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Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms

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Convertino VA, Grudic G, Mulligan J, Moulton S. Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. *J Appl Physiol* 115: 1196–1202, 2013. First published August 8, 2013; doi:10.1152/japplphysiol.00668.2013.— Trauma patients with "compensated" internal hemorrhage may not be identified with standard medical monitors until signs of shock appear, at which point it may be difficult or too late to pursue life-saving interventions. We tested the hypothesis that a novel machine-learning model called the compensatory reserve index (CRI) could differentiate tolerance to acute volume loss of individuals well in advance of changes in stroke volume (SV) or standard vital signs. Two hundred one healthy humans underwent progressive lower body negative pressure (LBNP) until the onset of hemodynamic instability (decompensation). Continuously measured photoplethysmogram signals were used to estimate SV and develop a model for estimating CRI. Validation of the CRI was tested on 101 subjects who were classified into two groups: low tolerance (LT; $n = 33$) and high tolerance (HT; $n = 68$) to LBNP (mean LBNP time: LT = 16.23 min vs. HT = 25.86 min). On an arbitrary scale of 1 to 0, the LT group CRI reached 0.6 at an average time of 5.27 ± 1.18 (95% confidence interval) min followed by 0.3 at 11.39 ± 1.14 min. In comparison, the HT group reached CRI of 0.6 at 7.62 ± 0.94 min followed by 0.3 at 15.35 ± 1.03 min. Changes in heart rate, blood pressure, and SV did not differentiate HT from LT groups. Machine modeling of the photoplethysmogram response to reduced central blood volume can accurately trend individual-specific progression to hemodynamic decompensation. These findings foretell early identification of blood loss, anticipating hemodynamic instability, and timely application of life-saving interventions.

hemorrhage; blood pressure; stroke volume; modeling; shock

ACUTE UNCONTROLLED HEMORRHAGE with subsequent hemodynamic decompensation (i.e., early stage of hemorrhagic shock) is a leading cause of traumatic death, both domestically (7, 32) and on the battlefield (3, 19). Casualty survival rates increase when patients with ongoing hemorrhage are identified early and appropriate treatment is rendered (5, 33). Current methods for assessing the severity of hemorrhage during the early stages of compensation are severely limited, however, because they are based on standard vital signs (e.g., heart rate, systolic and diastolic blood pressure, electrocardiogram, respiratory rate, pulse oximetry). As a result, many clinicians have wrongly assumed that hypotension and other signs and symptoms of hemorrhagic shock mark the beginning of circulatory compromise, rather than the beginning of decompensation (11, 13, 26). Consequently, unrecognized volume loss during the early compensatory phase of hemorrhage can quickly lead to poor tissue perfusion, progressive acidosis, and sudden, unexpected hemodynamic decompensation, a condition that may lead to less effective interventions and potentially irreversible shock. As such, a profound need exists for advanced diagnostic approaches that identify the complex and dynamic nature of physiological compensation among individual patients "at risk" for hemorrhagic shock, well before they manifest unstable vital signs.

The shape and oscillatory pattern of arterial waveforms change when circulating blood volume is reduced. These changes occur in response to compensatory alterations in cardiac and vascular functions, which, in turn, alter features of the ejected and reflected pressure waves (4). With the emergence of advanced sensor technologies like photoplethysmography and volume-clamp pressure waveforms, the noninvasive recording of analog arterial waveform signals has become feasible, enabling real-time estimations of stroke volume during progressive reductions in central blood volume. Because of the photoplethysmogram relationship with cardiac filling and output, such measurements are characterized by greater specificity and sensitivity of the hemorrhage status of individuals compared with standard vital signs (13, 37). However, the diagnostic capability of models used to calculate an estimation of stroke volume from individual waveforms may be limited by their inability to include variability in pulse amplitude and frequency and pressure oscillations (12, 21, 28).

We have demonstrated that state-of-the-art feature-extraction and machine-learning techniques can be used to analyze analog waveform data in real time to reveal subtle waveform features that trend the compensatory phase of acute volume loss (8, 11, 25). The advantage of this approach is that multiple features of the photoplethysmographic waveform, including those features that contribute to the variability and oscillatory characteristics of hypovolemic waveforms, are simultaneously abstracted and normalized to determine how near or far an individual is from decompensation. This is unlike previous algorithms that have been derived for calculating stroke volume. It was the purpose of this investigation to evaluate the efficacy of a new concept, called the compensatory reserve index (CRI), designed to estimate how close an individual is to hemodynamic decompensation. We hypothesized that this algorithm could differentiate the tolerance of individual subjects well in advance of clinically significant changes in stroke volume or other currently available vital signs.

METHODS

Subjects and ethical approval. Two hundred one nonsmokers, consisting of 114 men and 87 women, volunteered to participate in this study (mean ± SE: age 30 ± 1 yr, height 172 ± 1 cm, weight 74.6 ± 1.4 kg). All experimental procedures were conducted in accordance with protocols reviewed and approved by the Brooke

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Army Medical Center Institutional Review Board and the Institutional Review Board of the Office of Human Research Protection under the US Army Medical Research and Materiel Command. Prior to inclusion, all subjects underwent a medical history and physical examination by a physician to ensure that they had no previous or current medical conditions that might preclude their participation. Female subjects were not pregnant, as confirmed by a urine pregnancy test 1 h prior to experimentation. Subjects were instructed to maintain their normal sleep patterns, refrain from exercise, and abstain from caffeine and other autonomic stimulants including prescription or nonprescription drugs for at least 24 h prior to each experiment. Subjects received a verbal and written briefing of all procedures and risks associated with the study and were made familiar with the laboratory, the protocol, and the instrumentation. Subjects were encouraged to ask questions of the investigators before giving their written informed consent to participate.

Experimental protocol. Subjects were instrumented with a standard four-lead electrocardiogram recording, and an integrated photoplethysmograph/volume-clamp finger blood pressure sensor (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) to record beat-by-beat finger arterial pressure. The Finometer blood pressure cuff was placed on the middle finger of the left hand, which in turn was laid at heart level.

Progressive stepwise reductions in central blood volume were induced by application of lower body negative pressure (LBNP) in order to simulate, as closely as possible in healthy human volunteers, the hemodynamic challenges associated with severe hemorrhage (16). Subjects assumed the supine position within an airtight chamber and were sealed at the level of the iliac crest by way of a neoprene skirt. Each subject completed a protocol designed to test his/her LBNP tolerance. The LBNP protocol consisted of a 5-min rest period (baseline) followed by 5 min of chamber decompression at −15, −30, −45, and −60 mmHg and then additional increments of −10 mmHg every 5 min until the onset of hemodynamic decompensation or the completion of 5 min at −100 mmHg. The attending investigator closely monitored each subject in real time to determine the onset of hemodynamic decompensation, identified by a precipitous fall in systolic arterial blood pressure concurrent with presyncopal symptoms such as bradycardia, gray-out (loss of color vision), tunnel vision, sweating, nausea, or dizziness. No subject completed 5 min at −100 mmHg, and all subjects expressed one or more subjective presyncopal symptoms that coincided with a precipitous fall in systolic arterial blood pressure below 90 mmHg (class III shock).

A machine-learning framework for estimating compensatory reserve index. As detailed previously (23, 25), state-of-the-art feature-extraction and machine-learning techniques were used to collectively process the arterial waveforms obtained from the Finometer blood pressure cuff during LBNP experiments. The CRI algorithm estimates the remaining proportion of physiological reserve available to compensate for changes in effective circulating blood volume by comparing waveforms over a 32-heartbeat window to reference waveforms obtained from humans during progressive central hypovolemia induced by the LBNP protocol. For this study, these reference waveforms were obtained from a subset of 100 of the original 201 subjects. We were not able to find a single feature or subset of features from a single waveform containing sufficient information to estimate CRI. Rather, robust CRI estimates required assessment of the entire waveform over 32 heartbeats and comparison to the reference waveforms. The estimated CRI value corresponds to the CRI value of the most similar reference waveform in the training set (Fig. 1).

For clinical simplicity, the CRI was normalized on a scale of 1 to 0 (100% to 0%), where "1" reflected the maximum capacity of physiological mechanisms (e.g., baroreflexes, respiration) to compensate for reduced central blood volume and "0" implied imminent cardiovascular instability and decompensation. Values between "1" and "0" indicated the proportion of compensatory reserve remaining. In concept, CRI is the following quantity:

$$\mathrm{CRI} = 1 - \frac{\mathrm{BLV}}{\mathrm{BLV}_{\mathrm{HDD}}} \qquad (1)$$

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

Within the LBNP model we use the relationship λ between LBNP and BLV as follows:

$$\mathrm{BLV} = \lambda \cdot \mathrm{LBNP} \qquad (2)$$

This allows estimation of CRI for an individual undergoing an LBNP experiment as follows:

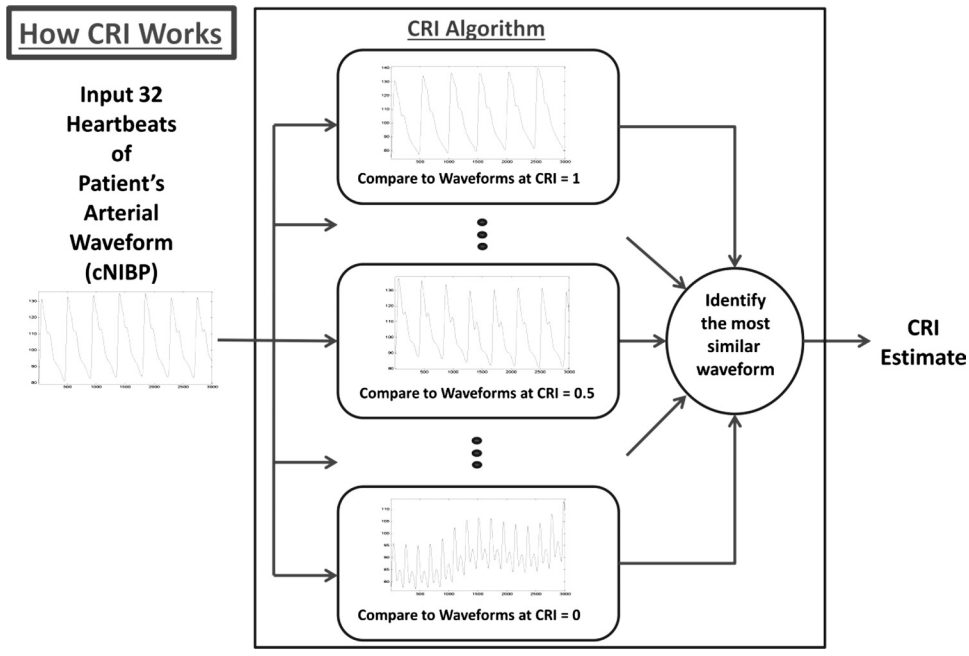

Fig. 1. Diagrammatic representation of compensatory reserve index (CRI) estimation generated from an algorithm designed to compare beat-to-beat arterial blood pressure waveform tracings over an interval of 32 heartbeats in a human subject. Waveform features were used to develop the machine-learning model based on comparisons with reference waveforms generated from progressive levels of CRI values from "1" to "0." See text for explanation. cNIBP, continuous noninvasive blood pressure.

$$\mathrm{CRI} = 1 - \frac{\mathrm{BLV}(t)}{\mathrm{BLV}_{\mathrm{HDD}}} \approx 1 - \frac{\lambda \cdot \mathrm{LBNP}(t)}{\lambda \cdot \mathrm{LBNP}_{\mathrm{HDD}}} = 1 - \frac{\mathrm{LBNP}(t)}{\mathrm{LBNP}_{\mathrm{HDD}}} \quad (3)$$

where LBNP(t) is the LBNP level that the individual is experiencing at time t and $\mathrm{LBNP}_{\mathrm{HDD}}$ is the LBNP level at which the individual will enter hemodynamic decompensation.

Therefore, LBNP protocols that require hemodynamic decompensation formed a framework for a reference CRI. Figure 2 illustrates CRI estimates from the model vs. a linearized reference CRI from the LBNP protocol. Note that the reference can only be constructed after the subject's LBNP level at decompensation ($\mathrm{LBNP}_{\mathrm{HDD}}$) is known.

The model calculates the first CRI value estimate after 30 heartbeats of initialization and then, in real time, provides a new CRI estimate after every subsequent heartbeat. When using a medical monitor, the CRI output can include the visualization of a "bar" (36) with three colors that correspond to patient status of adequate compensation (green), moderately compromised (amber), and unstable (red). The times at which the CRI reached the thresholds of 0.6 (amber) and 0.3 (red) were compared with stroke volume responses across individual subjects.

Stroke volume and vital sign data analysis. Data were sampled at 500 Hz, digitized to computer (WinDaq, DATAQ Instruments, Akron, OH), and then imported into commercially available data analysis software (WinCPRS, Absolute Aliens, Turku, Finland). Individual R waves from the electrocardiogram were marked at their occurrence in time and used for subsequent identification of systolic arterial blood pressure (mmHg) generated from the Finometer. R-R intervals (ms) were used to calculate heart rate (beats/min). Oxygen saturation of arterial blood ($\mathrm{Sp}_{\mathrm{O}_2}$) was measured by standard pulse oximetry. Respiratory rate and end-tidal CO_2 were measured from a nasal CO_2 capnograph. With the arterial pressure waveform as an input, stroke volume (ml) was estimated on a beat-by-beat basis with the pulse contour method as previously outlined (23).

Identification of tolerance subgroups. After development of the CRI algorithm based on the LBNP data sets from 100 of the original 201 subjects, validation testing of the final machine-learning model was performed on the data sets generated from the remaining 101 test subjects. Individuals have been characterized as low tolerance (fainters) or high tolerance (nonfainters) based on their performance to standing (9). Since the results from previous experiments indicate that similar heart rate responses to standing mirror those of ~50 mmHg LBNP (9), an approach adopted from previous investigations (12, 14, 28, 31) was used to categorize 67 subjects into the group with high tolerance to reduced central blood volume based on entrance into the −70 mmHg LBNP level while the remaining 34 subjects were categorized into the low-tolerance group because of their failure to complete −60 mmHg of LBNP.

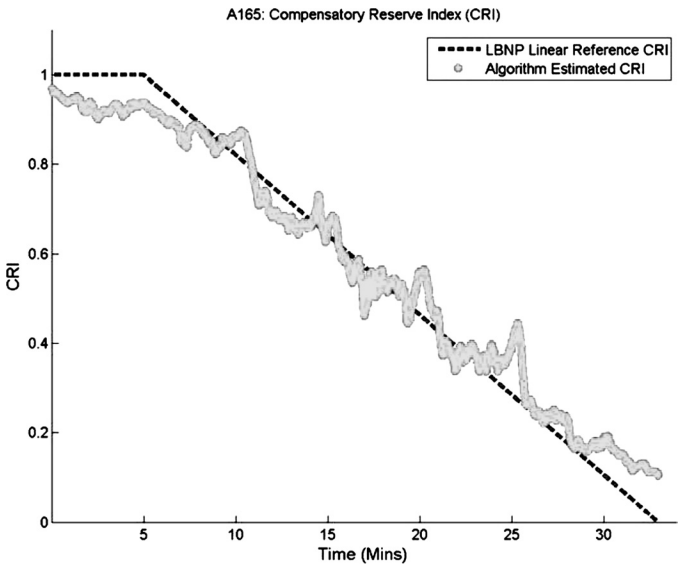

Fig. 2. Linearized reference CRI based on lower body negative pressure (LBNP) protocol and CRI estimated by the model.

Statistical analysis. The Pearson product correlation coefficient was used to assess the reliability of the time at which the CRI estimated hemodynamic decompensation to the actual time of decompensation. The group average times from baseline (CRI at supine rest) to CRI = 0.6 (amber) and CRI = 0.3 (red) were compared with the group average times for statistical changes in stroke volume, heart rate, systolic blood pressure, $\mathrm{Sp}_{\mathrm{O}_2}$, and R-R interval with t-tests for repeated measures. A t-test statistic for independent groups was used to compare subject demographic data and each CRI measure between subjects in the high-tolerance and low-tolerance groups. The probabilities of observing chance effects on the dependent variables of interest are presented as exact P values. All data are expressed as means ± 95% confidence interval (95% CI).

RESULTS

Subject populations. The random placement of subjects into subgroups for model development and testing resulted in average demographic data (age = 27.6 ± 1.7 yr, height = 172 ± 2 cm, weight = 73.2 ± 2.9 kg) of the 101 subjects (men = 54, women = 47) used for validation testing of the final machine-learning model being similar ($P \geq 0.21$) to the 100 original subjects (men = 60, women = 40) from whom the CRI algorithm was developed (age = 27.6 ± 1.5 yr, height = 173 ± 2 cm, weight = 76.0 ± 3.4 kg). The average demographics (age = 28.4 ± 2.3 yr, height = 172 ± 2.6 cm, weight = 74.8 ± 3.6 kg) of the high-tolerance subjects were not statistically distinguishable ($P \geq 0.20$) from those of the low-tolerance subjects (age = 27.0 ± 2.2 yr, height = 171 ± 3.7 cm, weight = 70.0 ± 4.7 kg).

Vital sign responses. The responses of heart rate, systolic and diastolic blood pressures, $\mathrm{Sp}_{\mathrm{O}_2}$, respiration rate, and end-tidal CO_2 to progressive LBNP in high- and low-tolerance subjects are illustrated in Table 1. Average baseline heart rate was higher ($P = 0.021$) in low-tolerance subjects compared with high-tolerance subjects and increased in both groups during progressively higher LBNP levels. Blood pressures were statistically similar in high-tolerance compared with low-tolerance subjects and across LBNP levels up to −45 mmHg. $\mathrm{Sp}_{\mathrm{O}_2}$, respiration rate, and end-tidal CO_2 were statistically unchanged throughout LBNP for both high- and low-tolerance groups.

Stroke volume responses. The response of stroke volume to progressive LBNP in high- and low-tolerance subjects is illustrated in Fig. 3. Stroke volume decreased ($P < 0.01$) in a linear fashion in both groups, with the average slope of the stroke volume response being statistically indistinguishable ($P = 0.568$) between the high-tolerance (−0.776 ± 0.050 ml/mmHg) and low-tolerance (−0.804 ± 0.097 ml/mmHg) groups. However, the average maximal reduction in stroke volume from baseline to decompensation for the high-tolerance subjects (−54.4 ± 3.7 ml) was greater ($P = 0.0001$) than that for the low-tolerance subjects (−41.7 ± 5.3 ml).

CRI responses. The mean ± 95% CI for tolerance time of the high-tolerance group was 25.86 ± 1.04 min vs. low-tolerance mean time = 16.23 ± 1.26 min. The low-tolerance group CRI reached the threshold value of 0.6 at an average time of 5.27 ± 1.18 min followed by a CRI value of 0.3

Table 1. *Vital sign responses*

Vital Signs	Baseline		−15 mmHg LBNP		−30 mmHg LBNP		−45 mmHg LBNP		−60 mmHg LBNP
	HT	LT	HT	LT	HT	LT	HT	LT	HT
Heart rate, beats/min	65 ± 3	70 ± 3	65 ± 3	71 ± 3	70 ± 3	77 ± 4	79 ± 4	88 ± 6	97 ± 5
Systolic BP, mmHg	129 ± 3	132 ± 5	130 ± 3	131 ± 5	127 ± 3	125 ± 5	124 ± 3	116 ± 5	117 ± 3
Diastolic BP, mmHg	75 ± 2	76 ± 3	76 ± 2	76 ± 3	77 ± 2	76 ± 3	79 ± 2	74 ± 4	78 ± 2
Sp_{O_2}, %	97.2 ± 0.3	97.0 ± 0.4	97.4 ± 0.3	97.1 ± 0.4	97.3 ± 0.3	97.1 ± 0.4	97.3 ± 0.3	97.0 ± 0.5	97.3 ± 0.2
Respiration rate, breaths/min	14.9 ± 0.9	15.8 ± 1.3	14.3 ± 0.9	14.7 ± 1.1	13.8 ± 0.8	14.1 ± 1.2	14.1 ± 0.8	14.4 ± 1.3	13.9 ± 0.8
End-tidal CO_2, %	5.8 ± 0.2	5.9 ± 0.2	5.7 ± 0.2	5.8 ± 0.2	5.6 ± 0.2	5.6 ± 0.3	5.4 ± 0.2	5.2 ± 0.3	5.1 ± 0.2

Values are means ± 95% confidence interval. LBNP, lower body negative pressure; HT, high tolerance; LT, low tolerance; BP, blood pressure; Sp_{O2}, oxygen saturation of arterial blood by pulse oximetry.

reached at 11.39 ± 1.13 min. In comparison, the high-tolerance group CRI that became 0.6 at an average time of 7.62 ± 0.94 min followed by a CRI value of 0.3 reached at 15.35 ± 1.03 min. The average times that the model estimated that the CRI would reach 0.6 and 0.3 in the low-tolerance group were 6.48 ± 0.50 min and 11.66 ± 1.18 min, respectively. The average times that the model estimated that the CRI would reach 0.6 and 0.3 in the high-tolerance group were 10.33 ± 0.41 min and 18.10 ± 0.73 min, respectively. A linear regression with slope of 0.80 and amalgamated correlation coefficient (r^2) of 0.965 described the combined relationship between average estimated and actual times of changes in CRI (Fig. 4). At the time of hemodynamic decompensation, the CRI value (CRI_{HDD}) in all high- and low-tolerance subjects was < 0.27; the CRI_{HDD} was < 0.1 in 69% (46/67) of the high-tolerance subjects (average high-tolerance CRI_{HDD} = 0.101 ± .009) and in 48% (16/33) of the low-tolerance subjects (average low-tolerance CRI_{HDD} = 0.129 ± 0.019) (P = 0.005).

DISCUSSION

The data in Table 1 reaffirm that arterial blood pressure is not a sensitive indicator of reduced circulating blood volume because of the rapidity of compensatory responses (1, 13, 26). As such, measurement of stroke volume has proven to be a useful tool for assessing reductions in central blood volume when standard vital signs often remain unchanged (13). Since stroke volume is associated with features of the arterial pulse waveform (10, 24, 27), we chose two methods of waveform analysis to assess their efficacy for providing early identification of hemodynamic instability in individuals. We hypothesized that a model developed to estimate compensatory status (CRI) with state-of-the-art feature-extraction and machine-learning techniques would differentiate individual subjects with varying tolerances to reduced central blood volume in advance of alterations in stroke volume estimated from the same waveforms. To test this hypothesis, we compared responses of arterial pulse waveforms in a model of progressive central hypovolemia in humans with high and low tolerance to reduced central blood volume. Both the CRI and stroke volume identified early and progressive reduction in central blood volume induced by LBNP. However, measurements of stroke volume failed to differentiate high- from low-tolerance subjects because of similarities in the trajectory (slope) and maximum magnitude of reduced stroke volume (Fig. 3). Also, measures of stroke volume failed to provide any indication of closeness to time of decompensation. Consistent with our hypothesis, CRI estimated earlier status of compensatory compromise in low-tolerance compared with high-tolerance subjects when stroke volume levels in these subjects were indistinguishable. These findings support the notion that advanced machine-learning techniques are essential for the identification of real-time subtle changes in the patterns and features of arterial waveforms that are directly associated with compensa-

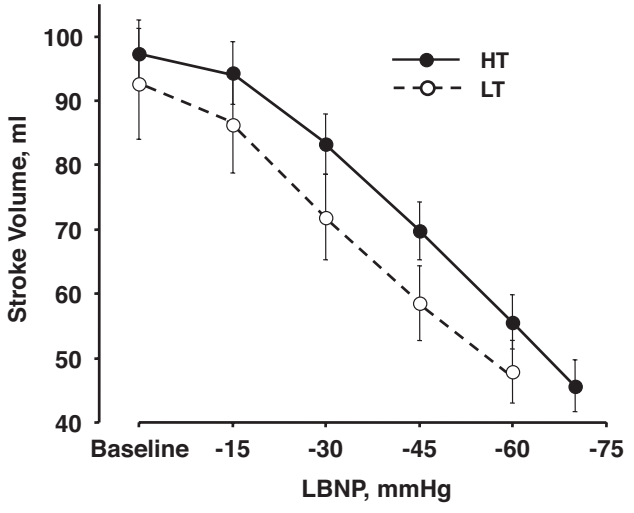

Fig. 3. Average [±95% confidence interval (CI)] responses of stroke volume in 67 subjects with high tolerance (HT) and 34 subjects with low tolerance (LT) during progressive LBNP.

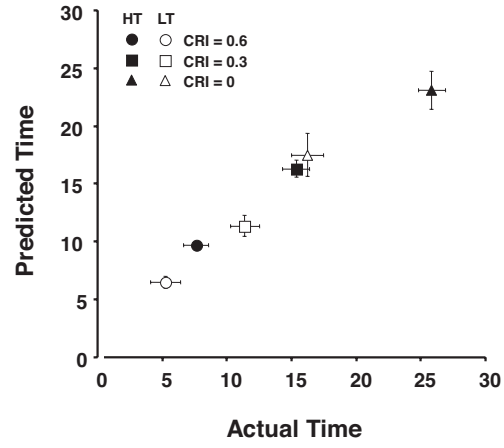

Fig. 4. Average (±95% CI) values of actual and estimated times for CRI at 0.6, 0.3, and 0 in 67 subjects with high tolerance (HT) and 34 subjects with low tolerance (LT). The linear relationship is defined by the following equation: estimated time = 0.92(actual time) + 3.4; amalgamated r^2 = 0.965.

tory mechanisms. These patterns and features differ across individuals and are unrecognized by traditional methods used to estimate stroke volume and evaluate standard vital signs.

The CRI model was specifically constructed from noninvasive analog blood pressure waveform signals to analyze and compare the entirety of each pulse waveform in a window of time to identify and combine features that are indicative of central blood volume reduction. As such, CRI reflects the estimated capacity of all contributing physiological mechanisms (e.g., baroreflexes, respiration, muscle contractions) to compensate for the volume of blood loss an individual can tolerate well before experiencing the signs and symptoms of cardiovascular instability (early decompensatory phase of shock).

Several physiological metrics that represent mechanisms of compensation have been examined as potential early markers of imminent cardiovascular instability. Heart rate variability has been considered an autonomic nervous system function that reflects reduced blood volume status (2, 6, 17, 18). However, significant inter- and intraindividual variance has resulted in failure to provide a clinical tool with acceptable specificity (22, 29, 30). Although maximal reserves for compensatory mechanisms (e.g., tachycardia, vasoconstriction, vagal withdrawal, sympathetic nerve activity) are significantly greater in individuals with high tolerance in response to reduced central blood volume (12, 15, 20, 31), these responses are similar in high- and low-tolerance individuals until the time of decompensation (28). Other monitoring technologies have been developed that provide trending hemodynamic measures (e.g., cardiac output, stroke volume, stroke volume variability, systemic vascular resistance, oxygen delivery) in addition to standard vital signs. Although providing such added decision support, these technologies are limited by algorithms based on population averages that require information such as age, sex, height, and weight as well as experienced clinicians for interpretation of patient status. For example, an indication that stroke volume was 60 ml and has fallen to 50 ml in a given period of time is not "individual specific"; that is, it is not possible to ascertain whether the patient is represented by the left curve (low tolerance) or right curve (high tolerance) of Fig. 3 (e.g., given multiple patients in the ER or ICU, which one needs immediate intervention?). Simply put, currently available technologies do not incorporate "machine learning" of individual patients. In contrast, the CRI algorithm is unique in that it "learns" the individual patient by estimating the amount of reserve remaining for compensation during central hypovolemia and accurately predicting the trajectory of time to decompensation without having to "know" demographics or any other information about the patient because its "machine learning" is based on having "learned" from hundreds of thousands of feature changes in arterial waveforms. As such, this work has led to the discovery that subtle features that determine the shape of the integrated waveform produced by the flow of blood through the arteries is what allows the algorithm to determine the CRI for each individual.

Distinct from signals traditionally associated with hemodynamic responses to central blood volume loss, oscillations in arterial blood pressure have long been known to be characteristic of hemorrhage (21). Most relevant to the differentiation between high- and low-tolerance individuals is the observation that oscillations in blood pressure associated with autonomic reflex control of circulation during progressive reductions in central blood volume are significantly greater in high- compared with low-tolerance individuals (8, 28). Unlike algorithms for estimating stroke volume, the CRI algorithm is capable of identifying individuals during the compensatory phase of central blood volume loss by integrating real-time, moment-to-moment information about subtle changes in waveform features such as variability of heart rate and pulse pressure, heart rate, waveshape metrics, event timing, stroke volume, changes in peripheral vascular resistance, and particularly arterial waveform oscillations. By analyzing and integrating multiple waveform features and "learning" how these features change with central volume loss, the model used in the present investigation was able to, after every heartbeat, estimate how far or near an individual was from the point of decompensation.

A key consideration with our approach to identify the status of individuals during acute reductions in central blood volume was meeting the requirement to identify "navigable" paths of volume loss far enough ahead as to allow smooth trajectories of an individual subject. We were able to accomplish this goal by designing a protocol that resulted in the decompensation of all subjects. The effectiveness of the CRI algorithm to differentiate individuals with varying tolerances to reduced central blood volume is best represented in Fig. 4. The threshold times for estimating or reaching CRI of 0.6, 0.3, and intolerance were significantly less in the low-tolerance compared with the high-tolerance group. Consistent with our hypothesis, the CRI correctly differentiated the tolerance of individuals with varying magnitudes of reduced central blood volume and provided an earlier response on average than the actual physiological (clinical) condition that was indicated by standard vital signs.

We hypothesized that the average CRI_{HDD} would become zero in both high- and low-tolerance groups at the time of decompensation. Against expectations, we found that the CRI for low-tolerance subjects at the time of hemodynamic decompensation (0.13) was statistically higher (30%) than that of the high-tolerance subjects (0.10). This result might be explained by the underlying stepwise LBNP protocol used to develop the algorithm, where a single step reduction in pressure represents a significant transition on the CRI scale for a low-tolerance individual. The protocol represents a fixed rate of "hemorrhage" for all subjects, but this defines a much higher rate of transition toward decompensation for low- compared with high-tolerance individuals. Since subjects typically collapse shortly after a step transition in pressure, there are unlikely to be enough heartbeats for the algorithm to accurately observe the transition to presyncope. The relative significance of a single step for low-tolerance individuals contributes to this uncertainty around the CRI. This failure of the CRI to recognize an accurate "navigable" path of reaction to central blood loss in a timely fashion in the low-tolerance subjects would be analogous to a robot that has the capability to negotiate the correct path of movement but collides with a wall because it is moving too fast. As such, we hypothesize that further refinement of the CRI model is required based on increased reference sensitivity to continuous reduction of more rapid profiles of reduced central blood volume. This hypothesis can be effectively tested with LBNP profiles that rapidly ramp to decompensation levels rather than following the current stepwise profiles.

We developed a novel mathematical model capable of identifying subjects at risk for hemodynamic decompensation well in advance of clinically significant changes in stroke volume or currently available vital signs. This model (the CRI) was developed with the use of a large database "library" of noninvasive arterial pressure waveforms. The CRI algorithms analyze and compare the entirety of each waveform in a window of time to trend waveform features that reflect the status of compensation reserve for a particular central blood volume. Our experiment demonstrated the physiological relationship between subtle changes in waveform features and the underlying absolute reserve capacity that dictates significant differences among individuals.

Perspectives

Our current generation of physiological monitors lack "intelligence" insofar as they are designed to provide emergency medical practitioners raw vital sign data for early identification of underlying pathophysiology in patients rather than to generate statistically unbiased, beat-to-beat "interpreted" information required to direct appropriate intervention. This approach of relying on standard vital signs for decision support has been driven by a legacy "bias for favoring less important but immediately measurable variables, (e.g., mean arterial blood pressure) over more important but less measurable variables" (34, 35). In the present investigation, we challenged traditional bias by introducing the continuous noninvasive measurements of the features of peripheral arterial waveforms obtained from finger photoplethysmography. We introduced these signals into a machine-learning model designed to estimate a value called the compensatory reserve index (CRI) that represents a new paradigm for measuring the physiological "reserve" of integrated cardiopulmonary mechanisms (e.g., tachycardia, vasoconstriction, breathing) that compensate for reduced central blood volume (8, 11). The CRI recognizes the compensatory reserve well before an individual experiences signs and symptoms of cardiovascular instability. As such, the results of this investigation demonstrate for the first time a novel approach for medical monitoring that provides the capability to forewarn of the onset of hemodynamic instability earlier than traditional vital signs, and overcome the limitation of stroke volume by accurately differentiating those individuals at greatest risk for early decompensation (i.e., low tolerance to blood loss). The CRI can be integrated into any standard monitor that generates an arterial waveform, including a finger pulse oximeter that is available in the medical kits of US Army combat medics and civilian first responders. Such a capability can enhance the support for better-informed triage decisions in the prehospital setting and prove to be a "game changer" for improved patient outcomes.

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DISCLOSURES

G.Z. Grudic and J. Mulligan are cofounders of Flashback Technologies Inc. and developers of the CRI model utilized in this study. S.L. Moulton is a cofounder and medical consultant to Flashback Technologies Inc.

AUTHOR CONTRIBUTIONS

Author contributions: V.A.C., G.Z.G., J.M., and S.L.M. conception and design of research; V.A.C., G.Z.G., and J.M. performed experiments; V.A.C., G.Z.G., and J.M. analyzed data; V.A.C., G.Z.G., J.M., and S.L.M. interpreted results of experiments; V.A.C. and G.Z.G. prepared figures; V.A.C., G.Z.G., and S.L.M. drafted manuscript; V.A.C., G.Z.G., J.M., and S.L.M. edited and revised manuscript; V.A.C., G.Z.G., J.M., and S.M. approved final version of manuscript.

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