able to estimate how near or far an individual may be from hemodynamic decompensation.

CONCLUSION: Machine modeling can quickly and accurately detect and trend central blood volume reduction in real time during the compensatory phase of hemorrhage as well as estimate when an individual is "running on empty" and will decompensate (CRI, 0), well in advance of meaningful changes in traditional vital signs. (*J Trauma Acute Care Surg*. 2013;75: 1053–1059. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Hypotension; lower-body negative pressure; pulse oximetry.

Acute hemorrhage initiates a complex cascade of physiologic responses that are triggered and mediated by cellular signals, resulting in a wide array of cardiopulmonary changes throughout the body. Some of these changes can be measured using standard vital signs (e.g., heart rate [HR], systolic and diastolic blood pressures, electrocardiography, respiratory rate, and pulse oximetry). Researchers and clinicians who have studied and observed how these parameters change in the setting of acute blood loss have long assumed that hypotension and other signs and symptoms of hemorrhagic shock mark the beginning of circulatory compromise, rather than the beginning of decompensation. This fundamental assumption has been based on the observation that humans are able to compensate for large volumes of blood loss with little change in standard vital signs. As a result, unrecognized volume loss during the compensatory phase of hemorrhage can quickly lead to poor tissue perfusion, progressive acidosis, and sudden, unexpected hemodynamic decompensation, a condition that is usually recognized in its latter stages when resuscitative therapy is less effective and more difficult to control.

We hypothesized that state-of-the-art feature extraction and machine learning techniques could be used to analyze human vital sign waveform data, to reveal subtle waveform features that trend and correspond with the compensatory phase of hemorrhage. We further hypothesized that the resulting algorithm could differentiate low-tolerant (i.e., those most likely to develop early shock) from high-tolerant subjects, well in advance of clinically significant changes in currently available vital signs. We took our clue from recent work in robotics, which has used similar machine learning methods to design and develop autonomous robot navigation systems for use in unknown, outdoor unstructured environments. A key issue in the field of autonomous robot navigation is the need to identify safe or navigable paths far enough ahead of the robot, to allow smooth trajectories at acceptable speeds. A similar issue exists in clinical medicine and in particular the management of acute blood loss: clinicians need to know the clinical trajectory of a patient, so that they can anticipate the needs of the patient and intervene early, when the physiology is less complex and more likely to respond to therapy.

In general, there are many similarities in the types and amounts of data generated in robotics and medicine. Both fields rely on a variety of sensors to continuously investigate and respond to real-world situations, where previous knowledge and experience may be unknown or uncertain. A robot uses sensors and interpretive algorithms to explore its environment and make decisions about the actions it should perform to reach its intended goal. Clinicians are responsible for interpreting growing volumes of clinical data to identify underlying

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physiologic disturbance(s), anticipate the needs of the patient, and determine a course of action. Unfortunately, our current generation of physiologic sensors is relatively "dumb," insofar as they are designed to generate raw vital sign data, rather than to generate statistically unbiased, beat-to-beat "interpreted" information from these raw data.

We describe a novel mathematical algorithm that is capable of identifying and monitoring patients during the compensatory phase of reduced central blood volume. The original algorithm monitored continuous noninvasive blood pressure waveforms. This work led to the discovery that the shape of the waveform produced by the flow of blood through an artery is what allows the algorithm to determine the degree of compensation. As a result, the current algorithm only monitors pulse oximetry waveforms and in real time analyzes how a select group of waveform features change over time, from normovolemia all the way to decompensation. By simultaneously monitoring multiple waveform features and knowing how these features change with central volume loss, the algorithm is able to instantaneously determine how far or near a patient may be from the point of decompensation. The algorithm outputs a single value in beat-to-beat fashion, termed the compensatory reserve index (CRI) (Fig. 1). CRI is displayed as a fuel gauge, where the number 1 represents replete central volume or a "full tank of gas" and 0 is empty. Values between 1 and 0 indicate the compensatory reserve of the patient or the proportion of reserve capacity that remains to compensate for central volume loss before the onset of decompensation.

PATIENTS AND METHODS

Lower-Body Negative Pressure

The US Army Institute of Surgical Research (USAISR) has an ongoing research program using lower-body negative pressure (LBNP) to simulate loss of central blood volume (i.e., hemorrhage) in humans.[1–10] Subjects for the present study were healthy, nonsmoking normotensive males or females, with ages ranging from 18 years to 55 years. Subjects were required to lie on their back with their lower body sealed in a steel vacuum chamber (Fig. 2). As the vacuum chamber applied increasing amounts of negative pressure to each subjects' lower body, blood was redistributed from the upper body to the lower body (below the iliac crests). The LBNP experimental protocol consists of a 5-minute baseline period followed by stepwise exposure to 5 minutes of decompression at each of the following negative pressures: −15, −30, −45, −60, −70, −80, −90, and −100 mm Hg. A designated physician or advanced cardiac life support provider is present during each experiment, and each subject is taken to a point where symptoms of hemodynamic instability are evident, such as gray-out, a progressive diminution of systolic blood pressure (SBP) less than 80 mm Hg, voluntary subject termination caused by discomfort (such as sweating, nausea, or dizziness), or until completion of the −100 mm Hg level. In any of these instances, the LBNP is discontinued, and blood that has pooled in the lower body is immediately redistributed to the body as a whole. The subject then recovers for a 1-hour period.

Continuous waveform data were collected at 500 Hz using WinDaq data acquisition software (Dataq Instruments, Akron, OH). Deidentified waveform data were analyzed at Flashback Technologies, Inc. (Boulder, CO), where feature extraction and advanced statistical methods were used to build models of central volume loss culminating in collapse physiology. Following initial evaluation of multiple signals, noninvasive arterial blood pressure waveform data generated by a Finometer PRO blood pressure monitor (Finapres Medical Systems, Amsterdam, the Netherlands; see www.finapres.com) was identified as a feature rich signal for algorithm development. An unbiased

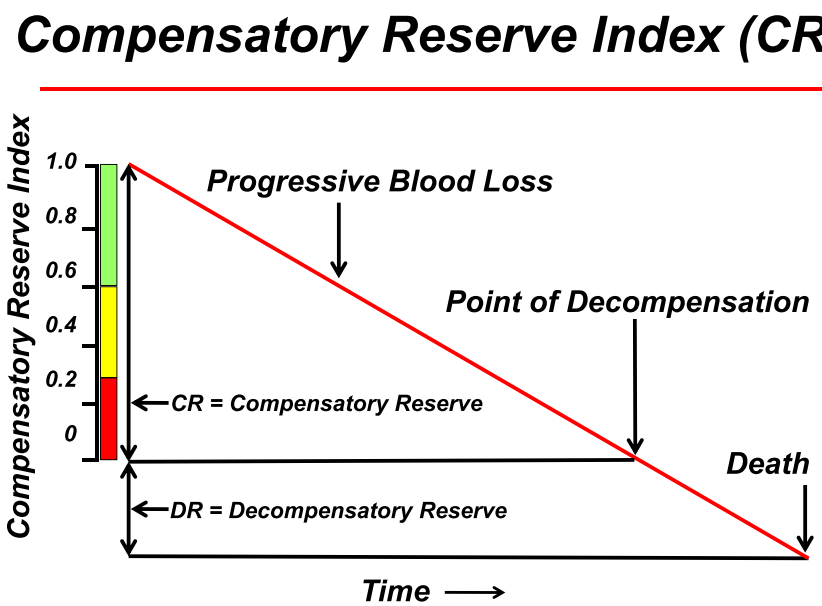

Figure 1. The CRI is indicative of the individual-specific proportion of intravascular volume remaining before the onset of cardiovascular collapse. The *red line* shows a hypothetical decline in CRI over time in the setting of blood loss caused by hemorrhage or plasma leakage. A calculated CRI of 1 represents normovolemia, whereas a calculated CRI of 0 represents the point of hemodynamic decompensation.

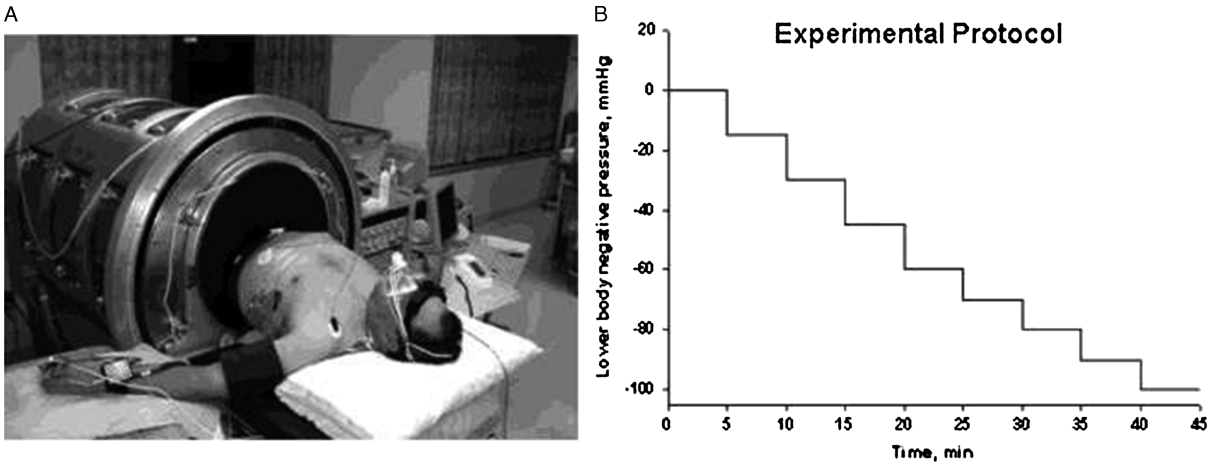

Figure 2. Subject in the LBNP device (*A*) and the LBNP protocol (*B*). See Convertino et al.[2]

estimate of the accuracy of the modeling approach was obtained by using data from each human subject as a true test subject. Thus, when testing on a specific test subject, only data from other subjects were used to construct the model. The test subject data were termed *test data*, and data from all other subjects were termed *learning data*, with no mixing between the two sets. This gave a statistically unbiased estimate of how accurate the modeling approach was for a subject not in the data set, that is, how well each approach worked on future test subjects.

Feature Extraction and Machine Learning

We hypothesized that noninvasive waveform data collected during LBNP experiments contained information on the compensatory phase of central volume loss; however, we did not know what components of the waveforms were important, whether some might be more important than others or whether some were more important at different levels of compensation. To address these questions, we turned our attention to feature extraction and machine learning methods, which have enabled robots to self-learn. Feature extraction is a form of dimensionality reduction that may be used to facilitate pattern recognition in image and signal processing. Machine learning is concerned with the design and development of algorithms that can be used to automatically extract information (features) from large volumes of data. The combination of these analytic technologies provides a unique computational "tool" to rapidly make sense of very large data sets. Our goal was to use an unbiased approach to learn the waveform features that correspond with the compensatory phase of central volume loss.

We evaluated a number of state-of-the-art discriminative machine learning algorithms, including a number of unsupervised and manifold techniques.[11–18] Unsupervised machine-learning algorithms are not provided with classification labels; their task is to develop classification labels independent of human bias and independently search for similarity between pieces of data to determine whether they can be characterized as forming a group. These groups are termed *clusters*. In unsupervised classification, often known as *cluster analysis*, the algorithm itself must independently group the data. This can be a potentially difficult but enlightening task because the algorithm works in iterative ways to reach a stable configuration that makes sense. Our experience developing algorithms for robotic situational awareness led us to apply a variety of clustering algorithms to vital sign waveform data generated during LBNP experiments. The appropriate clustering algorithm and parameter settings were varied, depending on the individual data set and intended result(s). This iterative process led to the selection of multiple features within the noninvasive arterial waveform that trend the compensatory phase of central volume loss.

CRI Algorithm

The CRI algorithm is designed to estimate the following quantity:

$$CRI = 1 - \frac{BLV}{BLV_{HDD}} \qquad \text{(Eq.1)}$$

where BLV is the current blood loss volume of the patient and BLV_{HDD} is the BLV at which the patient will enter hemodynamic decompensation.

The CRI calculation (Eq. 1) assumes knowing both an individual's BLV at any given time as well as that individual's BLV_{HDD} caused by acute blood loss. Because of obvious ethical reasons, acquiring reference data in actual human blood loss studies is unacceptably dangerous to the well-being of the subject. We know, however, that LBNP closely mimics the hemodynamic,[6] autonomic,[2] respiratory,[19] and metabolic[20] responses of hemorrhage observed in anesthetized animal models.[4,21] Moreover, cardiovascular responses to LBNP are reproducible in the same subjects studied more than once in the same physiologic state.[3] As a result, we used LBNP as a scientifically justified, ethical substitute for modeling the reduction in central blood volume to hemodynamic decompensation in humans. Thus, we use the relationship λ between LBNP and BLV as follows:

$$BLV = \lambda \cdot \text{LBNP} \qquad \text{(Eq.2)}$$

This allows the estimate of CRI for an individual undergoing a LBNP experiment to be calculated as follows:

$$CRI = 1 - \frac{BLV(t)}{BLV_{HDD}} \approx 1 - \frac{\lambda \cdot \text{LBNP(t)}}{\lambda \cdot \text{LBNP}_{HDD}} = 1 - \frac{\text{LBNP(t)}}{\text{LBNP}_{HDD}} \qquad \text{(Eq.3)}$$

where LBNP(t) is the LBNP level that the individual is

experiencing at time t and $LBNP_{HDD}$ is the LBNP level at which the individual will enter hemodynamic decompensation.

Therefore, LBNP studies form the fundamental framework for development of the CRI.

Distinguishing Individual Variability

Based on individual tolerances to reductions in circulating central blood volume, subjects were classified as low tolerant (unable to complete −60 mm Hg of LBNP) or as high tolerant (completed at least −60 mm Hg of LBNP) based on previously defined criteria.[22] Models were built using Finometer waveform data from 183 LBNP subjects and were tested on the 184th. This process was repeated 184 times. Of these 184 subjects, 57 subjects were classified as low tolerant and 127 subjects were classified high tolerant.

RESULTS

The final model provided the first CRI value at 30 beats of the heart, and a new value was calculated with each subsequent beat of the heart. Figure 3 demonstrates the accuracy of the individual CRI estimation curve fit for estimated beat-to-beat values of LBNP (*green lines*) compared with the actual LBNP level (*red line*) in two subjects with low tolerance to reduced central blood volume (*left panels*) and 2 subjects with high tolerance to reduced central blood volume (*right panels*). These curve fits were typical of all 184 subjects whose waveform data have been analyzed. The average correlation coefficient between the estimated CRI and the CRI reference (Eq. 3) was $r^2 = 0.94$, with a mean (SD) absolute difference of CRI of 0.1 (0.09). For all 184 subjects, the CRI value dropped to less than 0.3 before the subject went into collapse. The correlation between predicted and actual LBNP level for hemodynamic decompensation was 0.89.

DISCUSSION

Humans are able to compensate for significant hemorrhage through various neural and hormonal mechanisms, allowing their vital signs to remain relatively stable until these adaptive compensatory mechanisms are gradually overwhelmed, resulting in hemodynamic compromise and the onset of hemorrhagic shock. Unfortunately, traditional vital signs such as HR, blood pressure and SaO_2 are notoriously unreliable until late in the setting of acute blood loss, leading us and other authors to question their value in assessing the hemodynamic state of a patient.[23,24] We previously reported that the vital signs obtained from subjects, who are included in the cohort of those participating in the current study, failed to change during the early period of compensation to reduced central blood volume.[25] Combined parameters such as the shock index (HR / SBP) and algorithms that use waveforms from multiparameter monitors have also failed to reliably discriminate patients with ongoing hemorrhage.[26] These clinical observations are supported by numerous experimental studies, demonstrating the human body's ability to compensate for acute reductions in central volume (Table 1).[1,2,7,20,25,27–30] The lack of specificity associated with traditional vital signs has limited their usefulness in the early detection and monitoring of acute blood loss. The resulting challenge has been to find

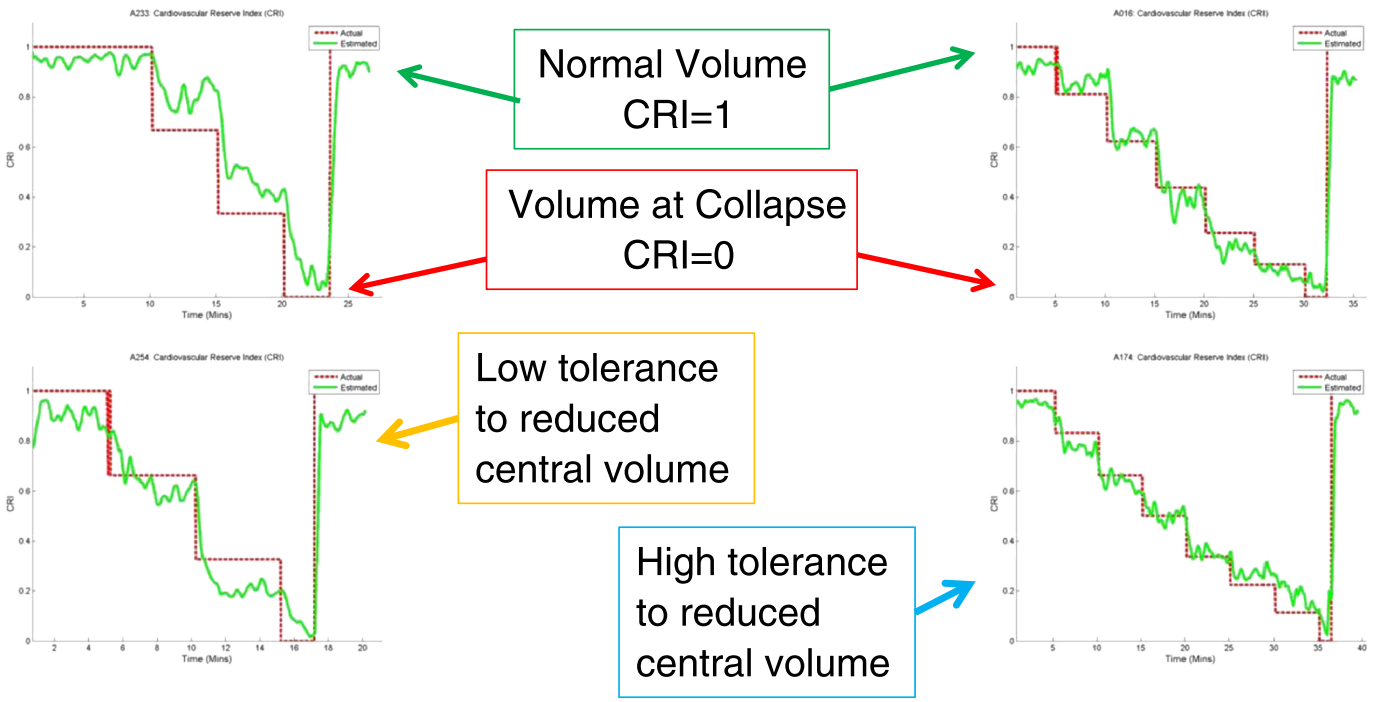

Figure 3. CRI estimation accuracy results on 4 of the 184 LBNP subjects who went to presyncope during LBNP studies. The *red line* indicates the ground truth CRI value, which can only be determined using the maximum tolerated LBNP (blood loss) after a subject achieves hemodynamic decompensation. The *green line* shows the beat-to-beat CRI estimates by CipherBP. As can be seen from the plots, there is a wide range of reserve volumes between subjects, and they can be generally classified as having low or high tolerance to blood loss. In either case, the CRI estimates by CipherBP effectively track the true CRI value.

TABLE 1. Changes in Traditional Vital Signs and Hemodynamic Parameters During Progressive Central Hypovolemia

Vital Sign or Parameter	Change During Progressive Central Hypovolemia	Reference(s)
SBP	Late	Convertino et al.[1]
		Cooke et al.[27]
		Convertino et al.[2]
Diastolic blood pressure	Late	Convertino et al.[1]
		Convertino et al.[2]
Mean blood pressure	Late	Convertino et al.[1]
		Convertino et al.[2]
		McManus et al.[28]
HR	Not specific	Cooke et al.[27]
		Convertino et al.[2]
Shock index (HR / SBP)	Late	Vansickle et al.[29]
O_2 saturation (pulse ox)	Late	Convertino et al.[2]
		Soller et al.[30]
Radial pulse	Late	Ryan et al.[7]
End-tidal CO_2	Late	McManus et al.[28]
Respiratory rate	Late	McManus et al.[28]
Glasgow Coma Scale (GCS) score	Late	Ryan et al.[7]
Blood pH	Late	Convertino et al.[2]
		Ward et al.[20]
Blood [lactate]	Late	Convertino et al.[2]
		Ward et al.[20]
Blood base excess	Late	Convertino et al.[2]
		Ward et al.[20]
CRI	Early	Convertino et al.[25]
		Vansickle et al.[29]

physiologic waveform metrics that represent the mechanisms of compensation.

We used novel analytic tools to analyze a large database of continuous noninvasive waveform recordings obtained from human LBNP subjects, who underwent controlled reductions in central blood volume from normovolemia to decompensation. In support of our hypothesis, we were able to develop an algorithm that accurately tracks the compensatory phase of central volume loss for high- and low-tolerant subjects. Previous studies have shown that individuals who are tolerant to reduced central blood volume display higher sympathetic nerve activity and HR,[31] more blood pressure oscillations,[32] and greater vasoconstrictor reserve,[33] compared with low-tolerant individuals. By leveraging recent developments in machine learning, advanced statistical methods, and fast computing technology, we have, in essence, teased apart the physiology of compensation for individual subjects.

The ability of the CRI algorithm to accurately distinguish individuals with varying tolerances to reduced central blood volume can be attributed to a unique function of the algorithm, which analyzes and compares the entirety of each waveform in a window of time to trend subtle features that correspond with varying degrees of central volume loss. This analytic advantage is based on the relationship described by the arterial waveform (ejection wave) and peripheral vascular resistance (reflected wave). As such, all mechanisms associated with compensation for central volume loss are represented in each waveform. Thus, subtle changes in waveform features, which are detected by the algorithm, allow it to differentiate individual patients (i.e., those with high or low tolerance to central volume loss) within the first 30 beats of monitoring and every beat thereafter.[25] Furthermore, because the algorithm is built upon a learning framework, it will become more accurate and more broadly applicable as it is exposed to increasing volumes of modeling data. We are unaware of any other clinical algorithm that is capable of providing real-time moment-to-moment insight into the compensatory phase of central volume loss for individual patients without a reference measurement at normovolemia.

Photoplethysmography of peripheral perfusion can be displayed by pulse oximeters, with the photoplethysmographic (PPG) signal being derived from the infrared light absorbtion waveform. Our realization that the entire shape of the arterial waveform had to be modeled to maximize computational model accuracy, in addition to existing literature on the correlation between features of the pulse oximeter PPG waveform and central blood volume,[34–36] led us to hypothesize that our methods could be applied to the pulse oximetry waveform. Such an approach would enable the development of a small, lightweight noninvasive sensor for monitoring central volume loss. With the use of the same approach, only this time applying feature extraction and machine-learning techniques to PPG waveforms generated by Masimo and Nonin pulse oximeters, CRI accuracy results have been obtained for 30 high- and low-tolerant LBNP subjects. CRI models for both devices are similarly accurate, with mean absolute differences between actual and expected CRI of 0.1, with an SD of 0.09. These findings have led to the creation of a CRI monitor based on a standard pulse oximeter signal that includes a user-friendly "bar" (Fig. 4) that moves up or down and changes color in accordance with patient status: adequate compensation (green: CRI > 0.6), moderately compromised (amber: CRI, 0.6–0.3), and unstable (red: CRI < 0.3).

Figure 4. CipherOx is a small bluetooth-enabled pulse oximeter with a wrist worn CRI display, mini-USB port for battery charging and data download.

Key characteristics of the CRI algorithm, which make it uniquely suited for real-time monitoring of central volume loss caused by hemorrhage or dehydration, include the following:

1. Directly estimates how close a subject is to hemodynamic decompensation, independent of how tolerant the subject is to volume loss.
2. First CRI estimate produced at 30 beats of the heart; thereafter, a new CRI estimate is made after each subsequent heart beat.
3. The algorithm does not require a baseline reading at normovolemia. Accurate and robust CRI estimates can be made at any stage of central volume loss, for both high- and low-tolerant individuals.
4. Can be put into a small, portable, and easy-to-use form factor (Fig. 4).

In contrast, other methods (such as stroke volume and cardiac output), which can be used to monitor volume loss (hemorrhage)

1. Need a baseline reading at normovolemia to assess volume status.
2. Cannot assess closeness to hemodynamic decompensation and therefore cannot effectively assess low-tolerant individuals.
3. Have much larger, more cumbersome form factors (e.g., the Finometer PRO, electrical bioimpedance).

Study Limitations

Ethical and real-world constraints limit the types and amounts of data available for describing significant human hemorrhage. For the same reason, direct comparisons between LBNP and severe hemorrhage are not possible. However, LBNP, as a surrogate model of acute blood loss leading to cardiovascular collapse, has provided an unequaled opportunity to analyze compensatory physiologic responses to progressive central hypovolemia. Although there seems to be no evidence to suggest that injury and pain would alter the fundamental features of the waveforms that were used to build the CRI algorithm, the possibility that trauma, in addition to central blood loss, could influence this relationship cannot be dismissed. Although the LBNP protocol limits enrollment to subjects who are 18 years to 55 years of age, newly acquired CRI measurements in children 3 years to 9 years of age (unpublished data) with hemorrhage due to Dengue virus demonstrate the ability of the algorithm to track changes in circulating blood volume in younger patients. We do not yet know how well the algorithm will perform in older age groups. Furthermore, because the LBNP protocol applies LBNP in a controlled stepwise manner and not in a continuous manner more akin to actual bleeding, we have not developed models that are able to predict time to collapse; we do, however, envision a future version of the algorithm with this capability. Notwithstanding these limitations, our premise that CRI is directly applicable to bleeding patients is supported by the striking similarity of physiologic responses observed during LBNP and severe hemorrhage.[2,3,6,8,9,37–40]

Balancing the limitations of the current study are the significant potential advantages of this technology. The CRI algorithm provides a continuous, beat-to-beat objective interpretation of continuous noninvasive blood pressure or PPG waveform data that do not require specialized expertise to interpret. The CRI algorithm does not require baseline or convalescent data, so it can be acquired in real-time during emergent or routine clinical encounters. Furthermore, the CRI algorithm can interpret waveform data from widely available low-cost devices, such as portable pulse oximeters. Thus, rapid translation of the present findings to low-resource settings seems highly feasible and would provide information that may not be obvious to clinicians and other health care providers. In light of these considerations, the present findings are highly encouraging for further evaluation of the CRI algorithm in actual trauma and numerous other clinical settings.

CONCLUSION

The application of feature extraction and machine learning techniques to noninvasive vital sign waveform data, derived from a human model of severe acute blood loss, has led to the discovery of several waveform features that can be used to monitor subjects throughout the compensatory phase of central volume loss to a point when they are "running on empty." The computer-based methods that underlie this technology are able to tease apart and recognize subtle, beat-to-beat changes within traditional waveform data of individual subjects, well before these changes are clinically apparent.

AUTHORSHIP

S.L.M., J.M., and G.Z.G. conceived the application of data analytics to test the hypothesis. S.L.M., J.M., G.Z.G., and V.A.C. developed the concept of CRI. V.A.C. performed and oversaw the data collection. J.M. and G.Z.G. developed the algorithms and analyzed the data. All authors participated in writing and revising the manuscript.

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DISCLOSURE

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