AWARD NUMBER: CDMRPL-18-0-DM180240

TITLE: A Novel Approach for Identifying Individual Responses to Compromised Cerebral Oxygenation Challenges and Guided Intervention Using Compensatory Reserve Measurement

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CONTRACTING ORGANIZATION: U.S. Army Institute of Surgical Research (USAISR)

REPORT DATE: October 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE		Form Approved OMB No. 0704-0188

1. REPORT DATE *(DD-MMM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
OCT-2021	Annual	1 OCT 2020 – 30 SEP 2021

4. TITLE AND SUBTITLE

A Novel Approach for Identifying Individual Responses to Compromised Cerebral Oxygenation Challenges and Guided Intervention Using Compensatory Reserve Measurement

5a. CONTRACT NUMBER

5b. GRANT NUMBER
CDMRPL-18-0-DM180240

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. Army Institute of Surgical Research
Fort Sam Houston, TX 78234

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)
USAMRDC

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

One of the primary challenges of effectively treating bleeding trauma patients is the difficulty with using relatively traditional vital signs to provide early and accurate detection for the onset of hemorrhagic shock. At present, an individual-specific, non-invasive method for early detection of patients at risk of progression to shock is a CDID gap requirement. The overall objectives of this research is to: (1) develop and validate a new algorithm that will provide early identification of hemorrhagic shock using real-time machine-learning technology for analysis of changes in features of non-invasive photoplethysmographic (PPG) waveforms specific to individual patients and clinical conditions (i.e., precision medicine); and (2) identify clinically useful genetic and epigenetic correlates of tolerance to blood loss as well as identify gene expression and metabolic changes that could reveal underlying molecular mechanism.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. IMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	74	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

One of primary challenges of effectively treating bleeding trauma patients is the difficulty with using relatively traditional vital signs to provide early and accurate detection for the onset of hemorrhagic shock. At present, an individual-specific, non-invasive method for early detection of patients at risk of progression to shock is a CDID and SOCOM gap requirement. The overall objectives of this research is to: (1) develop and validate a new algorithm that will provide early identification of hemorrhagic shock using real-time machine-learning technology for analysis of changes in features of non-invasive photoplethysmographic (PPG) waveforms specific to individual patients and clinical conditions (i.e., precision medicine); and (2) identify clinically useful genetic and epigenetic correlates of tolerance to blood loss as well as identify gene expression and metabolic changes that could reveal underlying molecular mechanisms.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

compensatory reserve measurement, lower-body negative pressure, machine learning algorithm, hemorrhage, shock, tissue oxygenation, guided intervention

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Develop a new machine-learning algorithm that accurately estimates the status of a patient's systemic delivery of oxygen (DO_2) by providing individual-specific measurements of compensatory reserve, train the algorithm to identify specific clinical conditions, and collect blood samples for multi-omic analyses. Months 1-12.

Major Task 1: Prepare regulatory and institutional documents (months 1-2)

Milestone Achieved: Data and Materiel transferred, methodologies refined and coordinated with sites (month 2)

- *STATUS: COMPLETED*

Subtask 1: Mayo Clinic submissions, reviews, and approvals for access to existing USAISR LBNP data under a previous US Army-Mayo Clinic CRADA that was funded by MRDC to a Navy SPAWAR IDIQ contract and received Navy SPAWAR HRPO review and approval

Subtask 2: Coordinate sites for PI agreements, submission, material and data transfer, modeling methodology, transition plans and coordinate with sites for all other aspects of the research

Major Task 2: Conduct Staff Training.
- *STATUS: COMPLETED*

Major Task 3: Algorithm Development.
Milestone Achieved: Validated working algorithm capable of predicting early onset of hemodynamic decompensation (i.e., shock) with a ROC AUC for sensitivity and specificity equal to or greater than the algorithm developed by Flashback Technologies
- *STATUS: COMPLETED*

Subtask 1: Retrieve and transfer data files of all necessary PPG waveforms collected and archived in the USAISR LBNP database to the Mayo Clinic SPPDG

Subtask 2: Analyze data and develop machine learning algorithm

Subtask 3: Perform algorithm validation analyses using existing USAISR LBNP data

Subtask 4: Perform head-to-head comparisons of the ROC AUC of the USAISR-Mayo Clinic algorithm with the Flashback algorithm

Major Task 4: New arterial waveform data collection from Mayo Clinic LBNP experiments

Subtask 1: Prepare regulatory and institutional documents - Mayo Clinic Anesthesiology Department investigators have submitted a protocol to the local IRB. Once approved, will be ready for MRDC HRPO submission, review, and approval for expanded clinical data obtained from cardiac surgery patients.
- *STATUS: COMPLETED*

Subtask 2: Conduct studies of patients undergoing cardiac surgery for collection of arterial pressure waveforms from direct art lines

Subtask 3: Transfer the SPPDG CRM algorithm based on PPG waveforms to an arterial line signal by testing and training a new model based on a new dataset of direct arterial waveforms obtained from arterial lines during cardiac surgery

Specific Aim 2: Perform comprehensive multi-omic analyses to determine molecular signatures of blood loss tolerance. Months 1-36.

Major Task 1: Conduct new LBNP experiments on human subjects for collection of blood samples
- *STATUS: IN PROGRESS*

Subtask 1: BHT CHIP IRB and HRPO/DoD IRB submissions, reviews, and approvals for new LBNP experiments and blood collection on healthy humans have been completed

Subtask 2: Conduct LBNP experiments on 150 human subjects for collection of 300 blood samples (one sample before and one sample after LBNP)

Milestone(s) Achieved: 150 LBNP experiments completed with 300 collected blood samples
- *STATUS: IN PROGRESS (Completed 47 LBNP experiments with 94 blood samples)*

Major Task 2: Analysis of blood samples collected during new USAISR LBNP experiments
- *STATUS: IN PROGRESS*

Subtask 1: HRPO/DoD IRB submission, review, and approval to exchange de-identified blood samples from USASIR to USACEHR for genetic typing

Subtask 2: Transfer/Receive all blood samples

Subtask 3: Perform genetic and epigenetic analyses for identification of individual subjects classified as having high or low tolerance to central hypovolemia

Milestone(s) Achieved: Analyses completed; Confirmation that specific genetic and epigenetic traits correlate with high and low tolerance to hypovolemia
- *STATUS: YET TO ACHIEVE*

Major Task 3: Write manuscripts
- *STATUS: IN PROGRESS (see list of publications in section on Products)*

Specific Aim 3: Determine the relationship between the physiological assessment (Compensatory Reserve algorithm, aim 1) and patient prognosis and guided intervention over the course of clinical observation. Months 1-36.

Major Task 1: New Arterial Waveform Data Collection from Patients with Various Clinical Conditions
- *STATUS: IN PROGRESS (Data collection has been accomplished in patients with burn injury >15% TBSA, hemorrhage from trauma and receiving blood transfusion, and cardiac surgery)*

Subtask 1: Prepare Regulatory and Institutional Documents

Subtask 2: All surgery data have been collected to be analyzed retrospectively at the Mayo Clinic. All data prospectively collected from burn patients in the USAISR Burn ICU and from trauma patients with hemorrhage and receiving blood transfusion have been analyzed by the research team.

Major Task 2: Data Analysis
- *STATUS: IN PROGRESS (Burn patient data has been analyzed)*

Subtask 1: Collect and retrieve all necessary data needed for analysis. Data from 80 cardiac surgery patients awaits retrospective analysis from the Mayo Clinic research team. Prospective

data from 8 burn patients at the USAISR Burn Center has been analyzed and summarized in a draft manuscript. Prospective data collected in the BAMC Emergency Department from 13 trauma patients with hemorrhage has been statistically compared with 77 trauma patients without hemorrhage (controls) and published (see list of publications).

Subtask 2: Analyze data and compile results

Milestone(s) Achieved: Data analysis and results are complete

- *STATUS: IN PROGRESS (Data analysis has been completed from the Burn patient and trauma patient investigations).*

Major Task 3: Write manuscripts

- *STATUS: IN PROGRESS (Two manuscripts have been completed).*

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific Aim 1: Develop a new machine learning algorithm that accurately estimates the status of a patient's systemic delivery of oxygen (DO_2) to tissue by providing individual-specific measurements of compensatory reserve, train the algorithm to identify specific clinical conditions, and collect blood samples for multi-omic analyses.

Methods and results for the reporting period:

Subtask 1: Mayo Clinic submissions, reviews, and approvals for access to existing USAISR LBNP data under a previous US Army-Mayo Clinic CRADA that was funded by MRDC to a Navy SPAWAR IDIQ contract and received Navy SPAWAR HRPO review and approval.

Subtask 2: Bi-weekly teleconferences were held at the Mayo Clinic to coordinate sites for PI agreements, submission, material and data transfer agreements, modeling methodology, transition plans and coordinate with sites for all other aspects of the research.

Key Findings or Accomplishments for Specific Aim 1:

A Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) of 0.9411 for sensitivity and specificity of the Mayo Clinic CRM algorithm was higher than the 0.9153 ROC AUC generated from the FDA-approved Flashback Technologies CRI algorithm, indicating the successful completion of the CRM.

Methods and results for the reporting period: These findings have been reported as a publication in the journal *Biosensors* (see appendix attachment).

Key Findings or Accomplishments for Specific Aim 1:

As a consequence of a deviation in the MRDC IRB and HRPO-approved protocol H-11-038, the MRDC IRB competed an investigation with an adjudication that continuation of subject recruitment is contingent upon the submission of a new protocol incorporating the corrective actions stipulated in a post-approval compliance monitoring report. As a result, the PI is revising the LBNP Step protocol to incorporate withdrawal of blood samples to complete Specific Aim 2.

Specific Aim 2: Perform comprehensive multi-omic analyses to determine molecular signatures of blood loss tolerance. Months 1-36.

Methods and results for the reporting period:

The shipment of 94 frozen blood samples to the laboratory of Dr. Rasha Hammamieh (WRAIR), for multi-omic data analysis was successfully completed. The closing of all human research activities at the USAISR from March 2020 through July 2021 due to the COVID-19 pandemic significantly delayed the completion of the project by FY21Q4. As a result, the PI requested and received a no-cost extension to allow for completion of Specific Aim 2.

Key Findings or Accomplishments for Specific Aim 2:

A MIPR for second year funding for $220,170 (total of $440,340) has been executed to support multi-omic analysis of blood samples at WRAIR.

Specific Aim 3: Determine the relationship between the physiological assessment (Compensatory Reserve algorithm, aim 1) and patient prognosis and guided intervention over the course of clinical observation. Months 1-36.

Methods and results for the reporting period:

The Mayo Clinic team demonstrated functionality of the proposed collection system with renewal of their software license designed to capture clinical analog arterial waveforms from patients who underwent cardiac surgery. The waveforms are currently being analyzed for calculation of compensatory reserve using the Mayo Clinic CRM algorithm with a target completion date of Q2CY22.

Key Findings or Accomplishments for Specific Aim 3:

1) The CRM algorithm developed by Mayo Clinic demonstrated that CRM provided an earlier indicator of transition from a non-infected state to sepsis in burn patients compared to standard clinical measures (see appendix attachment).

2) CRM was able to distinguish trauma patients who received blood transfusion or airway intubation from those who did not receive any interventions, and increased appropriately after such interventions were performed (see appendix attachment).

What opportunities for training and professional development has the project provided?

US Army Combat Capabilities Development Command (DEVCOM) virtual seminar presentation with new CRM algorithm results: Convertino, V.A., Accurate Decision Support for Combat Casualties Suffering with Hemorrhage: It's not about Monitoring – It's about Physiology, May 2021.
Virtual panel presentation with new CRM algorithm results: Convertino, V.A., Accurate Decision Support for Patients Suffering with Hemorrhage: It's not about Monitoring – It's about Physiology, Institute of Electrical & Electronic Engineers International Conference on Biomedical and Health Informatics Wearable & Implantable Body Sensor Networks, July 2021.
Virtual guest presentation with new CRM algorithm results: Convertino, V.A., Monitoring Shock, Trauma Hemostasis & Oxygenation Research (THOR) International Group Blood Chat, September 2021.

How were the results disseminated to communities of interest?

On virtual platforms (MS Teams or Zoom).

What do you plan to do during the next reporting period to accomplish the goals?

This is the final reporting period. However, a continuation to recruit and enroll subjects for the completion of Specific Aim 2 with follow-up shipment of frozen blood samples to WRAIR for genetic and protein-omic analyses is planned.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The development and clinical validation of the algorithm for measuring compensatory reserve has provided new insight into monitoring patients and combat casualties with severe blood loss due to traumatic injury. The technology provides the first and only monitoring capability for assessing clinical status of the individual patient (i.e., it provides the first 'precision medicine' monitor in the world). This technology will undoubtedly advance critical care medicine by providing early detection of hemorrhage before the onset of shock. The CRM can eventually be used to guide accurate resuscitation in prolonged field care scenarios during multi-domain operations. A major impact of these findings and algorithm technology development has been the

generation of the most in depth review that promotes novel insights and knowledge of the physiology of human hemorrhage and compensation that was published in the American Physiological Society journal named Comprehensive Physiology with an impact factor of 6.2

What was the impact on other disciplines?
Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Numerous federal, state and local governments and professional organizations have recognized multiple ways in which measuring compensatory reserve can have impact on other disciplines. As a result, the investigators of this project have received multiple national and international invitations during the reporting period for this grant to provide briefings on the applications of compensatory reserve measurement for use in emergency medicine, particularly as it relates to combat casualty care on the battlefield, to such organizations as:

- Department of Emergency Medicine and the Clinical Research Investigation and Systems Modeling of Acute Illness (CRISMA) Group, University of Pittsburg School of Medicine
- Zoll Biomedical Corporation
- U.S. Army Medical Research & Development Command Systems Biology Collaboration Center
- Trauma Hemostasis & Oxygenation Research International Consortium
- Joint Trauma System Tactical Combat Casualty Care Global Conference
- Assistant Secretary of Preparedness and Response at the U.S. Department of Health & Human Services Critical Care Innovation Forum
- Solving Sepsis Program at the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services
- National Institute of Biomedical Imaging & Biotechnology at the NIH
- US Army Combat Capabilities Development Command (DEVCOM)
- Biological Technologies Office, Defense Advanced Research Projects Agency

What was the impact on technology transfer?

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

The Medical Technology Enterprise Consortium (MTEC) released a Request for Project Proposal (RPP) focused on the development of a noninvasive technology for early diagnosis and provider alert of decompensation due to hemorrhage and hemorrhagic shock in order to inform earlier lifesaving interventions and improve patient outcomes. The compensatory reserve measurement (CRM) algorithm developed and tested within this project was specifically listed as a government laboratory resource that industry proposers could use in the development of a

monitoring capability designed to detect decompensation due to hemorrhage. As a result of this RPP, one of the 3 industry partners identified for MTEC funding has contacted the USAISR research team to fund testing of the CRM on human volunteers who will undergo lower body negative pressure protocols as a model of progressive hemorrhage with the goal of demonstrating the CRM capability to provide early diagnosis of ongoing blood loss. Also as a result of this project, the PI is currently working with ZOLL Biomedical Corporation to use government purpose rights for integration of the CRM algorithm on the ZOLL Propaq-M monitor for eventual FDA clearance and marketing.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

The principal investigator continues discussions with the curator and chairman of 'TEDMED' to consider the possibility of presenting a 'Ted Talk' designed to advance the public knowledge and understanding of how measurement of the compensatory reserve using a simple non-invasive device could be used by the public to benefit their personal care and behaviors toward optimizing their health. The PI has presented numerous in-service lectures to nurses, EMS personnel, and combat medics on advantages of using CRM as an early indicator of hemorrhagic and septic shock in clinical settings.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

There are no significant changes in either objectives or scope of the proposed clinical data collection. However, there are events and/or changes in strategies for clinical data collection required to meet the proposed clinical data collection.

The impact of COVID-19 has continued to affect both the USAISR and Mayo Clinic efforts during this reporting period as well as throughout the FY20 and FY21 execution periods of this project. This impact has detrimentally delayed human subject recruitment and experimentation for support of Specific Aim 2 (genetic and protein-omic analyses). In addition, renewal of the software license for the proposed data collection system was delayed.

In an effort to expand clinical data collection and analysis to be used for CRM algorithm validation, we have 'piggy-backed' onto two clinical investigations. In one study, analog electronic recordings of arterial waveforms using arterial lines and a Drager blood pressure monitor have been collected electronically from 12 patients with burn injury >15% total body surface area who progressed from a non-septic to septic status (under approved USAISR Protocol #H-16-038). In the second study, analog electronic recordings of arterial waveforms obtained from a non-invasive Clearsite blood pressure monitor have been collected electronically from 13 trauma patients with hemorrhage who subsequently received whole blood transfusion in the emergency department and were compared to 77 trauma patients without hemorrhage (under approved BAMC Protocol #C.2018.026). A draft of a manuscript documenting the burn patient case series results has been completed and submitted for publication in the journal *Burns* (see appendix) A manuscript on the trauma patients with hemorrhage in the emergency department has been published in the journal *Transfusion* (see appendix).

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The complete shutdown of human research activities at the USAISR since March 2020 due to the coronavirus pandemic has imposed significant delays in the execution of planned LBNP experiments with blood sample collection and transport for support of Specific Aim 2. We are only now initiating standard operating procedures to assure the safe opening of laboratory studies. As a result, we are significantly behind in meeting milestones specific to Special Aim 2.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Despite some subtle changes in strategies implemented for execution of data collection required for successful completion of project Specific Aims, there was no significant impact on funding expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

None to report.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications (cumulative list over period of the project). *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Convertino V. Mechanisms of inspiration that modulate cardiovascular control: the other side of breathing. *J Appl Physiol.* 2019; 127:1187-1196. doi: 10.1152/japplphysiol.00050.2019. PubMed PMID: 31225967.
    a. Review
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support - Yes
2. Mulder M, Eidelson S, Buzzelli M, Gross K, Batchinsky A, Convertino V, Schulman C, Namias N, Proctor K. Exercise-induced changes in compensatory reserve and heart rate variability in military personnel at the Army Trauma Training Department. *Aerosp Med Hum Perform* 2019; 90:1009-1015. doi: 10.3357/AMHP.5460.2019. PubMed PMID: 31747997.
    a. Original manuscript
    b. Published
    c. Indirectly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
3. Techentin R, Felton C, Schlotman T, Gilbert B, Joyner M, Curry T, Convertino V, Holmes III D, Haider C. 1D Convolutional neural networks for estimation of compensatory reserve from blood pressure waveforms. *Conf. Proc IEEE Eng Med Biol Soc*. 2019; 2019:2169-2173. doi:. PubMed PMID:.
    a. Original manuscript
    b. Published
    c. Indirectly related to SOW, specific aim 1
    d. Acknowledge of federal support - No
4. Schlotman T, Lehnhardt K, Abercromby A, Easter B, Downs M, Akers K, Convertino V. Bridging the gap between monitoring for Army prolonged field care and NASA exploration spaceflight: the compensatory reserve. *NJP Microgravity* 2019; 5:29. doi: 10.1038/s41526-019-0089-9. PubMed PMID: 31815179.
    a. Review
    b. Published

    c. Indirectly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
5. Koons N, Nguyen B, Suresh M, Hinojosa-Laborde C, Convertino V. Tracking DO_2 with compensatory reserve during whole blood resuscitation following controlled hemorrhage in baboons. *Shock* 2020; 53:327-334. doi: 10.1097/SHK.0000000000001367.Shock. 2020. PMID: 32045396
    a. Original manuscript
    b. Published
    c. Directly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
6. Schlotman T, Akers K, Cardin S, Morris M, Convertino V. Evidence for misleading decision support in characterizing difference in tolerance to reduced central blood volume using measurements of tissue oxygenation. *Transfusion* 2020; 60 Suppl 3: S62-S69. doi: 10.1111/trf.15648. PMID: 32478865.
    a. Original manuscript
    b. Published
    c. Directly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
7. Convertino V, Koons N. The compensatory reserve: potential for accurate individualized goal-directed whole blood resuscitation. *Transfusion* 2020; 60 Suppl 3: S150-S157. doi: 10.1111/trf.15632. PMID: 32478902.
    a. Review
    b. Published
    c. Directly related to SOW, specific aim 1
    d. Acknowledge of federal support – Yes
8. Koons N, Owens G, Parsons D, Schauer S, Buller J, Convertino V. Combat medic testing of a novel monitoring capability for early detection of hemorrhage. *J Trauma Acute Care Surg*. 2020; 89(2S Suppl 2): S146-S152. doi: 10.1097/TA.0000000000002649. PMID: 32118826
    a. Original manuscript
    b. Published
    c. Directly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
9. Benov A, Brand A, Rosenblat T, Antebi B, Ben-Ari A, Amir-Keret R, Nadler R, Chen J, Chung K, Convertino V, Paran H. Evaluation of sepsis using compensatory reserve measurement: a prospective clinical trial. *J Trauma Acute Care Surg*. 2020; 89(2S Suppl 2): S153-S160. doi: 10.1097/TA.0000000000002648. PMID: 32118823
    a. Original manuscript
    b. Published
    c. Directly related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
10. Schlotman T, Suresh M, Koons N, Howard J, Schiller A, Cardin S, Convertino V. Comparisons of measures of compensatory reserve and heart rate variability as early indicators of hemodynamic decompensation in progressive hypovolemia. *J Trauma Acute Care Surg*. 2020; 89(2S Suppl 2): S161-S168. doi: 10.1097/TA.0000000000002605. PMID: 32044875
    a. Original manuscript

b. Published
c. Directly related to SOW, specific aim 1
d. Acknowledge of federal support - Yes

11. Convertino V, Wampler M, Johnson M, Alarhayem A, Le T, Nicholson S, Myers J, Chung K, Struck K, Cuenca C, Eastridge B. Validating clinical threshold values for a dashboard view of the compensatory reserve measurement for hemorrhage detection. *J Trauma Acute Care Surg*. 2020; 89(2S Suppl 2): S169-S174. doi: 10.1097/TA.0000000000002586. PMID: 31972755.
    a. Original manuscript
    b. Published
    c. Directly related to SOW, specific aim 1 and 3
    d. Acknowledge of federal support - Yes
12. Zaar M, Herzig M, Fedyk C, Montgomery R, Prat M, Parida B, Hinojosa-Laborde C, Muniz G, Shade RE, Bauer C, Delacruz W, McFaul S, Bynum J, Convertino V, Cap A, Pidcoke H. Similar hemostatic responses to hypovolemia in hemorrhage and LBNP reveals a hyperfibrinolytic subset of baboons. 2020; *PLoS One.* 2020; 15(6):e0234844. doi: 10.1371/journal.pone.0234844. eCollection 2020. PMID: 32579572
    a. Original manuscript
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support - Yes
13. Thompson P, Hudson A, Convertino V, Bjerkvig C, Eliassen H, Eastridge B, Irvine-Smith T, Braverman M, Hellander S, Jenkins D, Rappold J, Gurney J, Glassberg E, Cap A, Ausset S, Apelseth T, Williams S, Ward K, Shackelford S, Stroberg P, Vikenes B, Pepe P, Winckler C, Woolley T, Enbuske S, De Pasquale M, Boffard K, Austlid I, Fosse T, Asbjørnsen H, Spinella P, Strandenes G. Risk of harm associated with using rapid sequence induction intubation and positive pressure ventilation in patients with hemorrhagic shock. *J Spec Ops Med.* 2020; 20: 97-102. PMID: 32969011
    a. Review
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support - Yes
14. Convertino V, Schauer S, Weitzel E, Cardin, S, Stackle M, Talley M, Sawka M, Inan O. Low-profile, wearable sensors with integrated predictive algorithms for advanced physiologic monitoring in critically injured trauma patients. *Sensors.* 2020; 20, 06413.
    a. Review
    b. Published
    c. Related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes
15. Convertino V, Koons N, Suresh M. The physiology of human hemorrhage and compensation. *Comp Physiol*. 2021; 11: 1531-1574.
    a. Review
    b. Published
    c. Related to SOW, specific aim 1
    d. Acknowledge of federal support - Yes

16. Schauer S, Naylor J, Dion G, April M, Chung K, Bynum J, Convertino V. An analysis of airway interventions in the setting of smoke inhalation injury on the battlefield. *Milt Med.* 2021; 185(5-6): e474-e479.
    a. Original Article
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support - Yes
17. Carius B, Naylor J, April M, Fisher A, Hudson I, Stednick P, Maddry J, Weitzel E, Convertino V, Schauer S. Battlefield vital sign monitoring in Role I military treatment facilities: a thematic analysis of after-action reviews from the Prehospital Trauma Registry. *Milt Med* 2021.
    a. Original Article
    b. Published
    c. Related to SOW, specific aim 1
    d. Acknowledge of federal support - No
18. Schauer S, April M, Arana A, Maddry J, Escandon M, Linscomb C, Rodriguez D, Convertino V. Efficacy of the compensatory reserve measurement in an emergency department trauma population. *Transfusion* 2021; 61:S174-S182.
    a. Original Article
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support - Yes
19. Convertino V, Johnson M, Alarhayem A, Nicholson S, Chung K, DeRosa M, Eastridge B. Compensatory reserve detects subclinical phases of shock with more expeditious prediction for need of life-saving interventions compared to vital signs and arterial lactate. *Transfusion* 2021; 61:S167-S173.
    a. Original Article
    b. Published
    c. Directly related to SOW, specific aim 1 and 3
    d. Acknowledge of federal support - Yes
20. Convertino V, Cardin S, Cap A, Crowder A, Stackle M, Talley M, Lurie K. Saving the brain after mild-to-moderate traumatic injury: a report on new insights of the physiology underlying adequate maintenance of cerebral perfusion. *J Trauma Acute Care Surg*. 2021; 19:S33-S39.
    a. Original Article
    b. Published
    c. Not related to SOW
    d. Acknowledge of federal support – Yes

21. Convertino V, Dacy A, Techentin R, Cardin S, Haider C, Holmes D, Joyner M, Curry T, Sawka M, Inan O. Advanced development for assessing low circulating blood volume during emergency medical care: comparison of compensatory reserve algorithms. *Biosensors*. 2022.
    a. Original Article
    b. In press
    c. Directly related to SOW – Specific Aim 1
    d. Acknowledge of federal support - Yes

22. Convertino V, Wagner A, Akers K, VanFosson C, Cancio L. Early identification of sepsis in burn patients using compensatory reserve measurement: a case series pilot study. *Burns*. 2022 (in review).
    a. Original Article
    b. In Review
    c. Directly related to SOW– Specific Aim 1 and 3
    d. Acknowledge of federal support - Yes
23. Convertino, VA, Johnson MC, Alarhayem A, Nicholson SE, Chung KK, DeRosa M, Eastridge BJ. Compensatory reserve measurement and pulse character enhanced potential to predict casualty urgency after injury. *Transfusion*. 2022.
    a. Original Article
    b. In Review
    c. Directly related to SOW– Specific Aim 1 and 3
    d. Acknowledge of federal support - Yes

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Convertino VA, Koons NJ. Autonomic response to hypovolemic shock. In: Primer on the Autonomic Nervous System, 4th ed., Chapter 55. I Biaggioni, K Browning, G Fink, J Jordan, P Low, J Paton (eds.). Amsterdam: Elsevier Sci. Pub., 2021 (in press).

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

1. Convertino V. May 2021. "Accurate Decision Support for Combat Casualties Suffering with Hemorrhage: It's not about Monitoring – It's about Physiology!" US Army Combat Capabilities Development Command (DEVCOM Soldier Center), Aberdeen Proving Ground, Maryland
    a. Virtual Oral Presentation (Seminar)
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged
2. Convertino V. July 2021. "Accurate Decision Support for Combat Casualties Suffering with Hemorrhage: It's not about Monitoring – It's about Physiology!" The Institute of Electrical

& Electronic Engineers (IEEE) International Conference on Biomedical & Health Informatics Wearable & Implantable Body Sensor Networks, Athens, Greece
    a. Virtual Oral Presentation
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged
3. Convertino V. Sep 2021. "Monitoring Shock". The Trauma Hemostasis & Oxygenation Research (THOR) Monthly Blood Chat, Bergen, Norway.
    a. Virtual Guest Oral Presentation
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

The primary technology resulting from this research activity is a machine-learning algorithm for measurement of a physiological phenomenon known as the compensatory reserve. Our vision is that we will be able to upload this computer software onto currently marketed medical monitors through partnerships with industry to provide novel advanced early detection of blood loss prior to the onset of hemorrhagic shock.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

The Special Purpose Processor Development Group at the Mayo Clinic has submitted a provisional patent application (16/934,805) in January 2020 entitled "Systems, Methods and Media for Estimating Compensatory Reserve and Predicting Hemodynamic Decompensation Using Physiological Data". The US Army (Dr. Convertino) is named as a co-inventor.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life.

- *Largest database in the world containing human physiological recordings to the point of onset of Class III shock*
- *Largest collection of genetic and multi-omic data collected on humans at the point of onset of Class III shock*
- *Software: First and only machine-learning algorithm that provides accurate prediction of the onset of Class III shock*
- *Model: Lower body negative pressure is the only capability in the DoD for the study of human hemorrhage*
- *Clinical interventions: Data provide information for the development of a clinical practice guideline for accurate goal-directed whole blood resuscitation*

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	Dr. Victor Convertino
Project Role:	Principal Investigator at USAISR
Nearest person month worked:	2
Contribution to Project:	Dr. Convertino has performed writing and submission of scientific manuscripts for publication, and regulatory / institutional documents for IRB review and approval, communicates regularly with Mayo Clinic and USACEHR collaborators, and conducted staff training
Name:	Mr. Brian Jordan
Project Role:	Co-Investigator at USAISR
Nearest person month worked:	6
Contribution to Project:	Mr. Jordan has replaced Dr. Taylor Schlotman in the role of conducting LBNP experiments for the project
Name:	Ms. Denise Woods
Project Role:	BHT CHIP Lab Research Assistant at USAISR
Nearest person month worked:	6
Contribution to Project:	Ms. Woods has performed oversight of all regulatory and institutional documents for IRB review and approval,

	recruits and consents human subjects, and maintains all human subject data files under HIPAA regulations. She also assists with the execution of LBNP experiments for the project
Name:	Ms. Natalie Koons
Project Role:	Graduate Student Intern at USAISR
Nearest person month worked:	2
Contribution to Project:	Ms. Koons has assumed the responsibility for analyzing CRM data collected during LBNP experiments and preparing / writing manuscripts for publication in scientific journals.
Name:	CPT Alisha Carlson
Project Role:	Graduate Student Intern at USAISR
Nearest person month worked:	2
Contribution to Project:	CPT Carlson replaced Dr. Taylor Schlotman's responsibility for preparing methodological documents for electronic data collection and analysis, and supervised the transfer of LBNP data sets to the SPPDG personnel at Mayo Clinic.
Name:	Dr. Rasha Hammamieh
Project Role:	Director, Systems Biology Group at WRAIR
Nearest person month worked:	0
Contribution to Project:	Dr. Hammamieh's laboratory performs the comprehensive multi-omic analyses of blood samples collected during the LBNP experiments conducted at USAISR
Name:	Dr. Clifton Haider
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Nearest person month worked:	3
Contribution to Project:	Dr. Haider has led the Mayo Clinic SPPDG effort in development of the CRM algorithm
Name:	Dr. Robert Techentin
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Nearest person month worked:	6
Contribution to Project:	Dr. Techentin has been instrumental in the Mayo Clinic SPPDG effort to develop the CRM algorithm software
Name:	Dr. David Holmes
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Nearest person month worked:	2

Contribution to Project:	Dr. Holmes has performed verification and validation testing on the early generations of the CRM algorithm
Name:	Dr. Michael Joyner
Project Role:	Anesthesiologist/Collaborating Investigator at Mayo Clinic
Nearest person month worked:	1
Contribution to Project:	Dr. Joyner has performed writing and submission of regulatory and institutional documents for IRB review and approval, conducted staff training at Mayo Clinic, and oversees data collection during cardiac surgeries
Name:	Dr. Tim Curry
Project Role:	Anesthesiologist/Collaborating Investigator at Mayo Clinic
Nearest person month worked:	1
Contribution to Project:	Dr. Curry has performed writing and submission of regulatory and institutional documents for IRB review and approval, conducted staff training at Mayo Clinic, and oversees data collection during cardiac surgeries
Name:	Ms. Shelly Roberts
Project Role:	Research Nurse at Mayo Clinic
Nearest person month worked:	1
Contribution to Project:	Ms. Roberts conducted staff training at Mayo Clinic, and has performed oversight of all regulatory and institutional documents for IRB review and approval, recruits and consents human subjects, and maintains all human subject data files under HIPAA regulations

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No changes to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Organization Name: Special Purpose Processor Development Group (SPPDG), Mayo Clinic
Location of Organization: Rochester, MN
Partner's contribution to the project

- Primary role is to develop machine-learning software
- Collaboration: SPPDG staff works closely with project staff on data analysis and writing of manuscripts related to the project

- Facilities: CPT Carlson is in constant communication with engineers at the Mayo Clinic to use the SPPDG facilities for learning, test and evaluation of the CRM algorithm

Organization Name: Department of Anesthesiology, Mayo Clinic
Location of Organization: Rochester, MN
Partner's contribution to the project

- Primary role is to collect arterial waveform data on cardiac surgery patients
- Collaboration: Mayo Clinic Department of Anesthesiology staff works closely with project staff on data analysis and writing of manuscripts related to the project

Organization Name: U.S. Army Center for Environmental Health Research (USACEHR), WRAIR
Location of Organization: Silver Spring, MD
Partner's contribution to the project

- Primary role is to conduct genetic and multi-omic analysis on blood samples
- Collaboration: USACEHR staff works closely with project staff on data analysis and writing of manuscripts related to the project

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report.

QUAD CHART:

A Novel Approach for Identifying Individual Responses to Tissue Oxygenation Challenges and Guided Intervention Using Compensatory Reserve Measurement
CDRMPL-18-0-DM180240 / DM180240

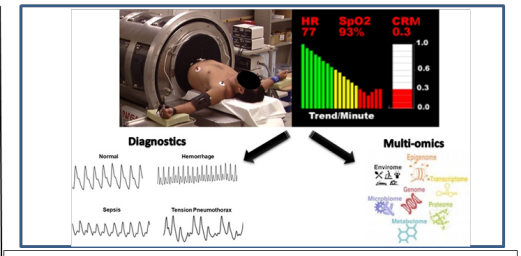
PI: Victor A. Convertino **Org:** US Army Institute of Surgical Research **Award Amount:** $2,032,601

Study/Product Aim(s)

- Develop a new machine-learning algorithm, train the algorithm to identify specific clinical conditions, and collect blood samples for multi-omic analyses during progressive central hypovolemia (e.g., hemorrhage).
- Perform comprehensive multi-omic analyses to identify genetic markers for distinguishing individuals with high and low tolerance to blood loss.
- Determine the relationship between the physiological assessment, patient prognosis, and guided intervention over the course of clinical observation.

Approach

- Develop and validate a new Compensatory Reserve Measurement (CRM) algorithm using machine learning that will provide for early identification of physiological conditions via real-time analysis of changes in non-invasive PPG waveforms specific to individual patients (i.e., precision medicine) caused by a variety of experimental and clinical conditions.
- Analyze blood samples obtained before and after exposure of humans to LBNP in an effort to determine the genetic, molecular and metabolic correlates of tolerance to blood loss via multi-omic analyses.



Accomplishment: Creation of a CRM algorithm and clinical validation are complete, with the latest version utilizing convolutional neural networks reaching ROC AUC 0.89. Next steps: further subject LBNP testing to complete multi-omic analyses for determination of any genetic basis for individual tolerance to central hypovolemia.

Timeline and Cost

Activities CY	18	19	20	21
Algorithm Development & Testing				
Experimental Data Collection & Multi-omics Analysis				
Clinical Data Collection & Analysis				
Complete data collection & analysis, Interpret/publish findings				
Estimated Budget ($K)		760k	705k	568k

Updated: 30 September 2021

FY19 Goals –Organization of study materials, coordination of groups doing work, begin experiments to collect & analyze data
☐ IRB approval, staff training, data transfer for algorithm development
☐ Collect new data for algorithm development and advancement
☐ Collect blood samples for multi-omic analyses
FY20 Goals –Collection of clinical data for algorithm advancement, experiments to collect & analyze data
☐ Collect experimental and clinical data for algorithm development and advancement
☐ Collect blood samples for multi-omic analyses and analyze genetic and molecular signatures of blood loss tolerance
☐ Train and validate the CRM algorithm to recognize different physiological conditions (i.e., become diagnostic)
FY21 Goals–Continue data collection and analysis, interpret/publish findings
☐ Collect clinical & experimental data for algorithm development and advancement; Train & Validate CRM algorithm for diagnostics
☐ Analyze findings and publish results
Budget Expenditure to Date
Projected Expenditure: $2,032,601 Actual Expenditure: $2,032,601

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

biosensors

MDPI

Article

AI-enabled Advanced Development for Assessing Low Circulating Blood Volume for Emergency Medical Care: Comparison of Compensatory Reserve Machine-Learning Algorithms

Victor A. Convertino [1,2,3]*, Robert W. Techentin[4], Ashley C. Dacy[5], CPT Ashli N. Carlson[1], Sylvain Cardin[5], Clifton R. Haider[4], David R. Holmes, III[6], Chad C. Wiggins[7], Michael J. Joyner[7], Timothy B. Curry[7], and Omer T. Inan[8]

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3 Department of Emergency Medicine, University of Texas Health, San Antonio, TX, USA
4 Special Purpose Processor Development Group, Mayo Clinic, Rochester, MN, USA; techentin.robert@mayo.edu (R.W.T.); haider.clifton@mayo.edu (C.R.H)
5 Naval Medical Research Unit, JBSA Fort Sam Houston, San Antonio, TX 78234, USA; ashley.c.dacy.civ@mail.mil (A.C.D.); sylvain.cardin.civ@mail.mil (S.C.)
6 Biomedical Analytics and Computational Engineering Laboratory, Mayo Clinic, Rochester MN, USA holmes.david3@mayo.edu (D.R.H.)
7 Department of Anesthesiology, Mayo Clinic, Rochester MN, USA; wiggins.chad@mayo.edu (C.C.W); joyner.michael@mayo.edu (M.J.J.); curry.timothy@mayo.edu (T.B.C.)
8 Georgia Institute of Technology, Atlanta, GA 30332, USA; inan@gatech.edu (O.T.I.)
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Abstract: Application of artificial intelligence (AI) has provided new capabilities to develop advanced medical monitoring for detection of clinical conditions of low circulating blood volume such as hemorrhage. The purpose of this study was to compare the discriminative ability of two machine-learning (ML) algorithms based on real-time feature analysis of arterial waveforms obtained from a noninvasive continuous blood pressure system (Finometer®) signal to predict the onset of decompensated shock: the compensatory reserve index (CRI) and the compensatory reserve metric (CRM). One hundred and ninety-one healthy volunteers underwent progressive simulated hemorrhage using lower body negative pressure (LBNP). The least squares means and standard deviations for each measure were assessed by LBNP level and stratified by tolerance status (high vs. low tolerance to central hypovolemia). Generalized Linear Mixed Models were used to perform repeated measures logistic regression analysis by regressing the onset of decompensated shock on CRI and CRM. Sensitivity and specificity were assessed by calculation of receiver-operating characteristic (ROC) area under the curve (AUC) for CRI and CRM using Generalized Estimating Equations. Values for CRI and CRM were not distinguishable across levels of LBNP independent of LBNP tolerance classification, with CRM ROC AUC (0.9268) being statistically similar (P = 0.134) to CRI ROC AUC (0.9164). Both CRI and CRM ML algorithms displayed discriminative ability to predict decompensated shock to include individual subjects with varying levels of tolerance to central hypovolemia. Arterial waveform feature analysis provides a highly sensitive and specific monitoring approach for detection of ongoing hemorrhage, particularly for those patients at greatest risk for early onset of decompensated shock and requirement for implementation of life-saving interventions.

Keywords: hemorrhage; shock; medical monitoring; compensatory reserve; machine learning; deep learning; artificial intelligence; sensor signals

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Biosensors* **2021**, *11*, x. https://doi.org/10.3390/xxxxx

Received: date
Accepted: date
Published: date

1. Introduction

Employment of early medical intervention(s) for patients suffering from traumatic injury has consistently been shown to result in improved clinical outcomes [1]. As such, early intervention relies on early and accurate diagnosis of patient status. Such diagnosis has proven historically challenging because of medical monitors that are limited to providing standard vital signs that change very little during the compensatory stage of hemorrhage [2]. To address this limitation, there has been emerging technology based on the application of artificial intelligence (AI) to identify real-time changes in the sum total of all physiological mechanisms involved in the compensation for low blood volume states (i.e., central hypovolemia). This physiological phenomenon has been defined as the compensatory reserve, with its measurement relying on a Machine learning (ML) approach that incorporates the interrogation of arterial blood pressure waveform features [1, 2, 3-7]. Reported measurements of the compensatory reserve have consistently proven to provide greater sensitivity in time (i.e., early) and specificity for identifying individual patient status when compared to traditional standard vital signs in both human experimental [2, 6, 8-13] and clinical [14-21] settings. In this regard, measurement of the compensatory reserve has proven to be "the most informative 'vital sign' to be captured in emergency medical care settings" because of its ability to provide earlier and individualized status of patients with hypovolemia [2].

If the physiological basis for compensatory reserve resides in the assessment of arterial waveform morphology, then its accurate measurement should be independent of any approach used to develop a ML monitoring tool designed to interrogate waveform features. In this study, we compared two independently-generated algorithms developed for measurement of the compensatory reserve based on application of different ML techniques with access to a common data set of arterial waveforms obtained from a large cohort of human subjects who underwent progressive reductions in central blood volume similar to that experienced during hemorrhage. We hypothesized that the algorithms would yield similar performance based on evaluation of sensitivity and specificity for tracking the compensatory status of the subjects.

2. Methods

2.1. Subject Volunteers

One hundred and nighty-one women (N = 88) and men (N = 103) with a mean (±SD) age of 27 ± 8 years, height of 164 ± 30 cm, and weight of 74.5 ± 16.1 kg volunteered to participate in this investigation after all procedures and potential risks were explained and their written informed consent was obtained. To assure a state of health, each subject completed a medical history survey and underwent a physical examination before experimentation. For at least 24 hours prior to an experiment, participants were instructed to abstain from use of alcohol, nicotine, caffeine, medications, and/or any drugs that could impact autonomic functions. Female subjects were excluded if they displayed a positive urine pregnancy test during their physical examination. All experimental procedures and protocols were explained to each subject prior to obtaining written informed consent.

2.2. Experimental Protocol

A two-group, repeated measures study design was used to compare the ability of the CRI and CRM to predict the onset of decompensated shock. The experimental protocol was designed to determine the tolerance to central hypovolemia of each volunteer subject by applying progressively increasing levels of lower body negative pressure (LBNP). Central hypovolemia induced by LBNP in humans has been shown to result in the integrated activation of compensatory mechanisms comparable to those observed during actual hemorrhage [1, 22]. Previous experiments have demonstrated that −30, −60, and − 90 mmHg LBNP approximates average blood losses of 450, 1,000 and 1,600 mL in a 70-kg human [23]. All subjects were supine for the duration of the testing session. Following a baseline resting period of 5 minutes, each subject underwent exposure to an experimental

profile that consisted of progressive LBNP levels at −15, −30, −45, −60, −70, −80, −90, and −100 mmHg for 5 minutes each. The LBNP protocol was immediately terminated at the time that a subject experienced the onset of clinical decompensated shock as defined by a fall in systolic blood pressure (SBP) to <80 mmHg with concurrent expression of any combination of pre-syncopal symptoms such as nausea, cold sweat, dizziness, or tunnel vision. Release of LBNP to ambient pressure resulted in rapid restoration of central blood volume to the central circulation with concurrent stabilization of hemodynamic stability.

2.3. Measuring the Compensatory Reserve

The compensatory reserve is a physiological phenomenon that represents the sum total of all mechanisms that protect against inadequate systemic delivery of oxygen (DO_2) to the tissues of the body. As such, the compensatory reserve was calculated as the difference in the capacity to compensate for hypovolemia in a resting baseline state (estimated as 100% reserve) and at the onset of hemodynamic instability when the capacity to compensate has been exhausted (i.e., 0% reserve) [1, 5-7, 25-28]. In this regard, each individual has a finite 'reserve' to compensate for low blood volume and flow states. For this investigation, we applied two independently-generated ML algorithms for calculation of an estimated valued of the compensatory reserve: 1) the compensatory reserve index (CRI; Flashback Technologies Inc., Denver, CO); and 2) the compensatory reserve metric (CRM; Mayo Clinic Special Purpose Processor Development Group, Rochester, MN). These algorithms provided state-of-the-art feature-extraction and ML methods for retrospective calculation of compensatory reserve based on changes in morphology of analog arterial pressure waveforms obtained noninvasively with an infrared finger blood pressure signal using the volume clamp technique (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) [1, 4, 5-7, 9, 10, 29].

2.3.1. Compensatory Reserve Index (CRI)

The proprietary CRI algorithm was developed from the application of feature extraction and ML methods used for robotic situational awareness that was translated to vital sign waveform data generated from LBNP experiments [4, 7]. The resulting training data included >650,000 training sample waveforms. This approach led to the identification of hundreds of features within each noninvasive arterial waveform that trend the compensatory phase of central blood volume loss. In this regard, the algorithm was constructed with use of the following generalized equation to calculate an estimate of CRI:

$$\text{CRI} = 1 - \frac{BLV}{BLV@HD}$$

where BLV is the current blood loss volume of the patient and BLV@HD is the BLV at which the onset of hemodynamic decompensation occurs in that patient. Within this construct, the calculated estimate of CRI relied on an assumption that an individual's BLV at any given time is known, as well as that individual's BLV@HD due to reduced central blood volume. The accuracy of this assumption is supported by experiments using non-human primates and human subjects that demonstrated how LBNP closely mimics physiologic responses observed when compared to hemorrhage [1, 23, 30-32]. These direct comparisons allowed for translation of -30, -60, and -90 mmHg LBNP to average equivalents of approximately 450, 1,000, and 1,600 ml blood loss in a 70-kg human [23, 31]. As such, the relationship between LBNP and BLV allowed for an ethically and scientifically justified substitute for modeling the reduction in central blood volume to hemodynamic decompensation in humans using the following calculation to estimate CRI:

$$\text{CRI} = 1 - \frac{BLV(t)}{BLV@HD} \approx 1 - \frac{LBNP(t)}{LBNP@HD}$$

where LBNP(t) is the LBNP level that the individual is experiencing at time t and LBNP@HD is the LBNP level at which there is an onset of hemodynamic decompensation in that individual [7].

2.3.2. Compensatory Reserve Metric (CRM)

A detailed description of the CRM algorithm has been previously reported [33]. In summary, a deep one-dimensional (1-D) Convolutional Neural Network (CNN) was trained on arterial waveform data generated from a larger set LBNP study subjects that included the 191 subjects used for comparison with the CRI. Similar to the approach used to construct the CRI algorithm, the CRM training target was modeled as a series of steps corresponding to the applied LBNP, with LBNP level used as a target of reduced central circulating blood volume. The predicted time for onset of hemodynamic decompensation (i.e., decompensated shock) was derived from the release of LBNP. Once the endpoint targets were defined, the analog arterial waveforms recorded from the Finometer® monitor were truncated to the experiment length and divided into equal segment lengths of 20 seconds. Each waveform segment was associated with a step-wise CRM training target with a binary flag marking the time of decompensation.

2.4. High versus Low Tolerance Classification

Participants were categorized as having high tolerance (HT) or low tolerance (LT) to reductions in circulating central blood volume (i.e., central hypovolemia) using statistical analysis of Kaplan–Meier "survival" curves [22]. By definition, LT participants experienced the onset of decompensated shock prior to completing a LBNP level of 60 mmHg (total protocol time < 1500 seconds including baseline rest), while HT participants tolerated LBNP levels that exceed 60 mmHg of LBNP (> 1500 seconds of the total protocol time). However, it should be noted that a single CRI and CRM model was constructed with Finometer® waveform data and applied to all 191 subjects independent of their tolerance to reduced central blood volume (i.e., there are no independent algorithms for HT and LT subjects).

2.5. Statistical Analysis

Differences in demographics between HT and LT groups were analyzed using a Student's t-test statistic for independent groups. CRI and CRM LS means with ± standard errors (±SE) were calculated for all 191 subjects (ALL) as well as HT and LT subjects across each of the LBNP levels (baseline to 100% tolerance). To test our hypothesis that the measure of compensatory reserve to predict the onset of decompensated shock would be similar when comparing the CRI and CRM values, generalized estimating equations (GEE) with logit link functions and random effects for subjects were used to perform repeated measures logistic regression analysis. There were two GEE models utilized in this study which regressed onset of decompensated shock for CRI and CRM. The predicted probabilities outputted from each model were used for comparison in a Receiver Operating Characteristic (ROC) Area Under Curve (AUC) statistical analysis. The predicted probabilities of onset of decompensated shock for both CRI and CRM were reported by LBNP levels (baseline to 100% tolerance). The probability that any differences between CRI and CRM values were not attributable to chance was analyzed using GEE models with compound symmetry covariance structures and expressed as P values. Statistical comparisons were also performed across all levels of LBNP and between LT and HT individuals. In an effort to assess the ability of each algorithm to reach the target LBNP level, amalgamated correlation coefficients (R^2) were generated from subject group averages of the final CRI and CRM values calculated at the end of each 5-minute level during progressive LBNP. In order to compare the strength of the relationships between scaled values of CRI vs CRM and LBNP, corresponding Pearson correlation coefficients were calculated and converted to z-scores using Fisher's r to z transformation, and Steiger's Z tests for dependent samples per each subject class (ALL, HT, LT).

3. Results

For a head-to-head comparison of CRI and CRM, we identified a subset of LBNP study subjects common to validation experiments conducted on CRI [7] and CRM [33]. CRI and CRM were computed every 10 seconds from the beginning of each experiment until the point of decompensation. Of the 191 subjects used for head-to-head comparisons of the CRI and CRM algorithms, 60 were classified as having low tolerance to central hypovolemia with a mean (±SD) tolerance time of 1286 ± 193 seconds while the remaining 131 subjects were classified high tolerant with an average tolerance time of 1838 ± 262 seconds ($P < 0.001$). Demographically, the HT group had a mean (±SD) age (27 ± 8 years), height (163 ± 32 cm), and weight (75.4 ± 15.2 kg) that were statistically indistinguishable ($0.617 \geq P \geq 0.258$) from the LT group (27 ± 8 years, 166 ± 27 cm, 72.5 ± 18.0 kg, respectively).

As presented in Figure 1, the GEE analysis produced a ROC AUC (±MSE) for predicting the onset of hemodynamic decompensation (decompensated shock) of 0.9164 (0.0066, 95% CI = 0.903-0.929) for CRI compared to the CRM ROC AUC of 0.9268 (0.0059, 95% CI = 0.915-0.938). The CRM ROC AUC was statistically greater at $P = 0.104$.

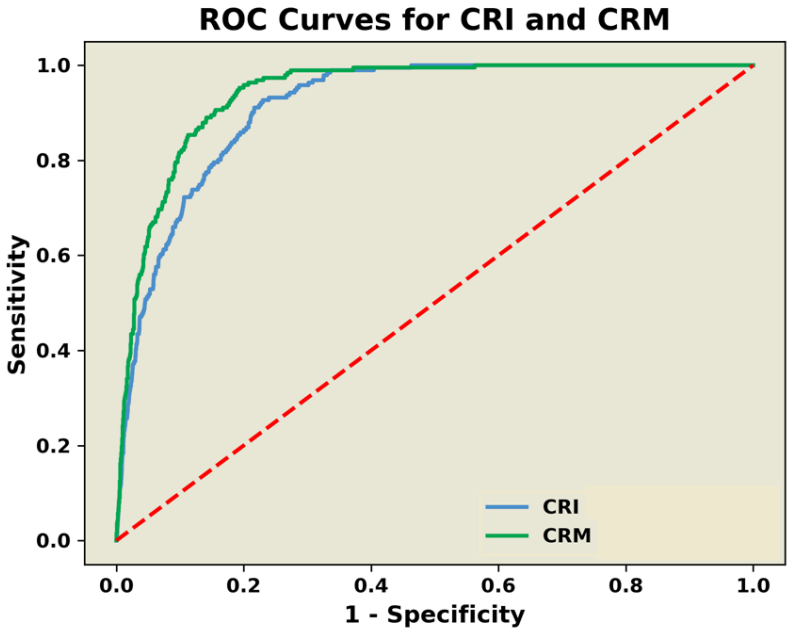

Figure 1. ROC AUC comparisons for prediction of the onset of decompensated shock between the compensatory reserve index (CRI – blue line) algorithm and the compensatory reserve metric (CRM – green line) algorithm.

Comparisons for average responses of compensatory reserve estimated by the CRI and CRM algorithms during progressive stepwise reductions in central blood volume in all 191 subjects are presented in Figure 2 (top panel). The number of subjects who progressed through each stage of LBNP is also presented. A model which compared CRI with CRM irrespective of time showed the calculated responses generated from two algorithms to be statistically similar ($P = 0.114$). However, a statistical comparison of LBNP-averaged values between CRI and CRM as functions of time revealed that the interaction between CRI and CRM with time was statistically different; a finding consistent with average baseline rest values of 96 ± 6% for CRM compared to 86 ± 6% for CRI ($P < 0.001$). Statistical analysis of estimated compensatory reserve responses for HT (Fig. 2, middle panel) and LT (Fig. 2, bottom panel) groups revealed statistically similar results ($P = 0.626$) compared to those generated by analysis of the entire group of subjects.

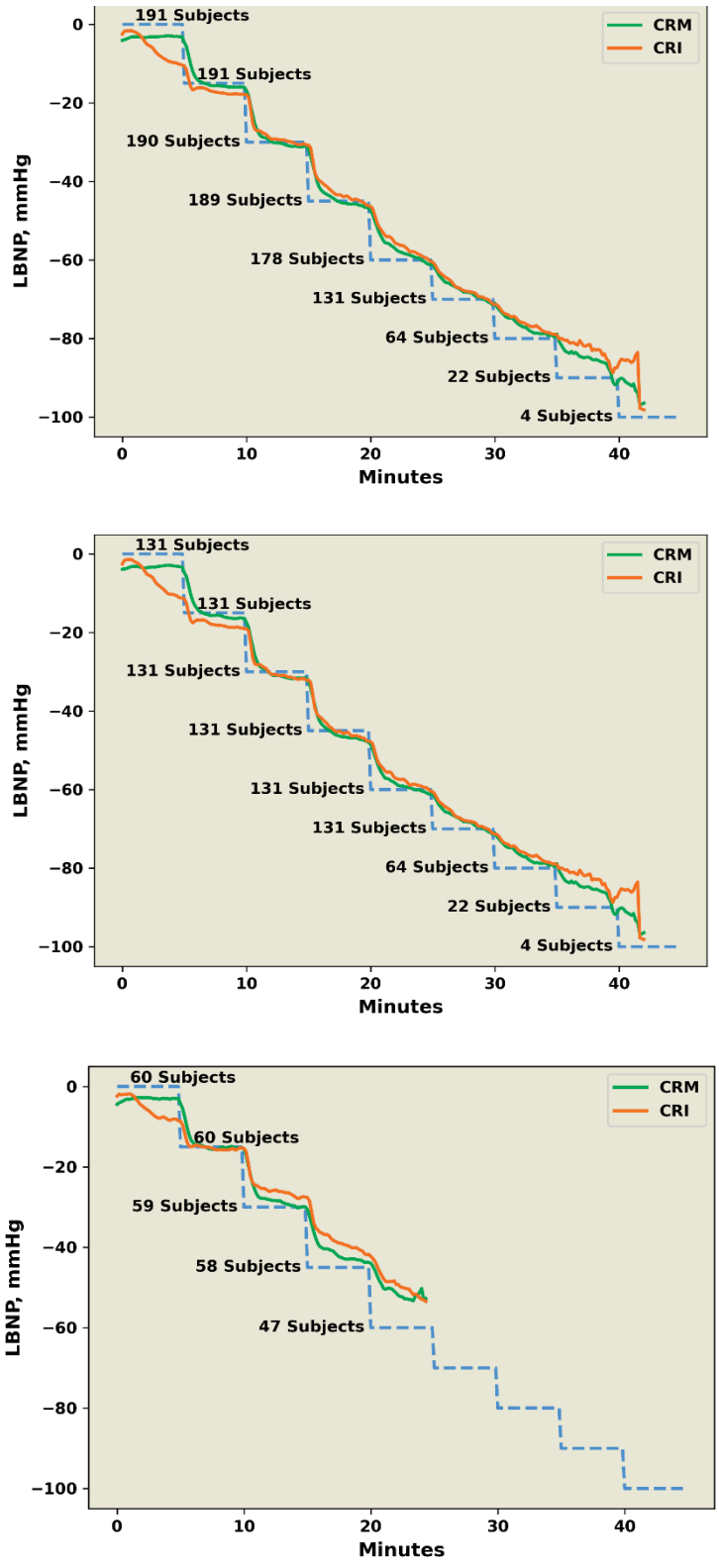

Figure 2. Average responses of compensatory reserve estimated by the CRI (orange line) and CRM (green line) algorithms for all 191 subjects (upper panel), 131 high tolerant subjects (middle panel B), and 60 low tolerant subjects (lower panel). LBNP profile steps used for model development as a target of reduced central circulating blood volume are indicated by the blue broken line (labelled on the y-axis).

The amalgamated correlation coefficients (R^2) between values of CRI and CRM across the progression of LBNP are presented in Table 1 and Figure 3. The strength of the relationships between LBNP and estimated compensatory reserve values were not statistically different between CRM and CRI for all 191 subjects ($p = 0.344$) and for HT subjects ($p = 0.232$). However, the strength of the relationship between LBNP and compensatory reserve values for LT subjects was statistically different ($p < 0.0001$) between CRM and CRI, with CRM displaying a stronger negative R^2 than that for CRI.

Table 1. Amalgamated corrleation coefficients (R^2) between LBNP and CRM and CRI for all subjects and those classified as having high (HT) and low (LT) tolerance to central hypovolemia.

		CRM, %	CRI, %	P value
	N	R^2	R^2	
All subjects	191	0.958	0.978	0.344
HT subjects	131	0.965	0.980	0.232
LT subjects	60	0.999	0.991	< 0.0001

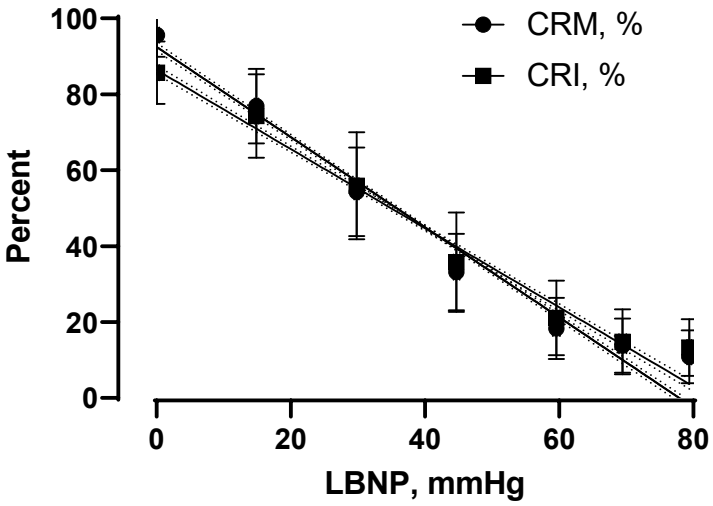

Figure 3. Plots of linear regressions calculated between progressive LBNP levels and measurements of compensatory reserve generated from CRM (circles) and CRI (squares) algorithms. Values are mean ± SD calculated at the end of each 5-minute step of LBNP from all data sets presented in Figure 2A.

4. Discussion

Data generated from numerous experimental and clinical investigations have demonstrated that measurement of the compensatory reserve based on real-time assessment of changes in arterial waveform features provides an earlier and more specific metric of patient status during conditions of reduced central blood volume compared to standard methods of medical monitoring. Within this conceptual framework, we hypothesized that algorithmic approaches that apply ML techniques to the same training library of analog signals in a model of progressive central hypovolemia should generate similar compensatory reserve values and predictive capabilities for the onset of hemodynamic decompensation. The results of this investigation support our hypothesis by demonstrating statistically similar sensitivity, specificity and values of compensatory reserve across a wide range of LBNP levels independent of differing ML approaches used in constructing the CRI and CRM algorithms. The significance of this finding is that it reflects the basic fundamental premise that the morphology of the arterial waveform represents the most accurate approach to measuring the integration of all compensatory mechanisms that best predicts the onset of circulatory shock in an individual patient [1-3, 5]. In other words, it is critical to appreciate that an efficacious algorithm for monitoring the capacity to compensate for reduced circulating blood volume is most dependent on physiological signals that best represent a specific clinical condition rather than the algorithmic approach *per se*.

A ROC AUC ≥ 0.9 can be considered as highly accurate compared to moderately accurate values of 0.7<AUC≤0.9 [34]. In this regard, the results of the present investigation are consistent with ROC AUC values ≥ 0.9 previously reported for predicting the presence of ongoing hemorrhage or the onset of hemodynamic decompensation using a measurement of CRI or CRM compared to moderate accuracy provided by standard vital sign measurements [2, 9, 10, 11, 12, 13, 18, 35]. These observations should be expected given that the added value of arterial feature waveform analysis to the assessment of clinical status in hypovolemic patients has been well documented [1, 2, 36-39]. As such, high accuracy associated with measurement of the compensatory reserve underscores the importance of including ML technologies for obtaining real-time changes in arterial waveform morphology for sensor development designed to advance medical monitoring capabilities.

The average group response measured with the LBNP-scaled CRM algorithm across levels of decreasing central blood volume (i.e., LBNP) was statistically different from LBNP-scaled CRI responses. With nearly identical patterns across the LBNP profile, the finding of a statistical difference is most likely attributed to differences in patterns and average values of compensatory reserve measured with CRI and CRM algorithms during the first stage of the protocol (Fig. 2, all panels). While CRM was stable at baseline rest (initial 5-minute protocol level), the CRI algorithm displayed instability with a progressive reduction in the absence of change in central volume. This comparison may necessitate additional investigation into the stability of the FDA-cleared CRI algorithm.

High sensitivity, specificity and accuracy of a real-time measurement of the compensatory reserve to predict the onset of decompensated shock was determined to be statistically similar for the entire subject population based on ROC AUC analysis. The algorithms also demonstrated a pattern of 'steady state' in compensatory reserve during each of the early stages of reduced central blood volume (Fig. 2). However, the inability to maintain a steady state compensatory reserve after the -45 mmHg LBNP level (i.e., third step) translates to a compromised capacity to sustain adequate tissue oxygen delivery after an average loss of approximately 700 to 750 ml of circulating blood volume for a 75-kg individual [1, 23]. However, the exceptionally high correlation coefficients generated from population averages of CRI and CRM at the end of each LBNP level provide the first compelling evidence to support the notion that 5 minutes is an adequate time for the algorithms to provide an accurate and validated measurement of the compensatory status of an individual.

A unique characteristic of the data sets used in the development of both CRI and CRM algorithms was the ability to include the classification of individuals with varying tolerances to reductions in central blood volume. As such, this large database consisting of analog arterial waveforms provided for the first time an ability to construct ML algorithms that are designed to distinguish 'good' from 'poor' compensators. This unique capability was further supported by the high correlation coefficients generated between CRI and CRM values with LBNP in this study. In this regard, both CRI and CRM accurately tracked the reduction in compensatory reserve in individuals independent of their capacity to compensate for progressive central hypovolemia induced by increasing levels of LBNP. This observation supports the conservation of the physiological compensatory response across individuals regardless of the magnitude of an individual's absolute compensatory reserve. Although an average low-tolerant individual reaches decompensation approximately twice as quickly as a high-tolerant individual [22], CRM and CRI were able to accurately correlate compensation capacity to simulated blood volume reduction for both groups of individuals. Indeed, being able to distinguish patients with relatively low tolerance to reduced central blood volume is key to providing early diagnosis of and intervention for those individuals at highest risk for the onset of decompensated shock, characteristics that are critical to development of efficacious wearable sensors. In this regard, the CRM appears to provide the most efficacious algorithm based on its statistically stronger relationship between reduced central blood volume and compensatory reserve measure in LT subjects. We are unaware of any other advanced technology with application of ML that provides such a capability for translation of precision medicine to patient monitoring. The performance results from both CRI and CRM algorithms with high sensitivity, specificity, and accuracy presented in this paper underscore the importance of accumulating data sets from healthy subjects exposed to an experimental protocol designed to elicit hemodynamic decompensation in all subjects prior to validating the algorithms with application in patients [14, 15, 17-21, 35]. Simply put, consistent success in accurately assessing the clinical status of patients with compromised circulating blood volume reflects the importance of generating algorithms that are based on the physiology of healthy individuals.

Although efforts were made to use the same data sets for algorithm comparisons, there were subtle differences in the approaches to develop the CRI and CRM algorithms that could have potentially influenced the interpretation of results generated from this investigation. For instance, the experimental design allowed for the same subset of 191 subjects to be used for algorithm performance analysis of ROC AUC calculations and compensatory reserve responses during progressive reductions in central blood volume (Figures 1, 2 and 3). However, subject data sets collected during the initial 184 LBNP experiments were used to develop the CRI algorithm [7] compared to a larger common data set with additional subjects used 6 years later to develop the CRM algorithm [33]. Also, CRI values were generated from averaging calculations across a 30-beat sliding window [7] while the CRM values were calculated based on 20-second waveform segments [33]. Despite these subtle differences in the specific approach for algorithm development, the remarkable similarity in CRI and CRM performance for calculating individual compensatory reserve values with high sensitivity and specificity reflects the incredible influence and stability imparted by the use of a data repository consisting of hundreds of thousands of arterial waveforms for 'learning'.

5. Conclusions

As technology advances with the application of novel monitoring capabilities designed to facilitate early and accurate diagnosis and triage of individual patients, the incorporation of sensors capable of supporting compensatory reserve measurements can ensure that patients who require emergency medical care prioritization receive timely and appropriate treatment interventions. As such, the development and availability of a single advanced monitoring system that includes wearable sensors capable of capturing analog

arterial waveforms or photoplethysmographic signals, and integrates them with application of ML algorithms will prove essential to advancing decision support with the goal of optimizing health, safety and wellbeing in prehospital and emergency room settings. In this regard, it is important to recognize that wearable sensors must be designed with the capability to capture arterial waveform analog signals in order to provide the clinical caregiver with real-time assessment of patient status that includes the highest sensitivity, specificity and accuracy for making clinical decisions easier within time-critical challenging situations. Finally, further research efforts should reveal that such sensor systems and associated algorithms such as the CRI and CRM may be applied to the diagnosis and/or management of other cardiovascular conditions that might compromise the health, wellbeing or safety of an individual (e.g., dehydration, hypoxia, sepsis, heart failure, pneumothorax, physical fatigue).

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: title, Table S1: title, Video S1: title.

Author Contributions: Conceptualization, V.A.C., A.C.D., R.W.T.; writing—original draft preparation, V.A.C.; writing—review and editing, A.C.D., R.W.T., C.R.H., D.R.H., M.J.J., T.B.C., S.C., C.C.W., and O.T.I.; data collection, V.A.C.; data analysis, V.A.C., R.W.T.; interpretation of results, V.A.C., A.C.D., R.W.T., C.R.H., D.R.H., M.J.J., T.B.C., S.C., C.C.W., and O.T.I.. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the U.S. Army Medical Research and Development Command (award numbers D-022-2011-USAISR and D-009-2014-USAISR) and the Congressionally Directed Medical Research Program (award number DM180240), and supported by the Office of Naval Research and Naval Information Warfare Systems Command under Contracts No. N66001-12-D-0088, N00014-18-D-7001, N00014-19-C-2017.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the U.S. Army Medical Research and Development Command Institutional Review Board (Protocol M-10138 initially approved 13 October 2011).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are not publicly available because they have been collected and maintained in a government-controlled repository that is located at the US Army Institute of Surgical Research. As such, these data can be made available through the development of a Corroborative Research & Development Agreement (CRADA) with the corresponding author.

Acknowledgments: The authors thank Ms. Iram Qureshi for assistance with statistical analysis and Ms. Adriana Torres for her assistance in preparing the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Disclaimer: Opinions, assertions, findings, conclusions or recommendations contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army and Navy, or the Department of Defense.

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Early identification of sepsis in burn patients using compensatory reserve measurement: a prospective case series study

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Prior Presentation: None

Funding: This work was supported in part with funding provided by the United States Army Medical Research and Development Command and the Congressionally Directed Medical Research Program (Award No. DM180240).

Investigator Disclosures: The authors have no financial conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors take responsibility for the integrity, accuracy and interpretation of the information and data presented in the review.

VAC, ARW, KSA, and CAV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

VAC, KSA, and CAV participated in the conception/design of this study

VAC, ARW, KSA, CAV and LCC participated in subject recruitment, data collection, analysis, and/or interpretation

ARW, KSA and CAV participated in study supervision with administrative, technical, or material support

All authors participated in drafting of the manuscript and provided critical revision of the manuscript for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship; all those who qualify for authorship are listed.

ABSTRACT

BACKGROUND: Early identification of sepsis can be lifesaving, but current diagnostic approaches rely on standard vital signs and biochemistry analyses that delay recognition. We postulate that early identification of sepsis could be accomplished with a clinical assessment of real-time changes in physiological responses that reflect compensation to relative hypovolemia, or the compensatory reserve measurement (CRM). In this pilot study, we measured CRM in burn patients who transitioned from a non-infected state to sepsis to determine if CRM would be reduced prior to clinical identification of sepsis using traditional standard-of-care criteria. M**ETHODS**: Each subject underwent placement of a radial arterial catheter upon arrival to the burn ICU. Morphology of analog arterial waveforms was recorded and analyzed based on a machine-learning algorithm, employing feature-extraction techniques that provided CRM values on a relative scale of 100% (normal) to 0% (onset of decompensated shock). CRM values one (D-1) or two (D-2) times prior to the day of sepsis diagnosis (D+0) were compared in time to standard diagnostic techniques. **RESULTS**: CRM was lower in all patients on D+0 compared to ICU admission day. Complete analyzable arterial waveform data collected on D-1 and D-2 were captured from 5 subjects. These patients demonstrated an average reduction ($p = 0.003$) in CRM from 48 ± 14% on D-2 to 31 ± 14% on D-1 prior to sepsis diagnosis with standard criteria on D+0. **CONCLUSION**: The results of this clinical investigation conducted in burn patients provide the first data to substantiate a capability for early diagnosis of sepsis by measurement of the compensatory reserve. Our findings support the notion that this novel technology could offer caregivers of at-risk burn patients with a user-friendly decision-support indicator of infection for individualized triage and treatment.

Key words: monitoring; infection; machine-learning algorithm

INTRODUCTION

Like general patient populations with trauma injury, early identification of sepsis in burn patients can be lifesaving because delay in effective treatment reduces the probability of survival (1-3). As a result of infected tissue and a pronounced inflammatory response, sepsis represents a clinical state of 'relative' hypovolemia. This state is defined by an increased intravascular space resulting from systemic vasodilation that must be perfused by normal circulating blood volume (4, 5). Although the practice of assessing clinical markers may be useful in defining sepsis in burn patients once infection has been established (6-9), use of these metrics are confounded by the fact that burn injury itself is a potent inflammatory stimulus, rendering the traditional criteria insensitive and nonspecific criteria (10). Furthermore, efforts to improve recognition of sepsis in burn patients on the basis of scoring systems such as the American Burn Association criteria, Mann-Salinas criteria, or the quick Sequential Organ Failure Assessment, which are derived from clinically available data elements (i.e., heart rate, blood pressure, arterial oxygen saturation, respiration and mental status), have not proved to be highly accurate in this population (6-10). Additionally, changes in standard vital signs often appear late in the progressive development of septic shock, reflecting depletion of compensatory mechanisms (10, 11). Thus, currently available tools for early identification of sepsis in burn patients are inadequate and new approaches are needed to reduce mortality. In this regard, we postulate that early identification of sepsis could be accomplished with a clinical measurement of real-time changes in physiological responses that reflect compensation to relative hypovolemia rather than outcome measures influenced by compensatory mechanisms (e.g., standard vital signs).

There is recent evidence that measurement of the body's capacity to compensate for states of hypovolemia is more sensitive and specific than standard vital signs (12-19) and other

physiological indicators of compromised tissue perfusion and oxygenation (e.g., cardiac output, sympathetic nerve activity) (18, 20-22). This measurement, called the Compensatory Reserve or CRM (12, 14, 16, 17, 20-22), is based on a machine-learning algorithm with feature-extraction techniques designed to assess real-time subtle changes in the morphology of the arterial waveform that are characteristic of hypovolemia. The CRM is assessed on a relative scale of 100% to 0%, where 100% represents the 'normal' baseline state in healthy individuals with maximum capacity available to compensate for a state of hypovolemia while 0% represents the onset of decompensated shock (5, 13-15, 23, 24).

Because changes in arterial waveform features represent integrated compensatory responses (12-15), the CRM has proven capable of providing accurate assessment of hemodynamic instability earlier and with greater sensitivity and specificity than traditional vital signs and other clinical measures for conditions of both absolute and relative hypovolemia. Clinically, such hypovolemic states include Dengue hemorrhagic fever, trauma, hemorrhage, chronic orthostatic hypotension, burn injury, and sepsis (11, 13, 25-28). Within this context, we conducted a pilot study to explore the feasibility of using CRM for the early detection of the onset of sepsis in burn ICU patients at the U.S. Army Institute of Surgical Research. We speculated that CRM would track the transition of patient status from non-infection to the onset of sepsis, and that CRM would be reduced prior to clinical identification of sepsis using traditional standard-of-care criteria.

METHODS

Subjects. We conducted a pilot study on adult burn patients (age ≥18 years) admitted to the U.S. Army Institute of Surgical Research burn Intensive Care Unit from January 2018 to

August 2019. Eight patients met the criteria for enrollment to participate as subjects in this investigation. Inclusion criteria included all patients: 1) with ≥15% total body surface area (TBSA) burn injury who were admitted directly to the ICU and had no known or suspected infection at the time of ICU admission; 2) who received an arterial catheter and anticipated its continued use for the length of the study period; and 3) who progressed to demonstrating clinical sepsis. For this study, the presence of sepsis was defined by prescription of one or more broad-spectrum intravenous antibiotics in addition to any one or more of the following: initiation of vasopressors, or hypotension requiring bolus intravenous fluid administration, or drawing of blood cultures. We did not define an intravenous fluid bolus volume because the indication was for hypotension indicative of a sepsis syndrome, for which necessary fluid volume for resuscitation is highly variable depending on both host and disease factors. It is important to note that intravenous fluid bolus was not the only criterion, but was used adjunctively in combination with *de novo* prescription of antibiotics. Taken together, these treatment actions provide contextual evidence that the treatment team believed the patient was experiencing a sepsis syndrome requiring treatment. Appropriateness of antibiotic therapy was verified daily by staff physician and clinical pharmacists as part of interdisciplinary rounds; antibiotic therapy was adjusted based on culture and sensitivity data as appropriate. Exclusion criteria included subjects younger than 18 years, TBSA burn injury <15%, chemical or electrical cause of burn injury, pregnant females, prisoners, use of total parenteral nutrition, and empiric or directed antimicrobial treatment for infection within 7 days prior to enrollment. Patients identified as eligible for participation in the protocol were enrolled after written informed consent was obtained. Surrogate consent was obtained from a legally authorized representative (LAR) of subjects in cases where patients were unable to provide direct consent due to their severity of

illness. Participants or LARs were verbally informed about the purpose, objectives and methods of the study, provided the consent document to read, and given an opportunity to ask questions. All experimental procedures were conducted in accordance with a protocol (USAISR #H-16-038) reviewed and approved by the Institutional Review Board of the US Army Medical Research and Development Command.

Protocol. This pilot study lasted 4 to 6 days from the day that eligible patients were admitted into the Burn ICU as part of a larger sampling period. Patients were enrolled into the study once they met inclusion criteria. An overview of the protocol timeline is presented in Figure 1. Data collection days were defined as the first measurement day following ICU admission (D-2), the second measurement day following ICU admission (D-1) and the day of sepsis diagnosis (D+0). As a result of limited research staff who were unavailable on weekends and holidays for collection of data for calculation of CRM, the number of days between injury and enrollment as well as between D-2, D-1 and D+0 varied across individual patients (Table 1). As part of routine clinical care, each subject underwent placement of an arterial catheter upon arrival to the Burn ICU that remained in place for the duration of this study. Analog arterial waveforms were recorded for a 1-hour period and stored on a Drager Infinity Delta Digital Display Monitor at the same time on each study day to allow for retrospective analysis for CRM. Patients did not undergo physical therpay or wound care during the 1-hour data collection period. Study team caregivers were blinded from any information provided by the collection of data so that no interventions could be influenced by real-time CRM readings. As such, only standard of care was provided to all enrolled patients.

[**Figure 1 here**]

[**Table 1 here**]

Data collection. The Drager monitor provided a capability to record noninvasive monitoring of vital signs (blood pressure, pulse, oximetry, respiratory rate, ECG monitoring, end-tidal capnography, temperature) as well as an interface with the arterial catheter for invasive blood pressure monitoring and continuous arterial waveform recordings. These electronic arterial waveform recordings obtained on contiguous days were downloaded to a PowerLab data acquisition and integration system (ADInstruments, Model 16/35) for retrospective calculation of the CRM using an algorithm software for waveform feature analysis (29). Data collection was reassessed by the research team at intermittent intervals to ensure proper continued waveform capture. In an effort to optimize post hoc analysis of the data, all malfunctions were corrected and time recorded. Additional data collected included patient demographics, vital sign parameters, and resuscitative measures. All assessments of CRM were conducted prior to antibiotic administration.

Statistical Analysis. Descriptive statistics (mean ± SD) were used to characterize the demographics and injuries of the patients. Differences across study days in group average values for CRM and vital signs were analyzed using ANOVA and Student's t-test for repeated measures. A Tukey *post hoc* analysis was performed on variables in which ANOVA reveled $p \leq 0.05$. The probability that group mean differences were greater than chance alone were reported as exact 'p' values.

RESULTS

The patients were 7 men and 1 woman with a group mean (±SD) age of 32 ± 9 years (range 20 to 44 years), height of 177 ± 8 cm (range 160 to 188 cm), weight of 88 ± 19 kg (range 64 to 122 kg), and body mass index of 27.9 ± 5.5 $kg \cdot m^{-2}$ (range 20.1 to 34.5 $kg \cdot m^{-2}$). The median

(±SD) time between D-2 and D-1 was 2.0 ± 1.6 days (range of 1 to 5 days) and 2.0 ± 1.5 days (range of 1 to 4 days) between D-1 and D+0.

Individual results of tissue cultures and other blood measurements during the progression of care for all eight patients enrolled in the study are reported in Table 1. There were no clinically relevant patterns in blood lactate or glucose. Platelets and white blood cells increased while PF ratio decreased in six patients from the day of enrollment to the day of sepsis diagnosis. Positive blood, wound, or sputum cultures were identified for all included patients either the day before (2 patients), day of (4 patients) or the day after (2 patients) diagnosis of sepsis**.**

[**Table 1 here**]

CRM calculated from continuous collection of arterial waveforms revealed that compensatory reserve remained relatively stable throughout the one-hour data collection period on all days (Figure 2). We therefore chose to report values for CRM to be represented by one average value across the one-hour data collection period for each subject on each day (Figure 3). Since three of the eight patients transitioned from non-sepsis to sepsis the day after the initial day of CRM data collection, we were able to capture analyzable waveforms for D-2, D-1 and D+0 from only five patients (Figure 3). All five patients with at least 2 days of analyzable arterial waveform data on days D-2 and D-1 prior to sepsis diagnosis (TP001, TP002, TP004, TP005, and TP010) displayed a reduction in CRM from D-2 to D-1, with an average reduction ($p = 0.007$) in CRM from 48 ± 13% to 30 ± 14%.

[**Figure 2 here**]

[**Figure 3 here**]

A summary of group means (±SD) for vital signs recorded on D-2, D-1 and D+0 are presented in Table 2. Post hoc analysis revealed that systolic and diastolic blood pressures, pulse

pressure, mean arterial pressure, respiratory rate, and body temperature were statistically indistinguishable ($P \geq 0.0938$) across D-2, D-1, and D+0. Heart rates and Glasgow Coma Scale (GCS) scores were progressively increased ($p \leq 0.0468$) across days D-2, D-1 and D+0, with post hoc analysis revealing that only the average elevated heart rate from 103 bpm on D-1 to 120 bpm on D+0 was statistically distinguishable ($p \leq 0.0218$). Of all vital signs, post hoc analysis revealed that CRM was the only measurement that was statistically reduced ($p = 0.0302$) from D-2 to D-1.

[**Table 2 here**]

DISCUSSION

In this pilot observational study, we sought to test the utility of CRM for tracking the progression and early detection of sepsis onset compared to the use of standard clinical tools. We hypothesized that CRM would be reduced prior to clinical identification of sepsis using traditional standard-of-care criteria. The observation of an average 35% reduction in CRM from the initial day of study enrollment to the day before clinical diagnosis of incipient infection in our burn patients was consistent with our expectation. Importantly, CRM was the only measurement that showed a statistical change (decrease) between D-2 and D-1 compared to every standard vital sign (Table 3). That is to say, the reduction in CRM occurred earlier (i.e., between D-2 and D-1) than sepsis identification using standard clinical criteria. This supports the notion that CRM provided an earlier indicator for the development of sepsis by at least 24 hours and as much as 5 days in advance of the clinical identification of sepsis.

The early detection of sepsis apparent in the results of the present investigation may reflect the machine-learning capability of the CRM algorithm to ‘learn’ specific changes in the morphology of the arterial waveform unique to the pathophysiological condition of systemic

infection (12, 15, 30). (30, 31) . It has been previously illustrated that the reflected wave of the arterial waveform in sepsis is delayed in time as a result of vasodilation that is driven by septic physiology. It may be the ability of the CRM algorithm to recognize such differences in arterial waveform morphology that may be key in having provided an early recognition of sepsis physiology in the present investigation.

A primary factor that can contribute to unreliable prediction of the early onset of sepsis is the dependence of current standard clinical markers and monitoring technologies that fail to consider individual patient variability because of a reliance on algorithms based on population averages (14). Evidence generated from the clinical literature is clear, however, that compared to non-survivors, individuals who survive similar states of central hypovolemia display disparate compensatory responses that are not detected by monitoring approaches generated from population averages (11, 28, 32-34). In this regard, we took the opportunity to report for first time the compensatory responses of individual burn patients in the ICU who progressed from a non-septic to septic status. Our results demonstrate the importance of using a machine-learning approach such as the CRM that can provide caregivers with a monitoring technology based on 'precision medicine' capable of 'recognizing' individual patients exhibiting sepsis physiology.

The clinical significance of early diagnosis and treatment for sepsis has recently been demonstrated among patients at the U.S. Army Burn Center, in whom bacteremia of any cause was associated with an increase in mortality (2). Standard criteria of hypotension and acute kidney injury used for recognizing the onset of sepsis in severely burned patients have proven insensitive in time (i.e., delayed) as well as nonspecific to individual patients (4). Similar to observations reported for general surgical patients who developed sepsis (11), monitoring standard vital signs in the current investigation failed to provide an early diagnosis of the

transition from a non-infected to a clinically septic state in our severely burned patients. However, the significant 20-mmHg reduction in diastolic blood pressure from the initial day of study to the day prior to the diagnosis of sepsis is consistent with a state of systemic vasodilation that would be expected with the onset of sepsis (35). As such, the average reduction in the CRM from 48% to 31% may reflect the onset of a relative hypovolemia prior to the clinical diagnosis of sepsis. Since CRM has been shown to track systemic delivery of oxygen (DO_2) (24), our results reported in individual burn patients may suggest that the early stage(s) of sepsis may be associated with compromise to adequate DO_2 at least 24 hours in advance of clinically significant changes in standard clinical measurements.

Early detection of sepsis in burn-injured patients is an important step toward reducing the overall mortality of burn injuries. Infections and the resulting organ failure are major causes of burn-related mortality, accounting for as much as 65% of burn-related deaths (36, 37). Sources of potentially lethal infections in this population include burn wounds, intravascular lines, the respiratory tract, the urinary tract, and the gastrointestinal tract (37). Because of the systemic inflammatory response to a large (>20% TBSA) burn injury, normal indicators of infection (i.e., tachycardia, elevated temperature, or shifts in white blood cell count) may reflect this response to injury rather than an infection (6). After the resolution of burn shock, early detection of decompensation through methods such as the CRM may allow for earlier identification of potential infections and earlier source detection, resulting in earlier treatment and possible prevention of the secondary sequelae of sepsis.

The total integrated capacity of all compensatory mechanisms required to respond to the onset of sepsis remained compromised as indicated by a sustained depression of the CRM at 23% on the day of clinical classification of sepsis. With tachycardia representing a significant

compensatory mechanism during states of hypovolemia (13, 14), the elevated heart rate from D-1 to D+0 suggests that recruitment of chronotropic mechanism(s) may have contributed to maintenance of adequate DO_2 in the face of reduced cardiac output. This is a hallmark in the early stages of burn injury (38-41). Whether the tachycardia observed in the present study resulted from an infected state is complicated by a resuscitation status that is difficult to accurately quantify. However, our burn patients received continuous fluid resuscitation that would be expected to improve circulating blood volume across study days. CRM might be expected to increase with such expansion in circulating volume. Contrary to this expectation, CRM decreased across study days. This suggests that progressive reduction in CRM across D-2, D-1 and D+0 was likely affected by a relative hypovolemia associated with vasodilation rather than low circulating blood volume.

Given that tachycardia represents utilization of a primary mechanism that contributes to compensation in conditions of hypovolemia (13, 14, 42), the absence of a further reduction in CRM from the day before to the day of diagnosed sepsis was unexpected without a restoration of another compensatory mechanism(s). The use of vasopressors could provide a temporary restorative effect on compensatory reserve, but such an intervention is an unlikely explanation given that only one of the eight patients (TP014) received vasopressin in an effort to treat hypotension by maintaining MAP above 60 mmHg on the day of infection (D+0). A more likely mechanism may reside in the 'restoration' of capillary integrity to reverse fluid leak which usually appears in the early stage of burn, but may resolve with other cardiovascular mechanisms within 48 to 72 hours following injury (41, 43). Thus, it is possible that the amount of reduced compensatory reserve that results from an elevation in heart rate was counterbalanced by auto-

resuscitation of vascular volume following the mitigation of capillary fluid leak so that there was no net alteration in the CRM from the day before (D-1) to the day of diagnosed sepsis (D+0).

Previous investigations have promoted and validated a 'green-yellow-red' color-coded zone approach for qualitative assessment of CRM to represent a clinically compromised decline in the compensatory reserve (12, 14, 18)(28). These zones are depicted in Figure 3. It is noteworthy that all but one burn patient demonstrated progressive degradation in their capacity to compensate for the onset of infection over time. Several insights are apparent by interrogation of individual patient responses. Compensatory responses vary across individual patients. Patient #TP002 unexpectedly displayed a CRM in the 'green' zone at 70%, but declined in the next XX hours to reach a 'red' level of 29% by D+0 with sepsis. Patients #TP001, #TP005 and #TP010 started on D-2 in the amber 'zone' (36% to 50%), with continued decline to the 'red' zone by D-1. Patient #TP009 (no D-2 measure) was the most severely injured patient with the greatest total body surface area burn of 74%, of which 41% constituted third-degree (full thickness) burns. It was therefore not unexpected that Patient #TP009 entered the ICU with a severely compromised CRM in the 'red' zone (26%) that deteriorated to as low as 5% by D+0 and eventually expired. In all these cases, low CRM portended a progressive deterioration of patient course earlier than standard-of-care methods.

The presence of burn shock also may have influenced these findings. Burn shock is found in patients suffering from severe burn injury (usually >20% TBSA) for up to 48 hours after injury (38, 39). Burn shock is characterized by hypovolemia resulting from extravasation of fluid to the interstitium, which in turn reduces cardiac preload and stimulates an increased systemic vascular resistance (44) Patients who were not infected upon admission to the ICU likely experienced hypotension and reflexive tachycardia associated with burn shock, complicating the

analysis of the arterial waveform morphology. However, because the CRM analysis is based on the patient's current physiology, and not necessarily a "normal" physiology, the application of the CRM monitor during burn shock may have caused this deranged physiology to be the patient's baseline from which subsequent readings were measured. Therefore, if the patient was in burn shock during initial CRM measurements, any downward shift in CRM readings would reflect a continued decompensation, an important finding regardless of the cause.

The ability of the CRM to be a useful clinical tool in the assessment of septic patients was recently demonstrated by Benov and colleagues who reported significantly lower CRM in general surgical patients who developed sepsis compared to those without sepsis despite displaying similar vital signs (11). The results of the present investigation add insight to those of trauma patients for several reasons. First, we are unaware of any previous findings in which CRM has been reported in a group of septic burn patients. Second, results of the present investigation are the first to provide a time course during the progression from non-infection to the infected state that advances a novel approach for early and accurate real-time detection of the presence of sepsis in individual patients. The similarity in CRM values across trauma and burn patients supports the notion that changing states of hypovolemia represent one common physiological basis underlying the measurement of compensatory reserve. Our results are consistent with data generated from previously controlled human laboratory experiments and clinical studies of patients with varying physiological states of relative hypovolemia (5, 11, 13, 45), suggesting that the CRM has the potential to provide early detection of sepsis associated with infection-induced systemic vasodilation.

Like any clinical investigation, our study is not without limitations. Our interpretation of results may be limited by a small sample size of patients and measurements (three one-hour

averaged CRM values recorded on 3 different days) that might create bias against representing a more general population of septic patients. Despite efforts to execute experiments at the same time of day, data collection scheduling varied based on patient availability that was influenced by standard patient care (e.g., bathing, wound care). However, the small probability that the reduction in CRM from D-2 to D-1 was by chance alone despite limited number of patents and control of daily data collection times suggests a significantly large effect independent of sample size and measurement time variability. The original purpose of this study was to compare non-septic (control group) to septic patients. However, all non-septic patients transitioned to sepsis. Thus, we cannot dismiss the possibility that CRM might vary in patients with burn or critical injuries over time regardless of infection. The definition for presence of sepsis was limited by the subjective decision-making process employed by the attending physician to initiate the drawing of blood cultures when starting antibiotics. As such, we cannot dismiss the possibility that this process could have delayed the actual time of infection onset. In any case, such a subjective process appeared to be overcome by daily observation of changes in CRM. Another limitation to the study was our inability to perform continuous CRM recordings over 24 hours due to patient care, limiting the ability to characterize the accuracy of the time course of compensatory status in individual burn patients. Nevertheless, these one-hour averaged daily observations were generally correlated with clinical status, consistent with findings reported by Benov and colleagues (11) in a separate sepsis population. Despite these limitations in sample size, test scheduling, a control group, and subjective sepsis diagnosis, our analysis approach of examining integrated compensatory responses in our patients demonstrated for the first time the sensitivity across time from non-infected to infected states, and patient specificity for early diagnosis of sepsis independent of population averages. Validation of our observations based on this pilot

study that CRM could provide an "early warning" capability for a life-threatening condition in patients where the development of sepsis is often clinically invisible due to the physiologic effects of the burn injury awaits further investigation. As such, our results lay a foundation for providing a future opportunity to investigate the efficacy of using CRM as a clinical tool for reducing morbidity and mortality in burn sepsis through earlier intervention.

Military Implications

The challenge of burn injury management on the battlefield has been recognized for its usual occurrence with polytrauma from small arms and shrapnel fragments (46), and a 1.6-fold higher mortality than that of civilian patients with non-combat related burns (47). Additional concerns exist for complications of over- or under-resuscitation in the absence of adequate monitoring of intravascular fluid status (48). With anticipation of future battlefields immersed in the complexities of multi-domain operations (MDO) and/or large scale combat operations (LSCO) that might require prolonged field care due to delayed evacuation times (49), timely risk assessment and early intervention for the onset of sepsis is paramount. Within the context of limited medical resources, operational and clinical advantages of CRM include a methodology that is already FDA-approved, easy-to-read, color-coded 'fuel gauge' dashboard monitor, and a noninvasive assessment using a small light pulse oximeter that is currently available in the medical kits of combat medics (11, 29). As such, a technology like CRM monitoring can provide first responders and other military clinical caregivers with a decision support capability for early triage of combat casualties at risk for developing sepsis from polytrauma with and without burn injury, and accurate goal-directed resuscitation (24, 48).

CONCLUSION

We provide for the first time preliminary results from data collected in burn patients who transition from a non-infected state to sepsis that validate the efficacy of CRM as a potential monitoring tool for early diagnosis of sepsis. Our findings are consistent with those previously reported in trauma patients that CRM outperformed standard vital signs as an early indicator of severe hypovolemia (11, 14, 25-28, 50). These results support the notion that this novel monitoring technology could offer caregivers with a noninvasive, user-friendly decision-support predictor of septic shock for early individualized triage and resuscitation in burn patients.

Acknowledgements
The authors thank Amber Bishop, RN, Elsa Coates, RN, Catherine Rauschendorfer, RN, Melody Vargas, RN, and Valorie Baggenstoss, RN for their assistance in the execution of experimental data collection, Ms. Diane Villarreal for assistance with manuscript preparation, and Dr. Tuan Le for assistance with statistical analysis.

Table 1. Clinical measures of blood, renal function, and cultures in eight burn patients across the time course of transition from a non-infected state to the diagnosis of sepsis.

Study Day	Protocol Day	Time	Blood Lactate mmol/L	Blood Glucose mg/dL	Platelet Count x 10^3	WBC x 10^3	GFR ml/min	PF Ratio mmHg	24-hour Urine Output (mL)	Culture Source	Culture Growth
TP001											
0	DOI[a]	Unk	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	11:33	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
10	DOE	16:00	2.64	123	478	6.3	131.2	43	2,914	[b]	[b]
10	D-2	16:00	2.64	123	478	6.3	131.2	43	2,914	[b]	[b]
11	D-1	16:00	[b]	[b]	[b]	10	131.2	[b]	[b]	[b]	[b]
14	D+0[d]	10:00	1.17	123	946	14.9	128.3	371	2,970	Blood	*C. albicans; S. anginousus*
TP002											
0	DOI[a]	3:00	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	4:10	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
1	DOE	13:00	1.6	172	155	10.4	76.2	450	1,284 mL	[b]	[b]
1	D-2[c]	13:00	1.6	172	155	10.4	76.2	450	1,284 mL	[b]	[b]
2	D-1[d]	13:00	[b]	[b]	[b]	7.1	131.2	[b]	[b]	Sputum	*S. aureus; E. cloacae*
3	D+0	12:00	1.42	133	99	6.8	127.3	361	2,633 mL		
TP004											
0	DOI[a]	15:00	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	20:12	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
1	DOE	14:00	4.44	145	150	6.5	71	324	1,018 mL	[b]	[b]
3	D-2	14:00	[b]	[b]	[b]	2.17	89	[b]	[b]	[b]	[b]
7	D-1	14:00	[b]	[b]	[b]	9.05	83	[b]	[b]	[b]	[b]
11	D+0[d]	11:00	1.85	184	413	10.7	81.2	275	6,698 mL	Sputum	*S. agalactiae* group B
TP005											
0	DOI[a]	Unk	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	6:35	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
4	DOE	13:00	1.04	119	121	9	127.3	505	1,735 mL	[b]	[b]
5	D-2	13:00	[b]	[b]	[b]	5.18	126.7	[b]	[b]	[b]	[b]
13	D-1[d]	8:00	[b]	[b]	[b]	6.57	132.1	[b]	[b]	Sputum	*E. coli*
14	D+0	8:00	1.93	124	670	11.7	142.8	332	2,018 mL		
TP010											
0	DOI[a]	14:30	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	19:07	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
3	DOE	10:15	1.72	125	102	10.2	49.2	403	1,308 mL	[b]	[b]
4	D-2	12:00	[b]	[b]	[b]	10.68	56	[b]	[b]	[b]	[b]
5	D-1	12:00	[b]	[b]	[b]	15.27	54.6	[b]	[b]	[b]	[b]
6	D+0[d]	16:00	1.97	163	163	38.02	57.8	344	317 mL	Wound	*C. acnes*

TP009											
0	DOI[a]	7:05	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	9:49	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
1	DOE	14:45	2.33	114	95	15.37	129.2	220	126 mL	[b]	[b]
2	D-1	5:00	[b]	[b]	[b]	6.46	129.9	[b]	[b]	[b]	[b]
3	D+0[d]	3:50	2.45	47	98	3.42	137.8	366	109 mL	1. Blood 2. Sputum	*1. P. aeruginosa* *2. E. coli, S. aureus, K. pneumoniae*
TP014											
0	DOI[a]	4:00	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	11:00	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
1	DOE	13:00	1.64	163	218	12.93	176.4	445	1,635 mL	[b]	[b]
1	D-1	13:00	1.64	163	218	12.93	176.4	445	1,635 mL	[b]	[b]
4	D+0[d]	18:00	1.74	208	133	16.32	57.1	78	6,300 mL	[b]	[b]
5	D+1	9:00	[b]	[b]	[b]	[b]	[b]	[b]	[b]	1. Blood 2. Sputum	*1. MRSA, S. aureus* *2. S. aureus, MRSA*
TP015											
0	DOI[a]	Unk	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
0	DOA[a]	23:45	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
2	DOE	16:00	2.77	124	103	9.88	98.5	435	1,664 mL	[b]	[b]
3	D-1	9:00	[b]	[b]	[b]	8.41	88.9	[b]	[b]	[b]	[b]
6	D+0[d]	9:00	1.51	153	129	10.78	96.5	160	2,692 mL	[b]	[b]
11	D+1	9:00	1.51	153	129	10.78	96.5	160	2,692 mL	Sputum	*S. anigosus, C. testosteroni*

WBC, white blood cells, GFR, glomerular filtration rate; PF ratio, ratio of inspired oxygen to arterial partial pressure; D+0, day of clinical indications of infection; D-1, day of second compensatory reserve measurement prior to infection; D-2, day of first compensatory reserve measurement prior to infection; DOI, day of injury; DOA, day of hospital ICU admission; DOE, day of enrollment.

[a] Data not collected on these days.

[b] Data not available in patient record.

[c] First compensatory reserve measurement was less than 48 hours after day of injury.

[d] Day and time when antibiotics were initiated.

Table 2. Measurements of nine standard vital signs and compensatory reserve (CRM) performed on the first measurement day (D-2)and second measurement day (D-1) prior to the day of sepsis diagnosis (D+0). F ratios and exact 'p' values were generated from one-way ANOVA.

Vital Sign	D-2	D-1	D+0	F ratio	P value
Heart Rate, bpm	89 ± 21	103 ± 23	120 ± 14 †	7.964	0.0152
Systolic Blood Pressure, mmHg	135 ± 31	118 ± 10	130 ± 9	1.472	0.2919
Diastolic Blood Pressure, mmHg	75 ± 18	55 ± 7	66 ± 14	4.4030	0.0531
Mean Arterial Pressure, mmHg	95 ± 22	76 ± 7	87 ± 12	3.2570	0.1054
Pulse Pressure, mmHg	60 ± 16	63 ± 10	64 ± 8	0.1423	0.8411
Respiratory Rate, breaths/min	19 ± 3	19 ± 6	30 ± 19	2.1860	0.2089
Body Temperature, °F	95.7 ± 3.7	99.6 ± 2.3	101.5 ± 1.7	4.2050	0.1079
Glasgow Coma Scale Score	5 ± 2	7 ± 3	9 ± 2	4.7500	0.0468
CRM, %	48 ± 13	30 ± 14 *	26 ± 5 *	11.4800	0.0144

Values are mean ± SD. * indicates statistical difference compared with D-2 value determined by Tukey post hoc analysis; † indicates statistical difference compared with D-1 value determined by Tukey post hoc analysis.

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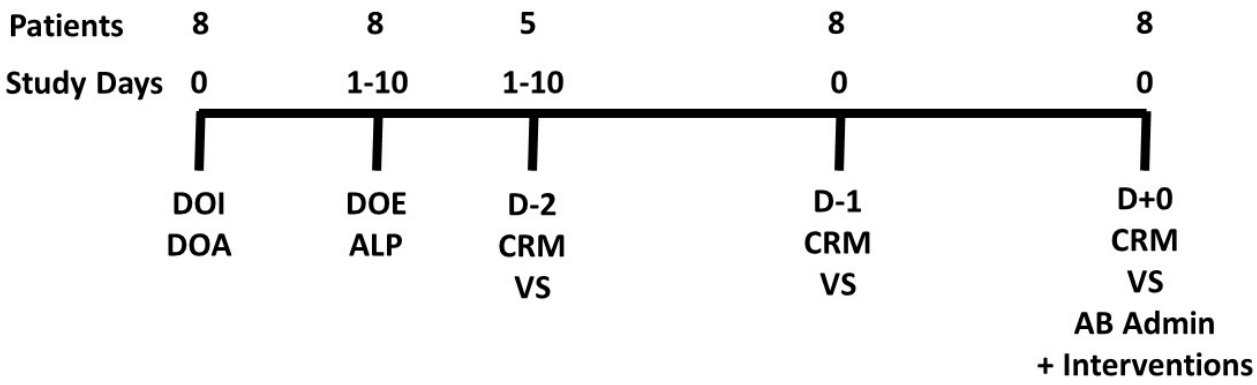
Figure Legends:

Figure 1. Graphical representation of the study protocol timeline for eight burn patients. All subjects were admitted to the burn intensive care unit (BICU) on the day of burn injury (study day 0). One to ten days after BICU admission, subjects were enrolled in the study (DOE) and an arterial catheter (ALP) was inserted. Measurements of compensatory reserve (CRM) and eight standard vital signs (VS) were performed on the first measurement day (D-2) and second measurement day (D-1) prior to the day of sepsis diagnosis (D+0) in 5 of the patients while only D-1 and D+0 measurements could be obtained on the remaining 3 subjects. Sepsis was determined when all 8 patients met the criteria of receiving antibiotics (AB) on day D+0.

Figure 2. Typical continuous recordings of compensatory reserve measurement (CRM) over time in a non-septic patient on the initial day of ICU admission and who later became septic on a subsequent day of study.

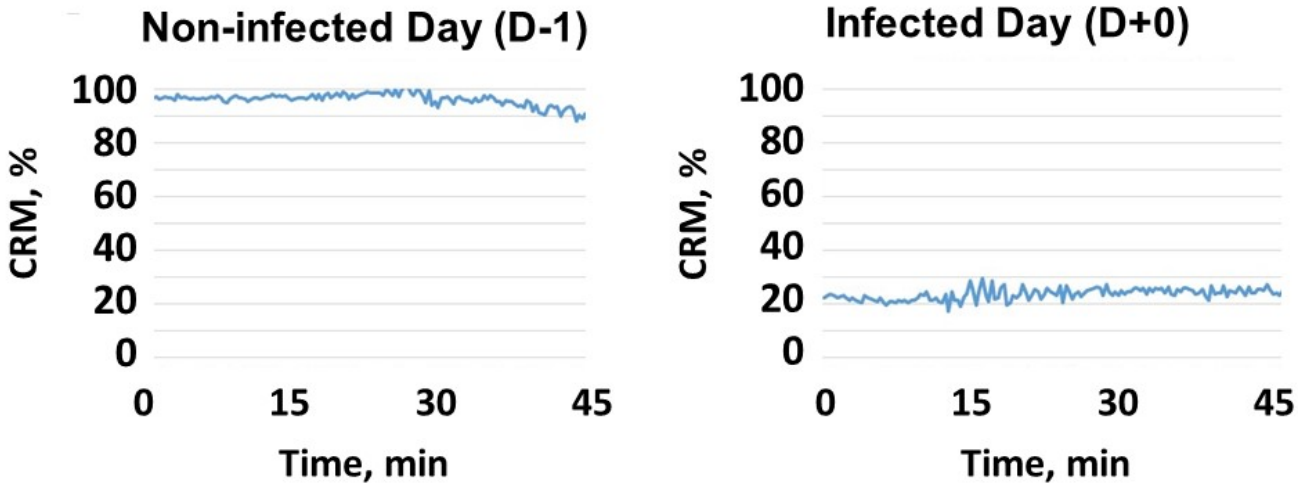
Figure 3. Bars indicating the average compensatory reserve measurement (CRM) obtained from 5 individual patients during 60 minutes of arterial waveform recordings during the initial day (D-2) and the second day (D-1) of arterial waveform data collection following BICU admission and on the first day of infection diagnosis (D+0). Horizontal colored broken lines indicate thresholds of CRM being 60% to 30% (yellow) and below 30% (red).

Study Protocol



DOI & DOA = Day of injury and hospital admission
DOE = Day of Enrollment into study
ALP = Arterial catheter placement
D+0 = Day of sepsis diagnosis
D-1 = Test day prior to sepsis diagnosis
D-2 = Test day prior to D-1
CRM = Compensatory Reserve Measurement
VS = Vital signs measurement
AB = antibiotics
Interventions = vasopressors, intravenous fluids, blood cultures

Figure 1


Non-infected Day (D-1)
CRM, %
100
80
60
40
20
0
0
15
30
45
Time, min
Infected Day (D+0)
CRM, %
100
80
60
40
20
0
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15
30
45
Time, min

Figure 2

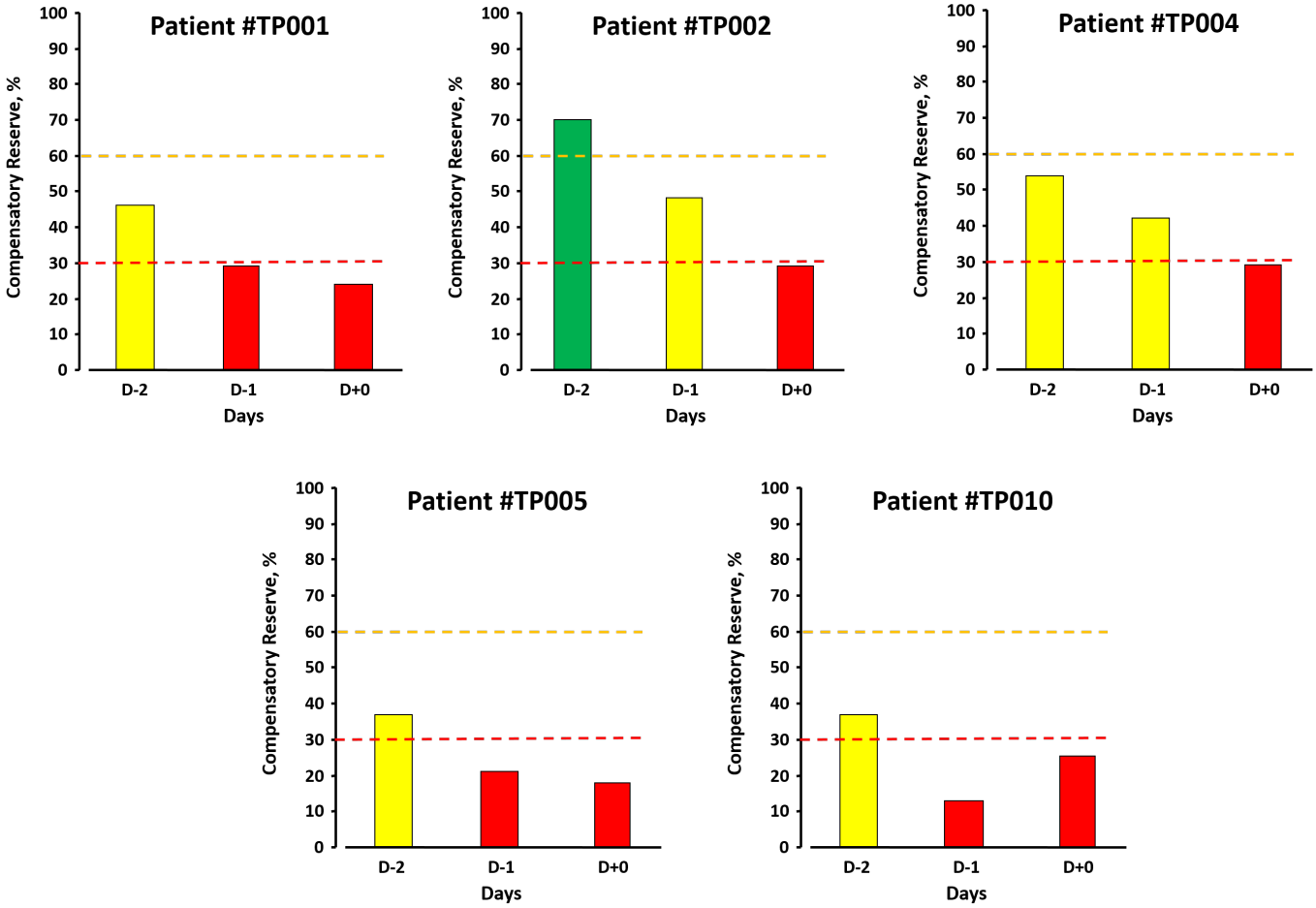
Patient #TP001
Patient #TP002
Patient #TP004
Patient #TP005
Patient #TP010
Compensatory Reserve, %
Days
D-2
D-1
D+0
0
10
20
30
40
50
60
70
80
90
100

Figure 3

Received: 29 December 2020 | Revised: 11 February 2021 | Accepted: 11 February 2021

DOI: 10.1111/trf.16494

SUPPLEMENT ARTICLE

TRANSFUSION

Compensatory reserve detects subclinical shock with more expeditious prediction for need of life-saving interventions compared to systolic blood pressure and blood lactate

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Funding information
US Army Combat Casualty Care Research Program under the Medical Research and Development Command, Grant/Award Number: W81XWH-14-2-0149; Research and Development; Combat Casualty Care Research Program

Abstract

Introduction: We conducted a prospective observational study on 205 trauma patients at a level I trauma facility to test the hypothesis that a compensatory reserve measurement (CRM) would identify higher risk for progression to shock and/or need a life-saving interventions (LSIs) earlier than systolic blood pressure (SBP) and blood lactate (LAC).

Methods: A composite outcome metric included blood transfusion, procedural LSI, and mortality. Discrete measures assessed as abnormal (ab) were SBP <90 mmHg, CRM <60%, and LAC >2.0. A graded categorization of shock was defined as: no shock (normal [n] SBP [n-SBP], n-CRM, n-LAC); sub-clinical shock (ab-CRM, n-SBP, n-LAC); occult shock (n-SBP, ab-CRM, ab-LAC); or overt shock (ab-SBP, ab-CRM, ab-LAC).

Results: Three patients displayed overt shock, 53 displayed sub-clinical shock, and 149 displayed no shock. After incorporating lactate into the analysis, 86 patients demonstrated no shock, 25 were classified as sub-clinical shock, 91 were classified as occult shock, and 3 were characterized as overt shock. Each shock subcategory revealed a graded increase requiring LSI and transfusion. Initial CRM was associated with progression to shock (odds ratio = 0.97; $p < .001$) at an earlier time than SBP or LAC.

Conclusions: Initial CRM uncovers a clinically relevant subset of patients who are not detected by SBP and LAC. Our results suggest CRM could be used to more expeditiously identify injured patients likely to deteriorate to shock, with requirements for blood transfusion or procedural LSI.

KEYWORDS

compensation, oxygen delivery, shock categorization, traumatic hemmorhage

1 | INTRODUCTION

Traumatic hemorrhage is the leading cause of preventable death on the battlefield and one of the leading

Abbreviations: ab, abnormal; CRM, compensatory reserve measurement; LAC, blood lactate; LSI, life-saving intervention; n, normal; SBP, systolic blood pressure.

causes of civilian death from traumatic injury.[1-5] Although traumatic brain injury is responsible for more deaths in the civilian arena, it is unlikely early intervention will ameliorate these types of injuries. Hemorrhage, on the other hand, represents an injury process that can be intervened upon early with the potential to drastically alter injury outcomes.

Civilian and military first responders continue to have limited toolsets in assessing traumatic hemorrhage. Early recognition of bleeding relies extensively on clinical cues and experience, but hemorrhage may be occult and difficult to identify clinically. These difficulties are further magnified by our continued reliance on basic vital signs such as blood pressure, heart rate, and oxygen saturation that display poor discriminatory ability.[6-10] In addition, a late recognition of hemorrhage when identified through vital signs means the patient is already experiencing the effects of significant volume loss and the window of opportunity to effectively intervene has more than likely passed. The latency in the current parameters used to identify shock in the field highlights the critical necessity to find more accurate assessment tools to effectively and continuously monitor those experiencing or likely to develop shock shortly after injury.

Prompt identification expedites mitigation and resuscitation strategies and improves outcomes. As such, identification of compensated shock during the early subclinical phase could potentially facilitate improved clinical decision making and accelerate the provision of life-saving interventions (LSIs). In this regard, the compensatory reserve measurement (CRM) has been consistently shown to reflect early stages of physiological compensation with greater sensitivity and specificity than standard vital signs in conditions of experimentally induced central hypovolemia,[11-15] controlled human blood loss,[16-18] and trauma patients with hemorrhage.[19-22] In the present clinical investigation, we captured for the first time CRM of trauma patients at progressive stages from a state of subclinical shock to overt hemorrhagic shock. We hypothesized that CRM would prove more useful in early detection of patients at risk of progressing to overt shock or in need of LSI compared to either systolic blood pressure (SBP) or blood lactate (LAC).

2 | METHODS

2.1 | Subjects

This prospective observational study was approved by the Institutional Review Board of the University of Texas Health Science Center, San Antonio, and was performed by analyzing the compensatory reserve during the acute resuscitation phase of injured patients evaluated at a level I trauma facility. Inclusion criteria included all patients with age >17, requiring trauma team activation, and transport directly from the scene of injury. Exclusion criteria included current pregnancy, and/or prisoner status. The initial recruited population for study consisted of 300 injured patients; however, analysis for this specific portion of the investigation included 205 patients who had the requisite inclusion measures of CRM, LAC, and SBP at admission.

2.2 | Protocol

All included subjects provided consent either in person or legal authorized representative after the acute resuscitative time period. CRM and SBP were measured upon arrival to the trauma emergency bay, and concurrent with LAC measurement. The CRM device consisting of a standard pulse oximeter sensor (PureLight model 8000AA, Nonin Medical Inc., Plymouth, MN) was placed on the finger and remained in place until discharge or transfer to the operating room or inpatient unit. The CRM was derived using a proprietary machine-learning algorithm capable of analyzing continuous real-time changes in specific features of the photoplehtysmogram that calculates a quantified scale from 100% (complete reserve) to 0% (depleted reserve) of the proportion of the sum total capacity of an individual patient to compensate for blood loss.[6, 11, 12] The CRM device was developed for investigational use only. A blood sample was obtained from an antecubital vein and analyzed for lactate through a standard panel at the University Health System chemistry lab. The SBP was manually obtained from a standard sphygmomanometer using a Phillips HeartStat MRx monitor. A composite outcome metric included any blood transfusion, procedural LSI, and mortality. LSI was defined as intubation, tube thoracostomy or hemorrhage control procedures (tourniquet, operation, and/or angiography).

2.3 | Group classification of shock

Discrete measures assessed as abnormal (ab) were SBP <90 mmHg, CRM <60%, and LAC >2.0 mmol/L. The graded categorization of shock (Table 1) was defined as follows: no shock (normal [n-SBP], n-CRM, n-LAC); sub-clinical shock (n-SBP, ab-CRI, n-LAC); occult shock (n-SBP, ab-CRM, ab-LAC; or n-SBP, n-CRM, ab-LAC); and overt shock (ab-SBP, ab-CRM, ab-LAC). Patients not represented by the above categories (i.e.: ab-SBP <90 but with n-LAC and n-CRM) were classified based upon the category of shock best represented

TABLE 1 Categorization of shock as defined by compensatory reserve measurement (CRM), blood lactate, and systolic blood pressure (SBP)

	Shock categorization			
	No shock ($N = 86$)	Subclinical shock ($N = 25$)	Occult shock ($N = 91$)	Overt shock ($N = 3$)
CRM <60%	−	+	+	+
Lactate >2.0 mmol/L	−	−	+	+
SBP <90 mmHg	−	−	−	+

TABLE 2 Shock categorization of variable combinations not consistent with the global categories depicted in Table 1

	Shock categorization			
	Occult shock	Overt shock	Overt shock	Overt shock
CRM <60%	−	−	+	−
Lactate >2.0 mmol/L	+	+	−	−
SBP <90 mmHg	−	+	+	+

Abbreviations: CRM, compensatory reserve measurement; SBP, systolic blood pressure.

by the abnormal parameter (Table 2). This meant the aforementioned example (ab-SBP <90, but with n-LAC and n-CRM) was placed into the overt shock category based upon the blood pressure derangement. Descriptive statistics and odds ratios (ORs) from multivariable ordinal and binary logistic regression models assessed associations between initial SBP and CRM in regards to subsequent measurements of deterioration to shock, positive lactate, and the composite outcome. Individual outcome parameters were categorized in relation to the defined subgroups of shock to determine the capabilities of a CRM-based algorithm of shock.

3 | RESULTS

Demographics of the overall sample population included patients being predominantly male (65%) with a mean age of 46 (18–87) and a racial composition of Caucasian (45%), Hispanic (50%), Black (4%), and others (1%). For the overall population, the mechanism of injury was 87% blunt and 13% penetrating, with an overall average ISS of 9 (range 1–75). Outcomes included 37 patients (18%) who received a LSI, 25 patients (12%) who received transfusion of packed red blood cells, and 3 patients (1.5%) who died.

Within the sample population, 3 patients (1.5%) had initial SBP <90, and CRM <60%, while 53 patients (25.9%) had SBP ≥90, and CRM <60%, and 149 patients (72.7%) had SBP ≥90, and CRM ≥60%. After incorporating lactate data (abnormal being defined as >2.0) into the analysis, 86 patients (41.9%) demonstrated no shock, 25 patients (12.2%) were classified as sub-clinical shock, 91 patients (44.4%) were classified as occult shock, and 3 patients (1.5%) were characterized as overt shock (Table 1). Table 2 provides criteria used to categorize shock with combinations of CRM, SBP, and LAC that were not defined by the categories depicted in Table 1. For each category of shock, injury characteristics and outcome parameters are shown in Table 3. Comparison across groups revealed graded elevations in hospital stay, intensive care unit (ICU) stay, and injury severity score (ISS). In addition, there was a graded increase in lactate with progression toward overt shock.

Proportional analysis of each shock subcategory revealed a graded increase in those requiring LSI, transfusion, and composite outcome (Figure 1). Rates of LSI and transfusion for each category revealed a progressive increase with no shock (7% and 3%), sub-clinical shock (13% and 9%), occult clinical shock (26% and 20%), and overt shock (100% and 67%). Logistic regression models showed initial SBP was not associated with progression to overt shock (OR = 1.00; $p = .60$) or abnormal lactate (OR = 1.00; $p = .67$), but was associated with the composite outcome (OR = 0.98; $p = .02$). Initial CRM was associated with progression to shock (OR = 0.97; $p < .001$), abnormal lactate (OR = 0.97; $p < .001$), and the composite outcome (OR = 0.97; $p < .001$).

4 | DISCUSSION

In the present investigation, CRM was concurrently measured with SBP and LAC in trauma patients who manifested various progressive stages of shock to test the hypothesis that CRM would provide an earlier detection

	No shock	Sub-clinical shock	Occult shock	Overt shock
Sex	65%	26%	72%	67%
Age (years)	45	52	46	58
Mechanism				
Blunt	88%	91%	87%	66%
Penetrating	12%	9%	13%	34%
ISS	7	10	11	13
Length of stay	3	4	6	4
ICU length of stay	0	2	2	1

TABLE 3 Demographics and outcomes for each shock subpopulation

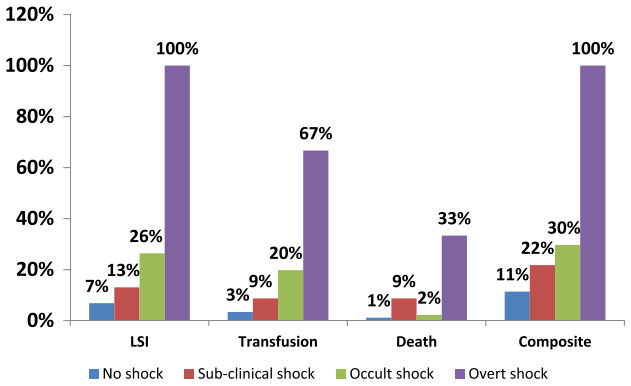

FIGURE 1 Percentage experiencing outcomes parameters (LSI, transfusion, death, and composite). Composite represents any patient experiencing at least one of the outcomes parameters. LSI, life-saving intervention

of progression toward overt shock and/or need of LSI. This hypothesis was supported by demonstrating that a CRM lower than a threshold of 60% became evident prior to threshold changes in either SBP <90 mmHg or LAC >2 mmol/L.

Our dataset provides several key insights to understanding the predictive capacity of CRM during the progression toward shock after trauma. First, we showed the improved predictive capabilities of CRM over SBP and LAC in recognizing pre-clinical shock and the need for intervention.

Second, we have established an earlier phase of shock by incorporating CRM into the classification schema. A conceptual framework for the physiology of hemorrhage has been proposed that includes reduced systemic delivery of oxygen (DO_2) contributed by immediate decrease in cardiac filling and output due to lost blood volume concurrent with lower oxygen carrying capacity from lost red blood cells.[6, 23, 24] Despite progressive reduction in DO_2, a state of compensated shock is manifested by no change in systemic oxygen uptake and LAC. The CRM has been shown to track DO_2 from the onset of hemorrhage to time of decompensation.[24, 25] Taken together, the immediate and early reduction in DO_2 is consistent with the results of the current investigation, supporting the observation that CRM proved to be a biomarker of pre-clinical shock that could not be recognized with the use of either SBP or LAC.

It has been well established that SBP does not consistently assess the current status of a traumatically injured patient. Unfortunately, we are limited to basic toolsets, especially in the field triage setting, as no substantially improved monitoring system has been established. This known inadequacy is further complicated by pre-existing pathophysiology commonly encountered in the elderly, those with multiple co-morbidities, large body habitus, medication use, and trauma mechanism. Recent studies have shown these contributing factors can have significant effects on the reliability of current field assessment strategies. The specificity of a machine-learning approach allows the CRM to overcome many of these monitoring limitations because the algorithm is based on a database of more than 650,000 waveforms that includes a wide demographic of age (18–55 years), sex, fitness, and body mass (BMI range = 17.3–39.4 kg/m^2) in a population of greater than 250 healthy humans.[11, 12, 24, 26] The capability of the algorithm to "learn" to recognize the physiology of progression to decompensated shock in healthy humans has provided a basis for the algorithm to consistently recognize the compensatory status of trauma patients with pathophysiology.[12, 19-22, 27]

Underlying pathophysiology is further complicated by individual patient variability in the capacity to compensate for blood loss caused by trauma, reflecting the need to move beyond overly simplified measurements of human physiology. First responders have long needed a way to individualize care and account for the innumerable patient variations experienced in the field. The measurement of compensatory reserve represents a definitive step toward individualizing care by its ability to distinguish individual capabilities to compensate for blood loss.[6, 12, 24, 26, 28] CRM also provides a dynamic and easily

available analysis of current patient status. By employing machine-learning technology, the first responder has the potential to quickly and accurately "learn" the patient, provide accurate assessment of perfusion status, and ensure care remains individualized to the patient.

Third, we propose a key development in our understanding of shock classification based on inclusion of the CRM. Extensive research has been performed focusing on the period of time from the onset of initial trauma-induced hemorrhage to the development of shock. Clinically, the overt presence of shock has been detected by derangements in vital signs. It has been well established that there is a critical time period between the overt signs of shock and the precipitating event.[6, 12] This time period represents underlying physiological changes in the complex integration of compensatory mechanisms that have historically been difficult to measure. With the results from this current clinical investigation, we now realize with the CRM that this time period represents a critical opportunity to intervene earlier and potentially impede the development of shock before irreversible changes to end organ function have occurred. Unfortunately, once the overt manifestations of shock (i.e., decreased blood pressure, increased LAC) have been recognized, the time period to intervene is lost.

Our results reveal that by using CRM over SBP and/or LAC, we were able to better predict those progressing to shock and requiring LSI. Although not temporally quantified in the current study, this earlier recognition has been shown to have significant translation in earlier identification of shock by civilian paramedics[29] and combat medics.[30]

Researchers have attempted to better predict or appreciate this "occult" shock through many devices such as tissue oxygen (StO_2) monitoring or lab analyses such as LAC and base deficit. Although these methods have shown promise, there remain questions in regards to their reliability and/or usefulness in the pre-hospital or forward-combat setting. For instance, measures of StO_2 have proven to be sensitive to progressive reductions in central blood volume,[31] but are not specific to individual patients as demonstrated by higher levels reported in individuals with earlier onset of decompensated shock.[13, 27] Although LAC has a similar ROC AUC as CRM once a patient is in shock,[32] it fails to increase during the early compensatory phase at a time of significant loss of central blood volume.[15, 33-35] By incorporating CRM analysis into the shock algorithm, we have established its capability to recognize a subset of bleeding patients who go on to develop shock and require significant intervention. This subset would not have been recognized by current physiologic assessments such as SBP. Even more sophisticated measurements such as LAC would have been unable to recognize this "early" shock state. Although there were no statistical differences between these subgroups of shock as it pertains to LSI, transfusions, and composite analyses (Figure 1), the clear clinical differences in time of diagnosis cannot go unappreciated. Interestingly, deaths within each subgrouping do not follow similar trends, but this is probably due to the low incidence of death in general except when overt shock has occurred.

Shock index (SI), defined as the ratio of heart rate (HR) to SBP, represents another tool that has been historically used by various emergency medical personnel to identify "occult" shock and the need for transfusion.[36-38] However, we purposely chose to exclude SI from our model of progressive stages from a state of subclinical shock to overt hemorrhagic shock for several reasons. First, SI displays relatively low sensitivity that can fail to distinguish trauma patients with hemorrhage from those without.[22] Second, poor sensitivity may also reflect that clinically significant elevations in SI occur late during the early compensatory phases of progressive central hypovolemia compared to CRM.[6, 11, 17, 39] Third, and perhaps most clinically important, is the evidence that SI displays relatively low specificity for the progression of stages of shock that can lead to misleading assessment of patient status. Individuals with low tolerance to central hypovolemia (i.e., poor compensators) who are at greater risk for early onset of occult and overt shock demonstrate a lower SI than those who compensate effectively with greater elevations in HR and subsequently higher SI.[12] As such, the data from the present study clearly support the notion that CRM represents a more sensitive and specific capability for early identification of sub-clinical shock than SI.

Our results further substantiate the intricate usefulness of the CRM for early recognition of shock by identifying a clinical subset not previously recognized by current parameters. This appreciation of a sub-clinical shock via CRM could more expeditiously identify those requiring significant intervention at a time when intervention may more significantly impact outcomes.

This study further substantiates the additional triage capabilities provided by incorporating measures of the compensatory reserve over current toolsets in evaluating the traumatically injured patient experiencing hemorrhage. Although previous studies, mostly experimental, have shown these capabilities, the results of this investigation represent the continued clinical assessment of CRM on one of the largest known cohort of traumatically injured patients. More specifically, our data represent a valid generalizability across populations of all trauma patients suffering from ongoing blood loss. By minimizing the exclusion criteria and essentially taking "all comers," we have provided data to substantiate the use of

CRM in an initial triage setting. This finding may have significant implications in both the pre-hospital and combat forward environments and further substantiate the clear improvement of CRM over typical vital sign evaluation specifically in regard to SBP and LAC assessments.

5 | CONCLUSIONS

Initial measures of compensatory reserve were significantly associated with progression to shock, abnormal lactate, and the composite outcome. Our results suggest that CRM could be used to more expeditiously identify injured patients likely to deteriorate to occult or overt shock, require blood transfusion, or procedural LSI.

ACKNOWLEDGMENTS

The authors thank Dr Alicia M. Schiller for her assistance with the CRM data extraction from pulse oximeter monitors, and Ms Diane Villarreal for assistance with manuscript preparation and submission. Study funding was provided by grants from the US Army Combat Casualty Care Research Program under the Medical Research and Development Command through the Broad Agency Announcement for Extramural Medical Research (Award No. W81XWH-14-2-0149) and Congressionally Directed Medical Research Program (Award No. DM180240).

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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How to cite this article: Convertino VA, Johnson MC, Alarhayem A, et al. Compensatory reserve detects subclinical shock with more expeditious prediction for need of life-saving interventions compared to systolic blood pressure and blood lactate. Transfusion. 2021;61:S167–S173. https://doi.org/10.1111/trf.16494