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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
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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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

16. SECURITY CLASSIFICATION OF:			17. IMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

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 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:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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 will be collected retrospectively at Mayo Clinic. All burn patient data will be collected prospectively at USAISR Burn Center under a different award, and data will be given to Dr. Convertino's team for analysis.

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 will be collected retrospectively at the Mayo Clinic and assessed. Prospective data from 60 burn patients at the USAISR Burn Center will be assessed.

Subtask 2: Analyze data and compile results

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

- *STATUS: IN PROGRESS*

Major Task 3: Write manuscripts

- *STATUS: IN PROGRESS*

What was accomplished under these goals?

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:

Nothing to report

Methods and results for the reporting period:

Key Findings or Accomplishments for Specific Aim 1:

The annual continuing report for protocol H-11-038 was approved by the MMRDC IRB and HRPO on 7 October 2019

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:

We enrolled and completed LBNP experiments on 47 subjects from June 24, 2019 through January 2020. Currently working with Dr. Rasha Hammamieh, USACEHR, to ship 94 frozen blood samples for data analysis. Estimate time of shipment is November 2020.

Key Findings or Accomplishments for Specific Aim 2:

Nothing to report

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 will be analyzed during Q2 through Q3 of CY21 for calculation of compensatory reserve using the Mayo Clinic CRM algorithm, and results correlated with blood loss and interventions documented during surgery.

Key Findings or Accomplishments for Specific Aim 3:

Nothing to report

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

BMES oral presentation with new algorithm results: Schlotman, T.E. et al., Analysis Of Compensatory Reserve In Clinical Populations Using 1D Convolutional Neural Networks, Biomedical Engineering Society (BMES) Annual Meeting October 2019, Philadelphia, PA

How were the results disseminated to communities of interest?

Nothing to report

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

Continue to recruit and enroll subjects. Ship the frozen blood samples to WRAIR for genetic and protein-omic analyses.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The development 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, and will 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 will be published in the American Physiological Society journal named Comprehensive Physiology with an impact factor of 6.2

What was the 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 invitations during the reporting period for this grant to provide briefings on the applications of compensatory reserve measurement for use in emergency medicine 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
- East Central Mississippi Trauma Care Region Symposium

What was the impact on technology transfer?

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.

What was the impact on society beyond science and technology?

- *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.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

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 affected the Mayo Clinic effort during this reporting period, with an incredible surge in COVID-19 cases which is the top priority for the clinical staff and infrastructure. In particular, Mayo Clinic redeployed staff into critical roles to respond to the pandemic and human subject research was deferred. In addition, renewal of the software license for the proposed data collection system was delayed. As a consequence of these events, the planned infrastructure ramp-up for capturing and analyzing clinical arterial waveforms from 80 cardiac surgeries has been delayed. As the number of cases and impact of COVID-19 lessened during the summer of CY20, the Mayo team demonstrated functionality of the proposed collection system by capturing analog arterial waveforms. Efforts will ramp up in CY21 as COVID-19 disruptions are anticipated to decrease.

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 a non-invasive Clearsite 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 arterial lines using a Drager 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). Drafts of manuscripts documenting these case series results are in progress.

Actual or anticipated problems or delays and actions or plans to resolve them

Difficulty with recruitment and enrollment of 60 burn patients may significantly delay the ability to obtain new arterial waveforms required to assess the compensatory reserve algorithm for patient prognosis and guided intervention over the course of clinical observation, thus reducing the final dataset for execution of Specific Aim 3, Major Task 1. To address this problem, we will complete this Aim and Task with a 'Case Series' study publication on 10 individual burn patients. The complete shutdown of research at the USAISR since March 2020 due to the coronavirus pandemic has imposed significant delays in the execution of planned experiments and blood sample collection and transport. 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.

Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing 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.

PRODUCTS:

- **Publications, conference papers, and presentations.**
- **Journal publications.**

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. DoD funding acknowledged

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. DoD funding acknowledged

3. 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. DoD funding acknowledged

4. 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. DoD funding acknowledged

5. 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. DoD funding acknowledged

6. 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. DoD funding acknowledged

7. 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. DoD funding acknowledged

8. 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. DoD funding acknowledged

9. 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. DoD funding acknowledged

10. 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
   d. DoD funding acknowledged

11. 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. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged

12. 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. DoD funding acknowledged

13. Convertino, V.A., N.J. Koons, and M. Suresh. The physiology of human hemorrhage and compensation. *Comp Physiol*. 2020.
    a. Review
    b. In Press
    c. Related to SOW, specific aim 1
    d. DoD funding acknowledged

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.
    a. Review
    b. In Press
    c. Related to SOW, specific aim 1
    d. DoD funding acknowledged

15. 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.* 2020.
    a. Original Article
    b. In Press
    c. Not related to SOW
    d. DoD funding acknowledged

16. 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* 2020.
    a. Original Article
    b. In Press
    c. Not related to SOW
    d. DoD funding acknowledged

Books or other non-periodical, one-time publications.

None to report.

Other publications, conference papers, and presentations.

1. Convertino V. Oct 2019. "The Compensatory Reserve: Potential for Accurate Individualized Whole Blood Resuscitation". Joint Trauma System Tactical Combat Casualty Care Global Video Teleconference, San Antonio, Texas
    a. Oral Presentation
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged

2. Convertino V. Nov 2019. "The Compensatory Reserve for Early Diagnosis of Shock". Assistant Secretary of Preparedness and Response at the U.S. Department of Health & Human Services Critical Care Innovation Forum, Washington, DC
    a. Oral Briefing
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged

3. Convertino V. Nov 2019. "Smart Monitoring is Not About Monitoring: It's About Physiology!" The NIH National Institute of Biomedical Imaging & Biotechnology, Bethesda, Maryland.
    a. Oral Presentation
    b. Presented
    c. Directly related to SOW, specific aim 1
    d. DoD funding acknowledged

4. Convertino V. Dec 2019. “New Approaches to the Early Diagnosis and Treatment of Shock”. Lecture presented at the East Central Mississippi Trauma Care Region Symposium, Meridian, Mississippi.
    a. Poster
    b. Presented
    c. Related to SOW, specific aim 1
    d. DoD funding acknowledged

5. Convertino V. Feb 2020. “Cardiovascular Effects of Prolonged Bedrest and Spaceflight”. Tripartite Rounds of the US Army Institute of Surgical Research, San Antonio, Texas.
    a. Lecture
    b. Presented
    c. Not related to SOW
    d. DoD funding acknowledged

6. Convertino V. July 2020. “IPR Therapy - Getting Positive Blood Flow from Negative Pressure”. Virtual webinar hosted by the Zoll Biomedical Corp., Minneapolis, Minnesota.
    a. Seminar
    b. Presented
    c. Not related to SOW
    d. DoD funding acknowledged

7. Convertino V. July 2020. “Overview of Department of Defense Careers in Research”. Wake Forest School of Medicine Summer Intern Career Program,
    a. Virtual Panel
    b. Presented
    c. Not related to SOW
    d. DoD funding acknowledged

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

The primary technology resulting from this research activity is a machine-learning algorithm for measurement of 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

The Special Purpose Processor Development Group at the Mayo Clinic has submitted a patent application in January 2020 for the Compensatory Reserve Algorithm (CRA).

Other Products

- *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 for accurately predicting 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*

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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 regulatory and 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:	CPT Alisha Carlson
Project Role:	Graduate Student Intern at USAISR
Nearest person month worked:	2
Contribution to Project:	CPT Carlson will replace Dr. Taylor Schlotman's responsibility for preparing for methodologies for electronic data collection and analysis, and will supervise the transfer of LBNP data sets to the SPPDG personnel at Mayo Clinic.
Name:	Dr. Rasha Hammamieh
Project Role:	Director, Systems Biology Group at USACEHR
Nearest person month worked:	0
Contribution to Project:	Dr. Hammamieh will perform the comprehensive mult-iomic analyses of blood samples collected during the LBNP experiments conducted at USAISR
Name:	LTC Jonathon Stallings
Project Role:	Research Scientist at USAISR
Nearest person month worked:	0
Contribution to Project:	LTC Stallings will be responsible for electronic data collection, storage, and analysis
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 to develop 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:	*Bi*omedical 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?

Nothing to report.

What other organizations were involved as partners?

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

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

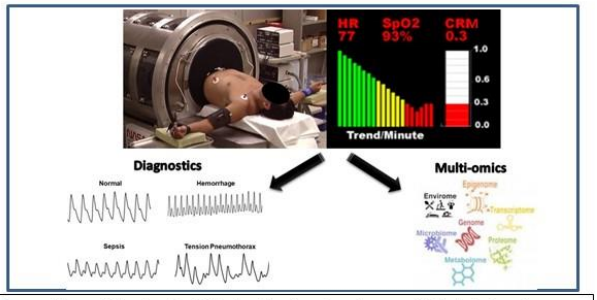
PI: Victor A. Convertino **Org:** US Army Institute of Surgical Research **Award Amount:** $2,032,601

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.
- Determine the genetic, molecular and metabolic correlates of tolerance to blood loss via multi-omic analyses.



Accomplishment: Creating the CRM algorithm is well underway, with the latest version utilizing convolutional neural networks reaching ROC AUC 0.89. Next steps: further subject testing and obtaining clinical data to make the algorithm diagnostic and multi-omic analyses to determine 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 2020

CY19 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
CY20 Goal –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)
CY21 Goal –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: $1,464,601

APPENDICES: