Video Article

Integrated Compensatory Responses in a Human Model of Hemorrhage

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Abstract

Hemorrhage is the leading cause of trauma-related deaths, partly because early diagnosis of the severity of blood loss is difficult. Assessment of hemorrhaging patients is difficult because current clinical tools provide measures of vital signs that remain stable during the early stages of bleeding due to compensatory mechanisms. Consequently, there is a need to understand and measure the total integration of mechanisms that compensate for reduced circulating blood volume and how they change during ongoing progressive hemorrhage. The body's reserve to compensate for reduced circulating blood volume is called the 'compensatory reserve'. The compensatory reserve can be accurately evaluated with real-time measurements of changes in the features of the arterial waveform measured with the use of a high-powered computer. Lower Body Negative Pressure (LBNP) has been shown to simulate many of the physiological responses in humans associated with hemorrhage, and is used to study the compensatory response to hemorrhage. The purpose of this study is to demonstrate how compensatory reserve is assessed during progressive reductions in central blood volume with LBNP as a simulation of hemorrhage.

Video Link

The video component of this article can be found at https://www.jove.com/video/54737/

Introduction

The most important function of the cardiovascular system is the control of adequate perfusion (blood flow and oxygen delivery) to all tissues of the body through homeostatic regulation of arterial blood pressure. Various mechanisms of compensation (*e.g.*, autonomic nervous system activity, cardiac rate and contractility, venous return, vasoconstriction, respiration) contribute to maintain normal physiological levels of oxygen in the tissues.[1] Reductions in circulating blood volume such as those caused by hemorrhage can compromise the ability of cardiovascular compensatory mechanisms and ultimately lead to low arterial blood pressure, serious tissue hypoxia, and circulatory shock that can be fatal.

Circulatory shock caused by severe bleeding (*i.e.,* hemorrhagic shock) is a leading cause of death due to trauma.[2] One of the most challenging aspects of preventing a patient from developing shock is our inability to recognize its early onset. Early and accurate assessment of the progression toward the development of shock is currently limited in the clinical setting by technologies (*i.e.,* medical monitors) that provide measurements of vital signs that change very little in the early stages of blood loss because of the body's numerous compensatory mechanisms for regulating blood pressure.[3-6] As such, the capability to measure the sum total of the body's reserve to compensate for blood loss represents the most accurate reflection of tissue perfusion state and the risk of developing shock.[1] This reserve is called the compensatory reserve which can be accurately assessed by real-time measurements of changes in features of the arterial waveform.[1] Depletion of the compensatory reserve replicates the terminal cardiovascular instability observed in critically ill patients with sudden onset of hypotension; a condition known as hemodynamic decompensation.[7]

The relationship between the utilization of the compensatory reserve and regulation of blood pressure during ongoing blood loss in humans can be demonstrated in the laboratory using a comprehensive set of physiological measurements (*e.g.*, blood pressures, heart rate, arterial blood oxygen saturation, stroke volume, cardiac output, vascular resistance, respiration rate, pulse character, mental status, end-tidal CO_2, tissue oxygen) provided by standard physiological monitoring during continuous progressive reductions in central blood volume similar to those that occur during hemorrhage. Lowered central blood volume can be induced noninvasively with progressive increases in Lower Body Negative Pressure (LBNP).[8] Using this combination of physiological measurements and LBNP, the conceptual understanding of how to assess the body's ability to compensate for reduced central blood volume can easily be demonstrated. This study depicts the prelab preparation, the demonstration of compensatory response in relation to other physiological responses during simulated hemorrhage, and the postlab evaluation of results. The experimental techniques necessary for making measurements of compensatory reserve are demonstrated in a human volunteer.

Protocol

Prior to any human procedure, the institutional review board (IRB) must approve the protocol. The protocol used in this study was approved by the US Army Medical Research and Materiel Command IRB. The protocol is designed to demonstrate the physiological responses of compensation to a progressive reduction in central blood volume similar to that experienced by individuals during ongoing hemorrhage in a controlled and reproducible laboratory setting. The laboratory room temperature is controlled at 23 - 25 ˚C.

1. Equipment Preparation

1. Turn on equipment and devices requiring warm-up and calibration.
   NOTE: Equipment and devices include a data acquisition system to record data at 1 Hz; two separate devices that provide noninvasive, continuous measurements of brachial artery blood pressure and arterial oxygen saturation (SpO_2) using two separate infrared finger photoplethysmography cuff sensors[9-11]; a capnograph for measurement of end-tidal CO_2 and respiratory rate; and a finger pulse oximeter to acquire peripheral pulsatile arterial waveforms for measuring Compensatory Reserve.
2. Synchronize all of the instruments with internal clocks by adjusting the time stamp on each instrument to match a laboratory master clock that will be used to mark time during the experiment.

2. Subject Preparation

1. Instruct the subject to avoid caffeine, alcohol, and strenuous exercise 24 h prior to testing, and to avoid eating at least 2 h prior to the protocol in the event that hemodynamic decompensation induces nausea.
2. Prior to initiation of the protocol, have the physician perform a medical screening exam to ensure the subject meets minimal health requirements, and ensures the absence of exclusion criteria (nicotine use, hypertension, autonomic dysfunction, or history of syncopal episodes). Since pregnancy is an exclusion criterion for participation, require female participants to take a standard urine pregnancy test on the day of the study.
   NOTE: For the safety of the subject, the study physician is certified in advanced life support, and is present during the study. A fully-equipped 'crash cart' is immediately available to support the subject's airway, respiration, and circulation in the event of loss of consciousness or an acute cardiac arrhythmia taking place during the LBNP procedure.
3. Inform the subject about the procedure, and obtain written consent to participate in the study.
   NOTE: Explain to the subject that the goal of the study is to apply LBNP until the onset of cardiovascular decompensation (presyncope). Explain that there are cardiovascular parameters that define this point, and LBNP will be terminated when these cardiovascular parameters are observed. Inform the subject that they may also experience symptoms typically associated with presyncope during the LBNP procedure. Instruct the subject to notify the investigator if these symptoms occur and LBNP will immediately be terminated.
4. Place the neoprene LBNP skirt on the subject. Ensure that the skirt is snug around the waist and torso in order to create an air-tight seal.
5. Instruct the subject to lay supine on the bed of the LBNP chamber while straddling a stationary post to secure the torso in place during LBNP. Instruct the subject to relax the lower body during LBNP exposure. Secure the subject into the LBNP chamber by sliding the bed into the chamber and attaching the neoprene skirt to the chamber opening to create an air-tight seal.
   NOTE: The LBNP chamber provides the capability of accurately (within 0.1 mmHg) controlling the internal pressure from 0 to -100 mmHg either manually or with a computerized profile. The chamber includes an adjustable saddle to secure the subject's body position. Clear plexiglass windows allow for visualization of the subject's legs. An adjustable aluminum waist board allows for an air-tight seal to be created by a neoprene skirt worn by the subject and the LBNP chamber at the level of the iliac crest (**Figure 1**).
6. Place electrocardiogram (ECG) electrodes on the right and left humoral-clavicular joints, and on the right and left lower ribs (total of 4) in a modified lead II configuration (**Figure 1**) for continuous measurement of heart rate.
7. Position the subject's arms on the arm rests, adjusted so that the hands are supported at heart level. Using appropriate size finger cuffs, place an infrared finger photoplethysmography device on the left and right middle fingers for continuous noninvasive beat-to-beat measurement of blood pressure.
8. Attach the finger cuffs to the pressure monitors. Calibrate the devices and record blood pressure according to the manufacturer instructions.[12] Enter subject information (age, sex, height, and weight) to enable the appropriate assumptions for calculation (estimation) of stroke volume, cardiac output and peripheral vascular resistance by the Modelflow algorithm if desired.[13,14]
9. Place the finger pulse oximeter on the right index finger for continuous measurement of compensatory reserve[1,12] (**Figure 2**).
10. Place a nasal cannula on the subject and instruct the subject to breathe through the nose to assure sensitive reflections in inspiration and expiration. Nasal air sampling will allow the subject to talk freely for self-reporting of developing symptoms. Connect the nasal cannula to the capnograph for the continuous measurement of respiration and end tidal CO_2.

3. Performing the LBNP Protocol

1. Start data recording by clicking the "Start" button on the data acquisition system. Record baseline data for 5 min. Initiate the first level of central hypovolemia by turning on the vacuum motor and setting negative pressure to -15 mmHg, and hold this pressure for 5 min. **Figure 3** outlines the protocol.
2. Increase the LBNP to -30 mmHg, and hold this pressure for 5 min.
3. Increase the LBNP to -45 mmHg, and hold this pressure for 5 min.
4. Increase the LBNP to -60 mmHg, and hold this pressure for 5 min.
5. Increase the LBNP to -70 mmHg, and hold this pressure for 5 min.
6. Continue to increase LBNP levels by -10 mmHg every 5 min until the end of the protocol (5 min at -100 mmHg LBNP) or the point of hemodynamic decompensation. Terminate the LBNP by pressing the pressure release button on the LBNP chamber.

NOTE: Hemodynamic decompensation is identified by a precipitous fall in systolic arterial pressure below 80 mmHg, or the subject reporting presyncopal symptoms such as grey-out (loss of color vision), tunnel vision, sweating, nausea or dizziness (**Figure 4**).

7. Continue recording data on the data acquisition system during 10 min after the cessation of LBNP (postLBNP recovery).
8. Stop recording data at the end of the 10-min recovery period by clicking the "Stop" button on the data acquisition system.
9. Detach all instrumentation from the subject and remove the subject from the LBNP chamber. Ask the subject to sit after stepping down from the LBNP platform to ensure they are symptom-free before leaving the laboratory. The study is now complete.
10. Download data files from the acquisition system for extraction of the Compensatory Reserve Index (CRI), Mean Arterial Pressure (MAP), heart rate, and SpO_2 values. [1,15,16]

Representative Results

The LBNP procedure causes a reduction in air pressure around the lower torso and legs. As this vacuum is progressively increased, blood volume shifts from the head and upper torso to the lower body to create a state of central hypovolemia. The progressive reduction in central blood volume (*i.e.*, LBNP) produces significant alterations in the features of the arterial waveform measured with the infrared finger photoplethysmograph (**Figure 5**). The Compensatory Reserve Index (CRI) is calculated from the recorded arterial pulse wave using a unique machine learning algorithm which analyzes changes in wave form characteristics to calculate an estimated compensatory reserve **(Figure 6)**.[1,15,16] Each continuous noninvasive photoplethysmograph waveform (represented as the monitored 'Patient's Arterial Waveform') is the input to calculate an estimate of an individual's compensatory reserve (represented as the 'CRI Estimate') based on comparison to a large 'library' of reference waveforms (represented as the 'Algorithm Waveform Library') generated from progressive levels of central hypovolemia.

In this experiment, a subject was exposed to LBNP until the onset of hemodynamic decompensation which occurs when the body is no longer able to compensate for the hypovolemia. The values for mean arterial pressure, heart rate, SpO_2, and CRI plotted against time (*i.e.*, progressive reductions in central blood volume caused by increasing levels of LBNP) are shown in **Figure 7**. The results of the experiment show that changes in mean arterial pressure, heart rate, and SpO_2 occur during the later phases of hemorrhage (*i.e.,* >15 min into the protocol for heart rate and >25 min for mean arterial pressure and SpO_2) while CRI decreases early and progressively throughout the multiple steps of LBNP.

Tolerance to reduced central blood volume is defined as the time from the start of the experiment to decompensation. In this example, tolerance was approximately 27.5 min at a level of -70 mmHg LBNP. Based on previous experiments that were designed to equate the magnitude of actual blood loss with LBNP,[8] the equivalent blood loss that our subject was able to tolerate was estimated at approximately 1.2 L.

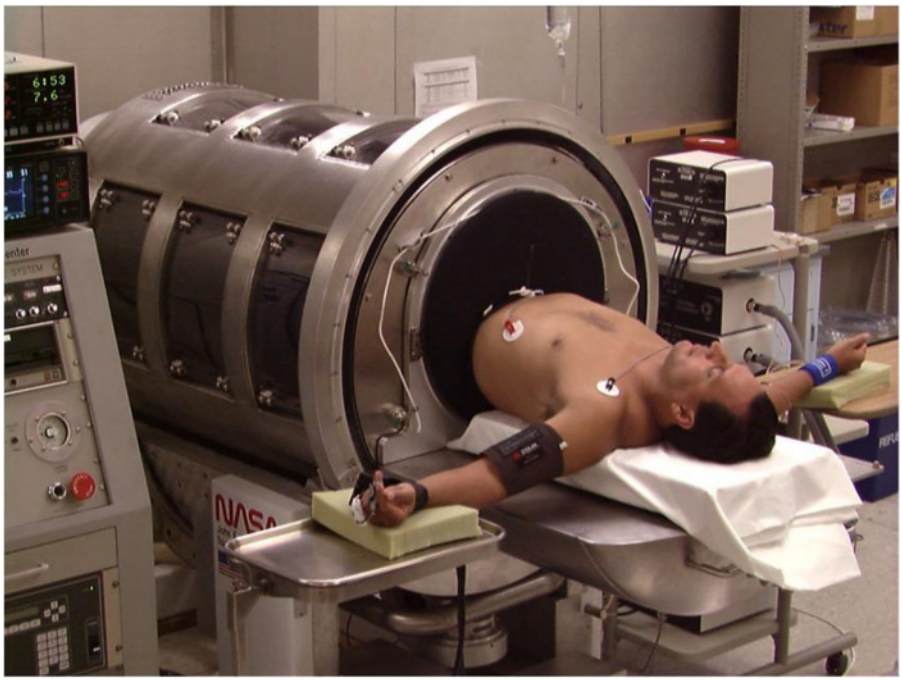

Figure 1: LBNP Chamber. A subject is shown in a supine position on the bed of the LBNP chamber. The neoprene skirt around the subject's waist is used to create an airtight seal within the LBNP chamber. Previously published in Cooke *et al.*[17] Please click here to view a larger version of this figure.

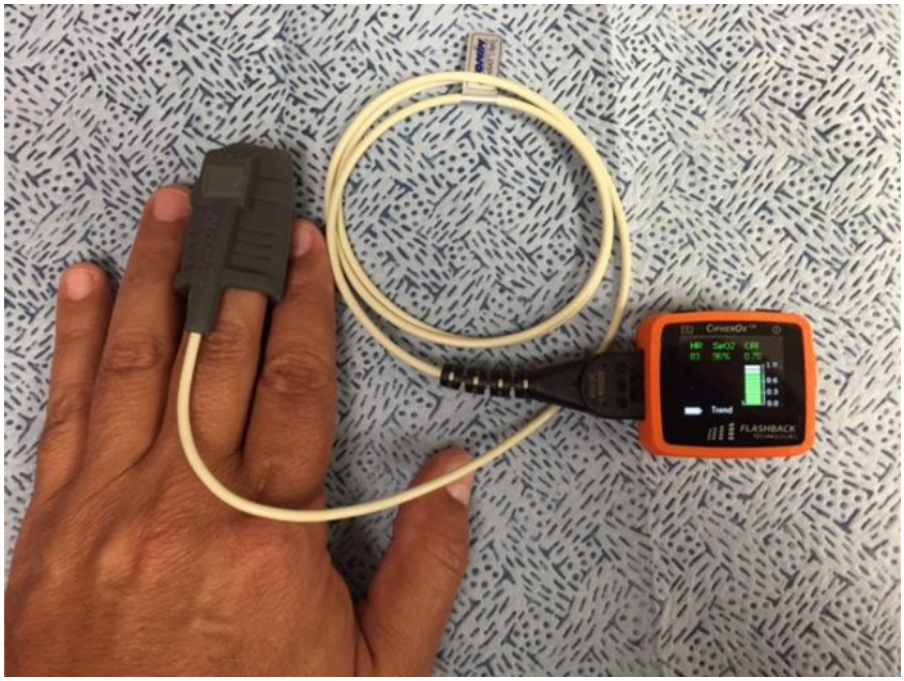

Figure 2: Compensatory Reserve Monitoring Device. The device consists of a noninvasive finger pulse oximeter that transmits pulse oximeter and waveform data via a USB connection to a compensatory reserve monitor. The monitor unit contains an algorithm which calculates a value for compensatory reserve known as the Compensatory Reserve Index (CRI)[1,12]. Data are recorded at each heart beat and displayed on the monitor and stored on a memory card. Please click here to view a larger version of this figure.

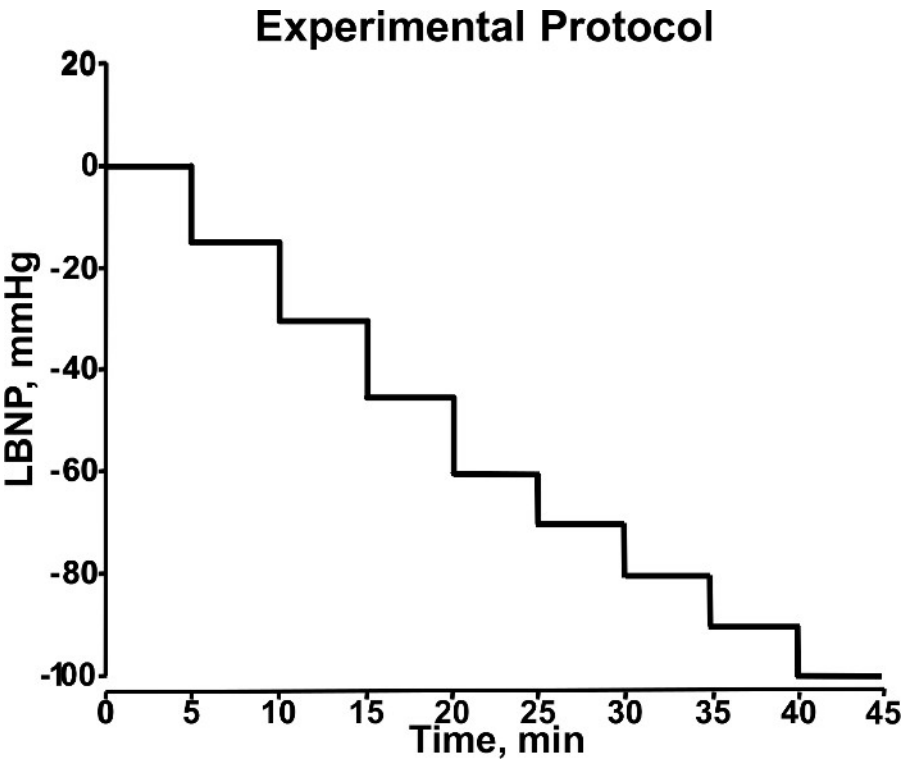

Figure 3. Stepwise Changes in LBNP During Experiment. During the experimental protocol, LBNP (mmHg) is adjusted in a stepwise manner (5 min/level) to induce progressive central hypovolemia. This diagram shows LBNP increasing from 0 to -100 mmHg during 40 min of an experimental protocol. Modified from Convertino *et al.*[18] Please click here to view a larger version of this figure.

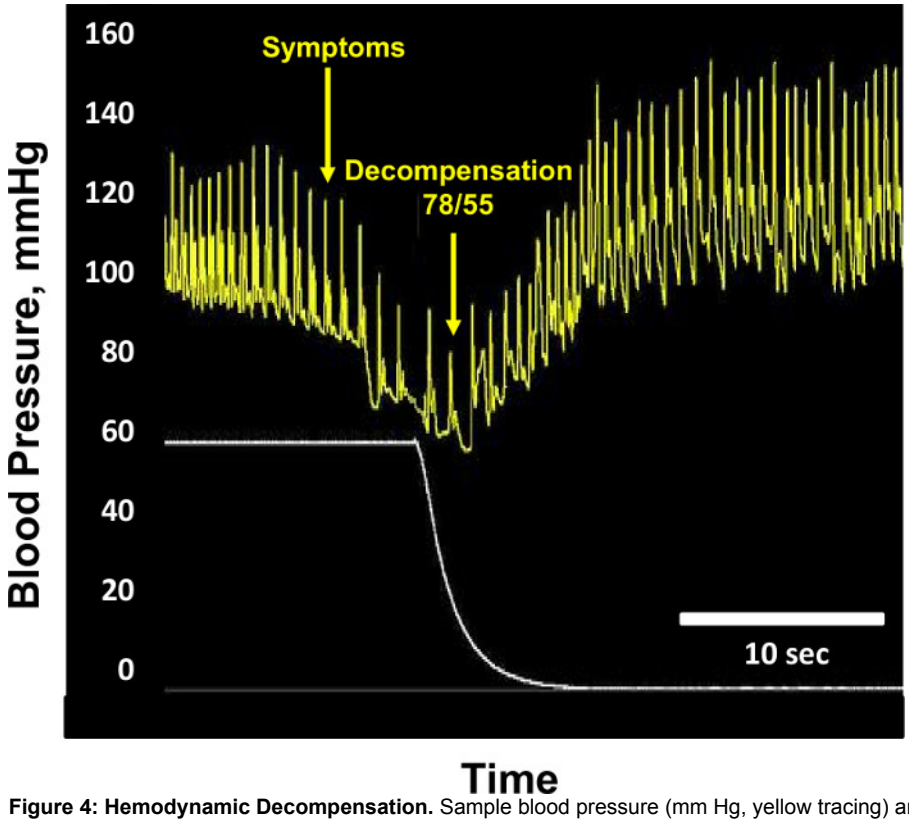

Figure 4: Hemodynamic Decompensation. Sample blood pressure (mm Hg, yellow tracing) and lower body negative pressure (mmHg, white tracing) recordings are shown from a subject at the point of hemodynamic decompensation. At the point of decompensation, blood pressure is 78/55 mmHg, and lower body negative pressure is -60 mmHg. Blood pressure returns to normal after cessation of lower body negative pressure. Modified from Convertino *et al.*[1] Please click here to view a larger version of this figure.

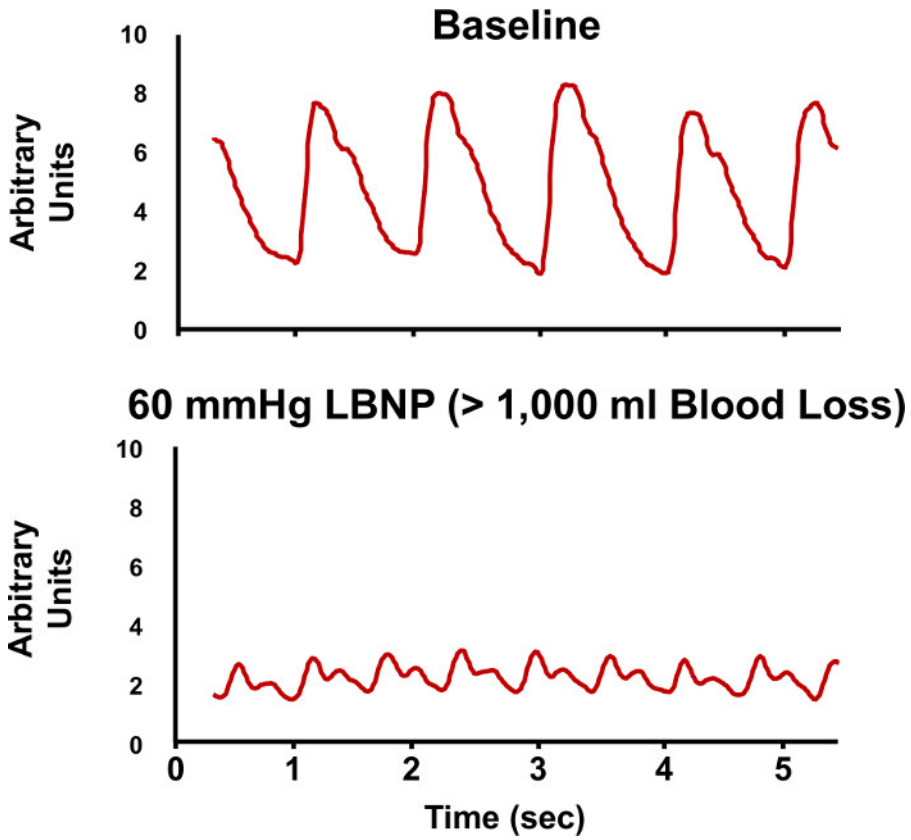

Figure 5. Arterial Waveforms During LBNP. Sample recordings of arterial pressure waveforms are shown during baseline (**upper tracing**) and during -60 mmHg lower body negative pressure (LBNP, **lower tracing**). The changes in the characteristic features of the arterial waveforms are evaluated to estimate compensatory reserve. Please click here to view a larger version of this figure.

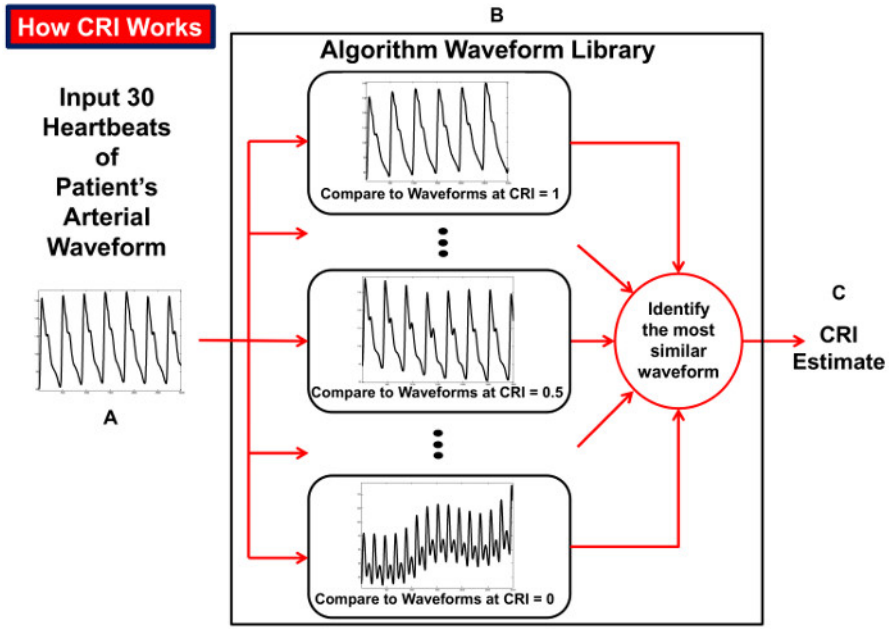

Figure 6: How the CRI is Calculated. Diagram illustrating the process of the compensatory reserve index (CRI) algorithm that compares beat-to-beat arterial blood pressure waveform tracings over an interval of 30 heartbeats (**A**) to a 'library' of waveforms (**B**) collected from humans exposed to progressive reductions in central blood volume for generation of an estimated CRI value (**C**). Reproduced from Convertino *et al.*[15] Please click here to view a larger version of this figure.

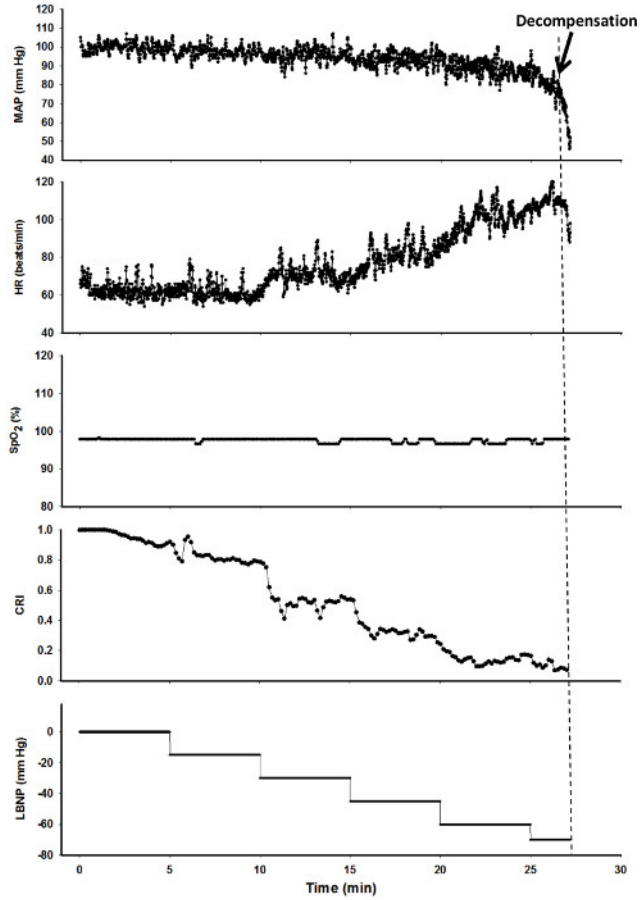

Figure 7. Sample Results of an LBNP Experiment. Values of Mean Arterial Pressure (MAP, mmHg), Heart Rate (HR, beats/min), arterial oxygen saturation (SpO_2, %), Compensatory Reserve Index (CRI) and Lower Body Negative Pressure (LBNP, mmHg) are shown for one subject during an LBNP experiment. The dashed line represents the onset of cardiovascular decompensation, Please click here to view a larger version of this figure.

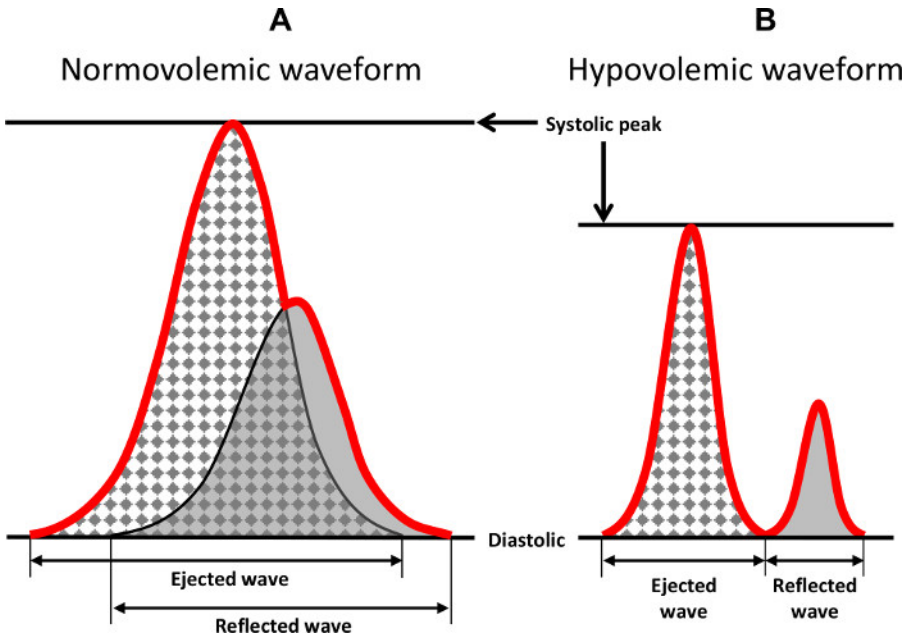

Figure 8: Characteristic Features of the Arterial Waveform. Two wave forms are shown that demonstrate the characteristic features of the arterial ejected and reflected waveforms during normovolemia and hypovolemia. The red line indicates the integrated waveform that is recorded and observed in a tracing. Previously published in Convertino *et al.*[1] Please click here to view a larger version of this figure.

Discussion

Using LBNP to cause progressive and continuous reductions in central blood volume, we were able to induce a typical response of hemodynamic decompensation in the subject, characterized by a sudden onset of hypotension and bradycardia (**Figure 7**). It is important to understand that the integrated compensatory response to hemorrhage is very complex,[19] resulting in significant individual variability in the tolerance to blood loss.[1] As such, some individuals have relatively responsive compensatory mechanisms while others do not compensate as effectively. Therefore, a critical step in the protocol is to conduct the experiment to the point of the onset of cardiovascular decompensation so that tolerance to hypovolemia can be accurately assessed. Premature termination of the experiment will not provide tolerance data. The experiments on more than 250 humans allowed us to classify individuals into two general populations[1,15,20-23] — those with relatively high tolerance (completion of the -60 mmHg level of the LBNP protocol) to reduced central blood volume (*i.e.,* good compensators) and those with low tolerance (poor compensators who failed to complete the -60 mmHg level of the LBNP protocol). One third (33%) of the humans we have tested has low tolerance, and two thirds (67%) of the subjects have high tolerance to hypovolemia. The subject tested in the presentation **(Figure 7)** would be classified as having high tolerance since he completed the -60 mmHg LBNP level.

LBNP is a well-established technique in the study of hypovolemia in humans, and troubleshooting is rarely necessary. However, using LBNP to assess TOLERANCE to hypovolemia requires that the experiment be conducted to the point of presyncope. A key factor in this experiment is maintaining a minimal risk of an adverse event (syncope) for the subject. As a result, all experiments are conducted in the presence of a study physician. In addition, all experiments are terminated immediately upon request of the subject or when systolic arterial pressure falls below 80 mmHg. The cessation of LBNP immediately redistributes blood volume to vital organs such as the brain and heart, subsequently restoring hemodynamic stability **(Figure 4)**.

As can be expected, the airtight seal around the waist of the subject is a critical requirement to allow the progressive increases in negative pressure in the chamber. Occasionally, especially at higher LBNP levels, the airtight seal can be compromised. At this point, modifications can be made to reinforce the seal by tightening the laces on the neoprene skirt or placing foam pads between the subject's waist and LBNP table. The LBNP vacuum device can accommodate minor leaks in the seal without affecting the pressure in the chamber.

The hemodynamic responses to LBNP have been shown to mimic those observed during hemorrhage.[8,17,24,25] We have used LBNP to study the compensatory responses to progressive bleeding in an effort to evaluate the body's integrative effort to maintain cardiovascular stability during blood loss (compensatory reserve) and to provide a measurement of compensatory reserve. While LBNP is a valid model for studying the compensatory responses to hemorrhage in humans, a limitation of this technique is the absence of other factors usually associated with hemorrhage such as trauma and pain. Clearly, the effects of these factors on the hemodynamic responses to hemorrhage cannot be assessed by LBNP induced hypovolemia in human volunteers.

Consistent with previously reported observations[1,15,16] we used the LBNP model of hemorrhage to demonstrate that measurement of the compensatory reserve identifies a trajectory to hemodynamic instability (decompensation) well in advance of clinically significant changes in currently available vital signs. This is an important point to understand since earlier recognition of clinical urgency is critical to improving patient outcomes, particularly in the emergency medical setting.[26-34] Existing methods for predicting cardiovascular decompensation rely on traditional vital signs that do not change until the onset of decompensation. The ability of the CRI algorithm to assess continuous changes in features of the arterial waveform allows machine-learning of the clinical status of the individual patient. In this regard, continuous real-time measurement of the compensatory reserve provides the most sensitive and specific technique to assess the tolerance of each individual to blood loss, and represents a significant improvement over existing methods for predicting hemorrhagic shock in the clinical setting.

It is important to recognize the CRI algorithm output as reflecting the integration of all physiological compensatory mechanisms involved in the compensation for a relative deficit in circulating blood volume. This notion is logical since the arterial waveform is made up of two distinct waves — the ejected wave (caused by contraction of the heart) and the reflected wave (caused by the arterial wave that reflects back from the arterial vasculature). All compensatory mechanisms that impact cardiac output (*e.g.*, autonomic nerve activity, cardiac filling, respiration, cardiac medications, *etc.*) are contained within features of the ejected wave while all compensatory mechanisms that affect vascular resistance (*e.g.*, sympathetic nerve activity, circulating catecholamines, arterial pH or CO_2, arterial elasticity, muscle contractions, *etc.*) are represented by features of the reflected wave.[1] As illustrated in **Figure 8**, the characteristic features change distinctly from an apparent single wave with a small notch in a normovolemic state (**left panel**) to two separated waves with smaller magnitudes of height and width in conditions of reduced central blood volume (**right panel**) such as occurs during hemorrhage. As such, changes in features of the arterial waveform in response to hemorrhage give a unique individual-specific predictive capability to assess one's capacity to compensate adequately for blood loss. Each individual's compensatory reserve is correctly estimated in real time because the machine-learning capability of the CRI algorithm accounts for compromised circulating blood volume as it "learns" and "normalizes" the totality of compensatory mechanisms based on the individual's arterial waveform features.[1] In this regard, the compensatory reserve is a superior measure of the physiological status of a bleeding patient than any one or combination of vital signs.

CRI has also been estimated in case reports beyond the standard LBNP laboratory environment. Compensatory reserve measurements were obtained from humans with conditions of compromised tissue perfusion caused by controlled hemorrhage [16], trauma [1], trauma followed by sepsis [35], acute appendicitis [35], burn injury [35], massive hematemesis [35], childbirth [35], cardiac arrest [35], postural orthostatic tachycardia [35], progressive hypovolemia with heat stress [35], and Dengue hemorrhagic fever. [1] These results indicate that the measurement of compensatory reserve using the CRI algorithm has provided accurate patient diagnosis in clinical conditions of compromised tissue perfusion associated with pain and tissue injury, and in varying environmental challenges.

The ability to measure the compensatory changes associated with blood loss is critical to providing acute care in emergency situations in both military and civilian scenarios. The LBNP technique will continue to be used as a valid model of human hemorrhage to provide data for creating, testing and refining future algorithms and devices to measure Compensatory Reserve.

Disclosures

The authors declare that they have no competing financial interests. The views expressed herein are the private views of the authors and are not to be construed as representing those of the US Department of the Army or the US Department of Defense.

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