Comparison of Compensatory Reserve During Lower Body Negative Pressure and Hemorrhage in Non-human Primates

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Running Title: Compensatory reserve during hypovolemia

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ABSTRACT

Compensatory reserve was measured in baboons (n=13) during hemorrhage (Hem) and lower body negative pressure (LBNP) using a machine learning algorithm developed to estimate compensatory reserve by detecting reductions in central blood volume during LBNP. The algorithm calculates compensatory reserve index (CRI) from normovolemia (CRI=1) to cardiovascular decompensation (CRI=0). The hypothesis was that Hem and LBNP will elicit similar CRI values, and that CRI would have higher specificity than stroke volume (SV) in predicting decompensation. Blood was removed in four steps: 6.25%, 12.5%, 18.75%, and 25% of total blood volume. Four weeks after Hem, the same animals were subjected to four levels of LBNP matched based on central venous pressure. Data (mean ± 95% confidence interval) indicate that CRI decreased (p<0.001) from baseline during Hem (0.69 ± 0.10, 0.57 ± 0.09, 0.36 ± 0.10, 0.16 ± 0.08, and 0.08 ± 0.03) and LBNP (0.76 ± 0.05, 0.66 ± 0.08, 0.36 ± 0.13, 0.23 ± 0.11, and 0.14 ± 0.09). CRI was not different between Hem and LBNP (p=0.20). Linear regression analysis between Hem CRI and LBNP CRI revealed a slope of 1.03 and an adjusted R2 of 0.96. CRI exhibited greater specificity than SV in both Hem (92.3 vs 82.1) and LBNP (94.8 vs 83.1) and greater ROC AUC in Hem (0.94 vs 0.84) and LBNP (0.94 vs 0.92). These data support the hypothesis that Hem and LBNP elicited the same CRI response, suggesting that measurement of compensatory reserve is superior to SV as a predictor of cardiovascular decompensation.

Key Words: blood loss, central hypovolemia, stroke volume, blood pressure, compensatory mechanisms
In military and civilian trauma patients, the primary cause of death within the first hour of injury is hemorrhage (2, 4, 13, 14). As such, early assessment of those bleeding patients at greatest risk for developing shock due to reduced central blood volume is critical for effective triage decisions and optimal clinical outcomes. Lower body negative pressure (LBNP) has provided an experimental model for the study of the physiology of human hemorrhage especially during the early compensatory stages of hypovolemia (12). The validity of LBNP as an experimental model of hemorrhage has recently been demonstrated by comparing LBNP to actual hemorrhage in baboons (17) and humans (19).

An experimental advantage to using LBNP is the capability of safely inducing a reproducible clinical outcome in each human subject in the form of decompensation (pre-syncpe). This approach has resulted in the identification of individuals with high and low tolerance to central hypovolemia (6, 8-10, 26). Based on our large database of more than 200 human LBNP experiments, a machine-learning algorithm based on analysis of arterial waveform features was developed to detect the reserve to compensate for reductions in central blood volume (8). We call this physiological measurement the compensatory reserve; the algorithm calculates a compensatory reserve index (CRI) which reflects the proportion of intravascular volume remaining before the onset of decompensation (21) and can distinguish those individuals with
low tolerance to central hypovolemia (6). CRI ranges from 1 to 0, where CRI=1 represents
normovolemia and CRI=0 represents hypovolemia at the point of decompensation (6, 21).

More recently, the measurement of compensatory reserve has been shown to be more specific
than standard vital signs in the tracking of circulating blood volume in humans during actual
mild (~10%) to moderate (~20%) hemorrhage (7, 22, 27). However, for obvious ethical reasons,
human hemorrhage experiments cannot be designed with decompensation endpoints to
demonstrate the capability of the CRI algorithm to distinguish individuals with high and low
tolerance to actual blood loss. As such, there exists no validation of the compensatory reserve
response during LBNP with actual hemorrhage.

Using the arterial blood pressure waveform data obtained during our previous study to
compare hemorrhage and LBNP in baboons (17), we took the opportunity to perform the first
head-to-head direct comparison between actual hemorrhage and matching LBNP applications
in which decompensation was elicited in low tolerant animals (i.e., animals who could not
tolerate 25% hemorrhage without experiencing decompensation during LBNP and
hemorrhage). With this retrospective analysis, we were able to test the hypothesis that the
measurement of the compensatory reserve can be used to accurately distinguish individuals
with low versus high tolerance to hemorrhage due to higher specificity.

METHODS
Animals. Adult male baboons (n = 13, 8-12 years old, 25-35 kg body weight) were used to compare responses to hemorrhage and LBNP. The protocol was approved by the Institutional Animal Care and Use Committee of the Texas Biomedical Research Institute, San Antonio, TX. This study has been conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The details of this protocol are presented in a previous publication (17) and are summarized below.

Surgical Procedures. On the day of each experimental session (hemorrhage or LBNP), the baboons were sedated and intubated to maintain an open airway and allowed to breathe spontaneously during the experiments. Arterial pressure and central venous pressure (CVP) were measured via catheters inserted in the axillary artery and vein, respectively. The CVP catheter was advanced to the right atrium. For hemorrhage experiments, two additional catheters were inserted in the femoral artery and vein for blood removal and replacement, respectively. After catheter placement, ECG leads were attached to monitor heart rate. At the completion of the hemorrhage and LBNP experiments, the catheters were removed and the skin incisions at the catheter insertion sites were sutured closed.

Hemorrhage Experiment. Arterial blood pressure, heart rate, and CVP were recorded continuously during the experiment. Baseline values were monitored for 20 minutes prior to a stepwise hemorrhage of 25% blood volume via the femoral artery. As an a priori protocol termination criterion, the hemorrhage procedure was stopped prematurely if a systolic arterial pressure less than 70 mmHg was attained prior to 25% blood loss. The four steps of
hemorrhage represented 6.25%, 12.5%, 18.75%, and 25% blood volume were achieved over a
28 minute period (7 minutes/step). The maximum hemorrhage level was 25%. Hemorrhage
blood volumes at each step were calculated based on an assumed total blood volume of 71
ml/kg which was measured in a separate group of animals (17). After the last step of
hemorrhage, shed blood was replaced via the femoral vein.

**Lower Body Negative Pressure Experiment.** Four weeks after the hemorrhage experiment, the
baboons were again sedated and instrumented for recording of arterial blood pressure, CVP,
and heart rate. The animals were placed supine in an LBNP chamber. Baseline values were
monitored for 20 minutes prior to a stepwise LBNP procedure to match the previous
hemorrhage steps. LBNP levels for each step were determined by matching CVP measurements
from the animal’s previous hemorrhage study. As in the hemorrhage experiment, a systolic
arterial pressure less than 70 mmHg was the termination criterion. However, unlike the
hemorrhage experiments, LBNP was applied until this termination criterion was attained
(decompensation). At the end of the procedure, the negative pressure was released, and
hemodynamic variables were allowed to stabilize for 20 minutes.

**Estimating Compensatory Reserve.** Arterial waveforms obtained during hemorrhage and LBNP
experiments were analyzed with an algorithm developed to estimate the compensatory reserve
called the CRI. The algorithm was originally developed based on extensive analysis of a large
body of waveform data obtained from human subjects during progressive central hypovolemia
induced with LBNP (6, 21). Figure 1 (11) illustrates the different characteristics of an arterial
pressure waveform during normovolemia (Fig. 1A) and hypovolemia (Fig. 1B). The arterial
The waveform is composed of the ejected wave (cardiac output) and the reflected wave (peripheral vascular resistance). The two waves overlap during normal conditions, but separate during hypovolemic conditions. The observed or recorded total waveform is outlined in red. The features of the total waveform are affected by the compensatory mechanisms involved in the control of cardiac output and peripheral vascular resistance during conditions of hypovolemia. The algorithm for measuring compensatory reserve evaluates the subtle changes in the features of the arterial waveform (red outline in Figure 1) and integrates all of the physiological compensatory mechanisms affecting these features. The algorithm can assess changes in waveform features in an individual-specific manner such that a CRI value is capable assessing an individual’s capacity to compensate to blood loss.

For this experiment the CRI model was calibrated to the waveform data from the baboon LBNP trials. The original model was developed from waveform analog data collected from a finger infrared photoplethysmogram during progressive LBNP experiments conducted on 100 human subjects and validated on 101 different subjects (6). Additional experimentation revealed a minimal requirement of 10 LBNP experiments using a stepwise profile similar to the original protocol for translation of the original human model to a baboon model. As such, the CRI model used for waveform analysis in the present study was calibrated to waveform analog data collected from the baboon LBNP trials during which the decompensation criterion was attained. Estimates of compensatory reserve for each baboon were based on a separate calibration from which that animal’s data were excluded, in order to provide statistically unbiased data analysis. The algorithm estimates the proportion of physiological reserve available to compensate for changes in effective circulating blood volume by comparing waveform features to those in the
model. The values of CRI range from 1 to 0, where CRI = 1 represents 100% capacity of physiological compensatory mechanisms to respond to changes in blood volume and CRI = 0 represents 0% capacity of compensatory mechanisms. Thus, during progressive central hypovolemia, CRI is theoretically expected to start at a value of 1 prior to volume loss (maximum compensatory reserve), and decrease during hypovolemia to a value of 0 at which point all compensatory mechanisms responding to the hypovolemia are exhausted resulting in cardiovascular collapse and shock.

**Data Analysis.** Continuous ECG, CVP, and arterial blood pressure waveform recordings were sampled at 500 Hz using Lab View data acquisition software during hemorrhage and LBNP experiments. Beat-to-beat stroke volume (SV) was derived from the arterial pressure waveform using the pulse contour method (18), and beat-to-beat compensatory reserve was estimated using the algorithm described above. These beat-to-beat SV and compensatory reserve estimations were averaged to provide one value for the last three minutes of each hemorrhage and LBNP step using a commercially available software program (WinCPRS, Absolute Aliens, Turku, Finland).

Statistical analysis was conducted with commercially available software packages (SigmaStat; Systat Software, Richmond, CA and SAS v9.2; SAS Institute, Cary, NC). The Pearson product correlation coefficient was used to assess the relationship between changes in SV and changes in CRI. The probabilities of observing chance effects that changes in the dependent variables over changing circulating blood volumes (time) were different from ‘zero’ change are presented as exact P values obtained from two-way repeated measures analysis of variance tests.
Generalized Estimating Equations (GEE) were used for repeated measures logistic regression. The criterion for decompensation (systolic blood pressure < 70 mm Hg) is assessed at each LBNP step in the experiment, and at each step subjects are classified as either (1) decompensated or (2) not decompensated. The repeated measures logistic regression procedure assesses how changes in SV and CRI are associated with this binary classification of decompensation at each step (i.e., SV and CRI are predictors of decompensation at each step of the experiment). Output from the logistic regression analyses for CRI and SV produced measures of the receiver operating characteristic area under the curve (ROC AUC), sensitivity and specificity. Sensitivity (true positives) and specificity (true negatives) were calculated based on logistic regression predicted probability cut-offs which optimized both values giving equal weight to sensitivity and specificity (15, 16). The ability of CRI and SV to correctly predict decompensation during progressive hemorrhage was compared using the $\chi^2$ test for the difference in ROC AUC.

RESULTS

The levels of LBNP which corresponded with 6.25%, 12.5%, 18.75% and 25% hemorrhage were -22±4, -41±4, -54±6, and -71±5 mmHg, respectively. Figure 2 shows that CRI decreased during each step of hemorrhage and LBNP ($p<0.001$). CRI values were statistically similar at baseline and responded equally to hemorrhage and LBNP ($p=0.20$).
The ability of LBNP to mimic the compensatory reserve response during hemorrhage was supported by correlation coefficient between CRI during hemorrhage and LBNP to be $0.96 \pm 0.04$, slope = 1.03 (Figure 3).

CRI correlated with SV during both hemorrhage ($r = 0.96 \pm 0.08$) and LBNP ($r = 0.89 \pm 0.24$). The ROC AUC was statistically greater ($P = 0.0006$) for CRI compared to SV during actual hemorrhage, but not LBNP (Table 1). Whereas CRI and SV displayed similar sensitivities during hemorrhage, CRI provided greater specificity (92.3 and 94.8) than SV (82.1 and 83.1) as a predictor of reduced central blood volume in both hemorrhage and LBNP.

Five baboons failed to complete the entire 28-minute hemorrhage period because of the onset of decompensation (i.e., SBP < 70 mmHg) before the target 25% blood withdrawal could be reached. Two animals completed 18.75% (21 minutes); 2 animals completed 23% (26 minutes); and 1 animal completed 24% (27 minutes) blood loss. Subsequently, the same 5 animals experience early decompensation during the LBNP protocol that was conducted 4 weeks after the hemorrhage experiment. These 5 animals that did not complete 25% hemorrhage were classified as having low tolerance to hypovolemia, and the remaining 8 baboons that completed the entire hemorrhage protocol were classified as having high tolerance to hypovolemia.

Analysis of SV responses comparing animals with low and high tolerance revealed similar reductions in SV (Fig. 4A). The slopes of the reduction in SV were not different between animals with low and high tolerance. In contrast, animals with low tolerance displayed a more rapid reduction in CRI (i.e., steeper slope) than those with high tolerance to hypovolemia (Fig. 4B).
DISCUSSION

In the present investigation, baboons were exposed to a progressive controlled hemorrhage and matched levels of LBNP that resulted in an average maximal reduction of approximately 25% of their estimated circulating blood volume. Similar to our previous findings on hemodynamic, metabolic and neuroendocrine responses (17), we found that the compensatory reserve response was similar during both hemorrhage and LBNP (Fig. 2). We hypothesized that a model developed with state-of-the-art feature-extraction and machine-learning techniques would provide earlier and more accurate estimates of blood volume loss in individual animals with varying compensatory responses. To test this hypothesis, we compared stroke volume responses and compensatory reserve measurements in a group of baboons who were able to tolerate the entire 25% hemorrhage (high tolerance group) to a group who experienced decompensation prior to completing the entire protocol (low tolerance group). Since stroke volume and compensatory reserve are both calculated from features of the arterial waveform, there was a high correlation between the two measures. However, consistent with previous observations in humans (6, 9, 25), data from this study reaffirmed that stroke volume failed to distinguish low from high tolerant baboons (Fig. 4A).

In contrast, the compensatory reserve as measured by CRI was progressively reduced at a faster rate in low compared to high tolerant baboons (Fig. 4B). This finding was further supported by lower specificity in the stroke volume measurements during both hemorrhage (82.1) and LBNP (83.1) compared to specificities of 92.3 (hemorrhage) and 94.8 (LBNP) for the CRI. Specificity is an important component in differentiating CRI from other measures because it corresponds to
its ability to distinguish high tolerant animals, which tend to be more prevalent than low
tolerant. Equally important is the fact that CRI exhibited greater ROC AUC values, indicating
that when considering sensitivity and specificity simultaneously, CRI was a better predictor of
decompensation than SV, particularly in the actual hemorrhage experiment. Recognizing that
CRI’s performance was the same in both hemorrhage and LBNP experiments also suggests that
it is a more consistent measurement of an individual’s response to blood loss than SV, which
was more responsive in LBNP than in the actual hemorrhage experiment. As such, measuring
the magnitude of the reserve to compensate for blood loss proved to be the most robust
marker of individual variation between subjects because it distinguishes those individuals at
highest risk for early decompensation.

Several unique features of measuring the compensatory reserve are demonstrated by the data
presented in Figure 4. The ability to distinguish a faster rate of reduced compensatory reserve
in low tolerant animals with the same volume of blood loss indicates the ability of the model to
provide individualized assessment of compensatory status (Fig. 4B). Differences in slopes of the
stimulus-response (blood volume-CRI) relationship have been shown to represent the individual
reserve required to compensate for the reduction in circulating blood volume (7). Previous
experiments using LBNP (6, 23) support the notion that individuals with relatively low tolerance
to reductions in central blood volume display more rapid depletion of their compensatory
reserve. The results of this investigation are unique in that they extend previous data by
demonstrating for the first time that a subgroup of animals who demonstrated early
decompensation could be described by a steeper (faster) depletion in their compensatory reserve (slope difference=1.43; p=0.06) during both progressive LBNP and actual hemorrhage.

The algorithm developed to calculate compensatory reserve was based on a LBNP protocol in conscious humans in which the initial baseline stage was executed under controlled experimental conditions (e.g., adequate hydration, sleep, food intake, etc.) with subjects in the supine posture (i.e., optimum central blood volume). Although a CRI of 1.0 represents an optimum reserve for compensation, humans have consistently demonstrated an average baseline CRI value of approximately 0.9 (6, 7). In the present study, the median value for CRI in baboons prior to either LBNP or blood loss experiments (baseline) was only 0.74. It is likely that this relatively low baseline value for CRI reflects the variability inherent in the baboon CRI algorithm derived for a relatively small cohort of animals. The algorithm for baboons was produce based on a model in which N-1 animals were used to evaluate data from the Nth animal. In the current study of 13 baboons, the baboon CRI algorithm was constructed using LBNP data from 12 baboons to produce a valid estimate for the 13th animal. This procedure was repeated 13 times so that CRI values for each animal were generated based on the algorithm model from the remaining 12 animals. Therefore, depending on how each animal presented at baseline relative to its peers (perhaps related to various factors that can compromise compensatory mechanisms such as the level of tolerance, sedation or hydration) it is possible that the model yielded a lower baseline CRI because that particular Nth baboon was more compromised at baseline. While this method is valid, it produced an algorithm that exhibited greater variability compared to our previous experience with the CRI algorithm
derived from human data (7, 27). As a result, the baboon CRI algorithm provided a wide range of baseline CRI values (0.9 to 0.4) that contributed to a low median value (0.74) relative to humans. However, comparison of changes in CRI to progressive LBNP and hemorrhage should not be altered by relatively low baseline CRI since the experiment was conducted as a repeated-measures design with the animals under the same experimental conditions (e.g., sedation). Finally, the slower rate of diminution of compensatory reserve in the high compared to the low tolerant animals during controlled hemorrhage in the present study is consistent with the notion that a faster rate of fall in CRI during progressive reduction in central blood volume is associated with earlier development of hypotension, and reducing the rate of CRI reduction can delay cardiovascular decompensation (23).

Measurement of stroke volume has proven to provide useful information about circulating volume status because of the relationship between cardiac filling and central blood volume (i.e., sensitivity to changing volume). Since stroke volume is associated with features of the arterial pulse waveform (5, 20, 24), it is not surprising that stroke volume showed a high correlation with blood loss similar to that of CRI. However, the rate of change in stroke volume during blood loss is similar in individuals regardless of their tolerance to hypovolemia (8, 21). This is demonstrated in the present study by the similar rate of stroke volume decrease (slope) in Figure 4A. At decompensation, humans with high tolerance to blood loss have relatively lower stroke volume than individuals with low tolerance (8, 21) which was also observed in the baboons (Fig. 4A). As a result, stroke volume as an independent measure does not predict decompensation. In contrast, changes in compensatory reserve occurred at a faster rate in
baboons with low tolerance (steeper slope) compared to those with high tolerance (Fig. 4B).

At decompensation, compensatory reserve was similar in baboons with low and high tolerance, thus accurately predicting decompensation in all baboons. This ability of changes in compensatory reserve to differentiate individuals with high compared to low tolerance to reduced central blood volume is reflected by the higher ROC AUC and specificity for the CRI compared to stroke volume in the present investigation. As such, our findings support the notion that, compared with measurements of stroke volume, advanced machine-learning techniques designed to identify real-time subtle changes in the patterns and features of arterial waveforms can improve the fidelity of decision support related to diagnosis and care of patients who are at greatest risk of early onset of shock in an emergency medical setting.

Traditional approaches designed to provide potential early markers of imminent cardiovascular instability have been limited by algorithms based on population averages with significant inter- and intra-individual variance and requirements for demographic information such as age, sex, height and weight. The algorithm for determining compensatory reserve is unique in that it captures the status of INDIVIDUALS by estimating the relative amount of reserve remaining for compensation during blood loss without having to ‘know’ demographics or any other information. Within this construct, it is noteworthy that compensatory reserve responses of baboons during either LBNP or hemorrhage are similar to those previously reported in humans during LBNP (6, 21, 23) or hemorrhage (7, 22, 27). This detailed model which captures individual status is best demonstrated by the different slopes of regression for baboons with low compared to high tolerance to progressive reductions in central blood volume (Fig. 4B).
The measurement of CRI reflects the status of compensation reserve for a particular central blood volume, and is based on the fundamental biophysics of pressure-flow relationships within the cardiovascular system that dictate changes in features of the arterial waveform with inputs from compensatory mechanisms (e.g., reflex-mediated autonomic nerve activity, tissue metabolism). The results of the present investigation demonstrate the physiological relationship between significant progressive central blood volume reduction and the underlying absolute reserve capacity that dictates differences among individuals.

We have previously demonstrated that hemorrhage and LBNP elicit similar hemodynamic responses, but a difference was observed in how vascular fluid shifts affect hematocrit (17). During hemorrhage, transcapillary fluid flux causes fluid shifts from extravascular to intravascular compartments resulting in hemodilution (1, 17). In contrast, the external negative pressure during LBNP reverses transcapillary fluid flux causing fluid shifts from intravascular to extravascular compartments which results in hemoconcentration (17, 29). Another difference between hemorrhage and LBNP was that hemorrhage caused a decrease in central venous saturation, while LBNP did not affect it (17). Importantly, the CRI values were similar between hemorrhage and LBNP despite these differences between the two models. The similar CRI values can be explained by the recruitment of compensatory mechanisms in the two models.

Based on estimates of average total blood volume, maximal hemorrhage volumes, and hematocrit values in our previous study (17), we estimated a 7% plasma volume increase during hemorrhage and a 10% plasma volume decrease during LBNP using the equations of van
Beaumont (28). This difference in circulating blood volume between the hemorrhage and LBNP model was not physiologically impactful to cardiac filling and central hemodynamics as evidenced by similar responses in the measured hemodynamic parameters (17). The similarity of hemodynamic responses between hemorrhage and LBNP most likely indicates that increasing circulating blood volume with transcapillary refill during hemorrhage acted to compensate for a greater reduction in mixed venous oxygen saturation. As such, during hemorrhage, transcapillary fluid flux acted as a compensatory mechanism to offset blood loss. In contrast, during LBNP, the compensatory mechanisms responding to the central hypovolemia did not include transcapillary refill. Thus, emphasizing that the CRI algorithm recognizes the sum of compensatory responses that are reflected by specific changes in the features of arterial waveform and explains why the CRI values were similar between the two models despite a slightly different combination of compensatory responses used during hemorrhage and LBNP. This notion is supported by our most recent work demonstrating that feature changes in the arterial waveform represents the sum total of all individual compensatory mechanisms which can be quite different across individuals (3). Comparisons of CRI and SV between low and high tolerant animals during hemorrhage (or LBNP) would not be affected by transcapillary fluid flux since changes in hematocrit were similar between groups within each experimental condition. The similarity in responses of compensatory reserve between LBNP and hemorrhage in the present study corroborates earlier findings that LBNP represents a valid physiological model of blood loss (17, 19), particularly for the study of the human response during the compensatory phase of hemorrhage.
In summary, the results of the present investigation demonstrated that LBNP mimics the response of the compensatory reserve that results from actual hemorrhage. Furthermore, the results of this investigation demonstrate for the first time that a novel measurement of compensatory reserve based on advanced machine learning and feature extraction analysis of arterial waveforms overcomes the limited specificity of stroke volume by accurately differentiating those individuals at greatest risk for early decompensation (i.e., low tolerance to blood loss).

**PERSPECTIVES AND SIGNIFICANCE**

Monitoring standard vital signs in the prehospital setting (civilian or military) is ineffective for the assessment of impending cardiovascular shock in a bleeding patient. The CRI algorithm has been developed to measure compensatory reserve from the features of the arterial waveform as a predictor of cardiovascular decompensation. The existing capability to integrate the CRI algorithm into any standard monitor that generates an arterial waveform (including a finger pulse oximeter available in the medical kits of US Army combat medics and civilian first responders) provides a dramatic ‘leap forward’ in prehospital triage decision support.

**ACKNOWLEDGEMENTS**

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DISCLAIMER:

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. C. Hinojosa-Labarde, J.T. Howard, and V.A. Convertino have disclosed no conflicts of interest. G.Z. Grudic and J. Mulligan developed the CRI model used in this study, and are cofounders of Flashback Technologies.

REFERENCES:


Table 1. Comparison of Receiver Operating Characteristics (ROC) Area Under the Curve (AUC), Sensitivity, and Specificity between Stroke Volume (SV) and Compensatory Reserve Index (CRI) during Actual Hemorrhage and Lower Body Negative Pressure Hemorrhage Simulation Experiments (N=13). Values for baseline and onset of decompensation are median ± interquartile range.

<table>
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<th>Baseline</th>
<th>Onset of Decompensation</th>
<th>ROC AUC (95% CI)</th>
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**FIGURE LEGENDS**

**Figure 1:** Illustration of the different characteristics of an arterial pressure waveform during normovolemia (A) and hypovolemia (B). The features of the arterial pressure waveform (red outline) are dependent on systolic and diastolic pressure; and the ejected and reflected waves of the pressure pulse. This illustration has been previously published (11).

**Figure 2:** Compensatory Reserve Index (CRI) during baseline and 4 steps of hemorrhage (filled circles) and LBNP (open circles) corresponding to 6.25%, 12.5%, 18.75% and 25% total blood volume loss. CRI values during hemorrhage or LBNP were not statistically different from one another. Data are mean ± 95% Confidence Interval. P values from two-way repeated ANOVA are shown.

**Figure 3:** Correlation between compensatory reserve index (CRI) during hemorrhage (filled circles) and LBNP (open circles) for baseline, 6.25%, 12.5%, 18.75% and 25% total blood volume loss. Linear regression analysis revealed an amalgamated correlation coefficient between CRI during hemorrhage and LBNP to be 0.96 ± 0.04. Data are mean ± 95% Confidence Interval.

**Figure 4:** Changes in stroke volume (left panel) and compensatory reserve (right panel) during baseline, 6.25%, 12.5%, 18.75% and 25% total blood volume loss in animals with low tolerance (open circles, broken lines) and high tolerance (closed circles, solid lines) to hemorrhage. Data are mean ± 95% Confidence Interval. P-values are reported for tests of difference in slopes between low and high tolerance for stroke volume and compensatory reserve index.
Figure 1
Figure 2
Figure 3
Figure 4

A

B

- O - Low Tolerance
- - High Tolerance

Stroke Volume, %Δ

Compensatory Reserve

% Hemorrhage

p = 0.98

p = 0.06
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<td>SV</td>
<td>60.2 (11.4)</td>
<td>25.0 (4.4)</td>
<td>0.92 (0.86-0.98)</td>
<td>0.369</td>
<td>0.5436</td>
<td>90.9</td>
<td>83.1</td>
</tr>
<tr>
<td>CRI</td>
<td>0.74 (0.11)</td>
<td>0.07 (0.04)</td>
<td>0.94 (0.88-0.99)</td>
<td></td>
<td></td>
<td>81.8</td>
<td>94.8</td>
</tr>
</tbody>
</table>