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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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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

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TABLE OF CONTENTS

1. INTRODUCTION:

One of primary challenges of effectively treating bleeding trauma patients is the difficulty with using 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 gap requirement for both the Army Medical (AMED) Capability Development Integration Directive (CDID) and Special Operations Command (SOCOM). 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 (i.e., who is at greatest risk for the early onset of life threatening circulatory shock) as well as identify gene expression and metabolic changes that could reveal underlying molecular mechanisms.

2. KEYWORDS:

compensatory reserve measurement, lower-body negative pressure, artificial intelligence, machine learning algorithm, hemorrhage, central hypovolemia, shock, tissue oxygenation, guided intervention, medical monitoring, precision medicine

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) 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

Major Task 1: Prepare regulatory and institutional documents

Major Task 2: Conduct staff training

Major Task 3: Algorithm development

All Milestones for Major Tasks 1 through 3 were achieved by the end of Y2Q4

Major Task 4: I In an effort to provide an adequate number of waveform signals for algorithm validation testing, data collection was expanded from three to five clinical investigations. Subjects included: 1) trauma patients in the emergency room suffering from hemorrhage (n = 300); 2) trauma patients in the emergency room receiving blood transfusion after significant blood loss (n = 13) or obstructive airways (n = 10); 3) patients with >25% body surface area burn

injury who developed sepsis (n = 8); 4) trauma patients suffering with sepsis (n = 100); and 5) patients undergoing cardiac surgery.

100% Milestone Achieved*: The PI met with the lead engineer from Mayo Clinic on 14 August 2023. The PI was informed that an initial assessment of the data set of 80 cardiac surgery patients for calculation of the compensatory reserve measurement (CRM) revealed that generating an accurate CRM value from use of the arterial waveforms collected from art lines would require significant 'transfer learning' of the algorithm. This result indicates that the cardiac surgery patient data were not usable for clinical validation due to contamination during waveform collection. However, the inclusion of validation with the use of data collected from the 5 clinical investigations (total sample size = 1,010 patients) involving CRM algorithm derivation from patients with sepsis in the emergency department, sepsis in burn patients, hemorrhage in trauma patients, and patients undergoing severe blood loss during liver transplant represents a more compelling alternative by demonstrating that the algorithm works across a broad spectrum of disease states from the emergency room to the operating room to the intensive care unit..*

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

Major Task 1: Conduct new LBNP experiments on human subjects for collection of blood samples

100% Milestone Achieved*: The USAISR Human Physiology Laboratory has completed 47 of the planned 150 LBNP experiments have been completed, but the remaining 103 experiments were suspended due to laboratory shutdowns during COVID-19. In addition, the LBNP chamber is underwent refurbishing of seals and updating to the pressure motor.*

Subtask 1: *Submission, review, and approval for a new USAISR LBNP USAISR standard operating procedure (SOP) protocol to be used in the multi-omics project has been completed. However, experiments and blood collection to be conducted on healthy humans in the BHT CHIP Human Physiology Laboratory has been suspended because of the replacement of blood samples collected on 80 human subjects at the Mayo Clinic LBNP Laboratory under a Mayo Clinic IRB-approved protocol.*

Subtask 2: Conduct LBNP experiments on 150 human subjects for collection of 300 blood samples (one sample before and one sample after LBNP).
With the addition of LBNP experiments on 80 subjects (160 blood samples) conducted at Mayo Clinic to the 47 subjects (94 blood samples) from experiments conducted at the BHT CHIP laboratory at USAISR, there will be 127 subjects rather than the originally proposed 150 subjects. However, preliminary multi-omics analysis on the USAISR BHT CHIP data revealed consistent results that suggest that the new sample size reduced by only 23 subjects will provide ample statistical power for distinguishing group differences in genetic expression between individuals with high and low tolerance to reductions in central blood volume (see manuscript with preliminary multi-omics results at the end of this report).

Major Task 2: Analysis of blood samples collected during new USAISR and Mayo Clinic LBNP experiments.

40% Milestone Achieved*: 94 blood samples collected from 47 subjects have been analyzed by the Medical Readiness Systems Biology (MRSB) laboratory at the WRAIR under the supervision of Dr. Rasha Hammamieh. In order to complete the multi-omics investigation, experiments using the exact same LBNP protocol were conducted on 80 human subjects in the LBNP laboratory at the Mayo Clinic supervised by Drs. Michael Joyner and Tim Curry providing an additional 160 blood samples for analysis. A Material Transfer Agreement #22-0328 has been executed to allow for the transfer of Mayo Clinic coded and de-identified blood samples to the MRSB laboratory at WRAIR. Dr. Hammamieh has submitted a protocol to the WRAIR IRB and is currently awaiting approval that will allow for the acceptance and analysis of the Mayo Clinic blood samples by the MRSB. Once the IRB has approved the protocol, it is anticipated that completion of this portion of the project should require no more than 3 months. A 12-month no-cost extension (NCE) to support blood sample analysis sent from Mayo Clinic has been approved for the period of 21 Apr 2023 through 20 Apr 2024.*

Major Task 3: Write manuscripts *(will be written upon completion of sample analysis)*.

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.

Major Task 1: New arterial waveform data collection from patients with various clinical conditions

100% Milestones Achieved by Y3Q4

Major Task 2: Data analysis

60% Milestone Achieved*: Ongoing pending completion of multi-omics analysis of blood samples collected from the Mayo Clinic LBNP experiments and arterial waveform feature analysis of electronic analog signals collected from cardiac surgery patients. MSRB awaiting IRB approval of submitted protocol that will allow for receiving and analysis of blood samples from Mayo Clinic.*

Major Task 3: Write manuscripts.

95% Milestones Achieved *by the end of Y5Q4. The following manuscripts have been written and published:*

1. Koons NJ, Owens GA, Parsons DL, Schauer SG, Buller JL, Convertino VA. Combat medic testing of a **novel** monitoring capability **for** early detection of hemorrhage. *J Trauma Acute Care Surg*. **89**:S146-S152, 2020
2. **Benov A, Brand A, Rosenblat T, Antebi B, Ben-Ari A, Amir-Keret R, Nadler R, Chen J, Chung KK, Convertino VA, Paran H. Evaluation of sepsis using**

compensatory reserve measurement: a prospective clinical trial. *J. Trauma Acute Care Surg*. 89:S153-S160, **2020**

3. Convertino VA**, Wampler MR,** Johnson MC, Alarhayem A, Le TD, Nicholson S, Myers JG, Chung KK, Struck KR, Cuenca C, Eastridge BJ. Validating clinical threshold values for a dashboard view of the compensatory reserve measurement for hemorrhage detection. *J. Trauma Acute Care Surg*. 89:S169-S174, **2020**
4. Convertino VA, Schauer SG, Weitzel EK, Cardin S, Stackle ME, Talley MJ, Sawka MN, Inan OT. Wearable sensors integrated with compensatory reserve monitoring in critically injured trauma patients. *Sensors.* **20**(22): 6463, 2020
5. Convertino VA, Koons NJ, Suresh M. Physiology of human hemorrhage and compensation. *Compr. Physiol*. 11:1531-1574, 2021
6. Schauer SG, April MD, Arana AA, Maddry JK, Escandon MA, Linscomb C, Rodriguez D, Convertino VA. Efficacy of the compensatory reserve measurement in an emergency department trauma population. *Transfusion* **61:S174-S182, 2021**
7. Convertino VA, Johnson MC, Alarhayem A, Nicholson SE, Chung KK, DeRosa M, Eastridge BJ. 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* **61:S167-S173, 2021**
8. Convertino VA, Techentin RW, Poole RJ, Dacy AC, Carlson AN, Cardin S, Haider CR, Holmes III DR, Wiggins CC, Joyner MJ, Curry TB, Inan OT. AI-enabled advanced development for assessing low circulating blood volume for emergency medical care: comparison of compensatory reserve machine-learning algorithms. *Sensors.* **22**, 2642, 2022
9. Koons NJ, Moses CD, Thompson P, Strandenes G, Convertino VA. Identifying critical DO_2 with compensatory reserve during simulated hemorrhage in humans. *Transfusion* 62:S122-S129, **2022**
10. **Ciaraglia AV,** Convertino VA, Johnson MC, Nicholson SE, DeRosa M, Eastridge BJ. Compensatory reserve and pulse character: enhanced potential to predict urgency for transfusion and other life-saving injuries after traumatic injury. *Transfusion* 62:S130-S138, **2022**
11. Convertino VA, Cardin S. Advanced medical monitoring for the battlefield: a report on clinical data that verify compensatory reserve measurements for early and accurate hemorrhage detection. *J Trauma Acute Care Surg*. **93:S147-S154,** 2022
12. Convertino VA, Wagner A, Akers KS, VanFosson CA, Cancio LC. Early identification of sepsis in burn patients using compensatory reserve measurement: a case series pilot study. *Burns* 6:137-145, **2022**
13. Gupta JF, Telfer BA, Convertino VA. Importance of feature analysis for compensatory reserve measurement to predict hemorrhagic shock. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc*. 2022:1747-1752, 2022
14. Gupta JF, Arshad SH, Telfer BA, Snider EJ, Convertino VA. Noninvasive monitoring of simulated hemorrhage and whole blood resuscitation. *Biosensors.* **22**, 1168, 2022
15. Bedolla CN, Gonzalez JM, Vega SJ, Convertino VA, Snider EJ. An explainable machine-learning model for compensatory reserve measurement: methods for feature selection and the effects of subject variability. *Bioengineering.* **10**, 612, 2023
16. **Ciaraglia AV,** Convertino VA, Wang H, Cigarroa F, Thomas E, Fritze D, Nicholson SE, Stewart R, Eastridge BJ. Intraoperative use of compensatory reserve measurement (CRM)

in orthotopic liver transplant: improved predictor for hypovolemic events. *Milit Med.* 2023 (in press)
17. Convertino VA, Thompson P, Koons NJ, Le T, Lanier JB, Cardin S. Superiority of compensatory reserve measurement to the shock index for early and accurate detection of reduced central blood volume status. *J Trauma Acute Care Surg*. **94**:2023 (in press)
18. Pramanik L, Felton CL, Techentin RW, Holmes DR III, Curry TB, Joyner MJ, Convertino VA, Haider CR. Towards a compensatory reserve metric lightweight classifier. *IEEE Eng Med Biol Soc*. 2023 (in press)
19. **Ciaraglia AV,** Osta E, Wang H, Cigarroa F, Thomas E, Fritze D, Nicholson SE, Eastridge BJ, Convertino VA. Evidence for beneficial use of the compensatory reserve measurement (CRM) in guiding interoperative resuscitation: a prospective cohort study of orthotopic liver transplant recipients. *Shock.* 2023 (in press)

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.

100% Milestones Achieved*: At end of Y4Q4.*

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

50% Milestone Achieved*: 47 experiments were completed prior to April 2019, but further delay has resulted due to the COVID-19 pandemic and revision required by the MRDC IRB for review and approval of a newly submitted LBNP SOP protocol designed to replace the original LBNP protocol (M-10138). The new LBNP SOP protocol (called the 'LBNP Reference' protocol USAISR #H-22-007) has been completed and approved by the MRDC IRBO. In order to complete Specific Aim 2 with an adequate number of human experimental data, additional experiments using the exact same LBNP protocol were conducted on 80 human subjects in the LBNP laboratory at the Mayo Clinic under the supervision of Drs. Michael Joyner and Tim Curry. Completion of Specific Aim 2 awaits the transfer and analysis of the additional 160 blood samples by the WRAIR Medical Readiness Systems Biology laboratory under the supervision of Dr. Rasha Hammamieh.*

Specific Aim 3: Determine the relationship between the physiological assessment (CRM algorithm, aim 1) and patient prognosis and guided intervention over the course of clinical observation

100% Milestone Achieved*: Data obtained from 5 clinical studies are completed with the publication of 7 papers in peer-reviewed journals (see Specific Aim 3, Major Task 3 above) that allowed for clinical CRM validation across 4 different patient populations (i.e., sepsis in the ER, sepsis with burn injury, hemorrhage caused by trauma, severe blood loss during liver transplant). Due to unanticipated quality compromise with art line signals, the data from this broad spectrum*

of clinical studies will suffice to meet the Specific Aim objective for CRM validation using clinical data and replace the original proposed data collection limited to only cardiac surgery patients.

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

Briefing presented to the Assistant Secretary of Preparedness and Response at the U.S. Department of Health & Human Services Critical Care Innovation Forum: "The Compensatory Reserve for Early Diagnosis of Shock". Wash, DC. November 2019

Seminar presented to the National Institute of Biomedical Imaging & Biotechnology: "Smart Monitoring is Not About Monitoring: It's About Physiology!" Bethesda, Maryland. November 2019

Lecture presented at the East Central Mississippi Trauma Care Region Symposium: "New Approaches to the Early Diagnosis and Treatment of Shock". Meridian, Mississippi. December 2019

Virtual panel presentation to the Excellence in Cardiovascular Sciences (EICS) ENGAGED Summer Research Program: "Career Paths in Industry, Government and Academia". July 2020

Virtual panel presentation to the Wake Forest School of Medicine Summer Intern Career Program: "Overview of Department of Defense Careers in Research". July 2020

Virtual seminar presentation given to the US Army Combat Capabilities Development Command (DEVCOM) with new CRM algorithm results: "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 to the Institute of Electrical & Electronic Engineers International Conference on Biomedical and Health Informatics Wearable & Implantable Body Sensor Networks: "Accurate Decision Support for Patients Suffering with Hemorrhage: It's not about Monitoring – It's about Physiology. July 2021.

Virtual guest presentation with new CRM algorithm results to the Trauma Hemostasis & Oxygenation Research (THOR) International Group Blood Chat: "Monitoring Shock". September 2021.

Panel talk presented at the AI/ML in Healthcare Symposium hosted by the University of Pittsburg Center for Military Medicine Research: "DOD needs for AI in Healthcare". Pittsburgh, Pennsylvania, May 2022

Virtual Keynote Speech presented at the Oak Ridge Institute for Science and Education (ORISE) Career Fair: "Career Paths in Translational Medicine: Recognizing and Leveraging Unique Career Opportunities". January 2023.

How were the results disseminated to communities of interest?

Results from this project were disseminated to scientific and clinical communities through publication in peer-reviewed journals (refer to list of publications under Specific Aim 3, Major Task 3). In addition, results were presented on virtual and in-person meeting platforms such as the annual Military Health System Research Symposium (MHSRS), American Physiological Society (APS) Summit, and the Trauma, Hemostasis & Oxygenation Research (THOR) international network meeting.

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

- *Supervise and coordinate the research team to assure the completion of analysis of blood samples collected for comprehensive multi-omic analyses to be performed by the Medical Readiness Systems Biology laboratory to determine molecular signatures of blood loss tolerance*
- *Supervise the application of the CRM algorithm to continue retrospective analysis of arterial waveforms collected during clinical studies on patients undergoing cardiac surgery at Mayo Clinic for transfer and testing of the SPPDG CRM algorithm for verification and validation in patients with arterial catheters*

4. IMPACT:

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

The development and clinical validation of the CRM algorithm for measuring compensatory reserve has provided new insight into the basic physiology that underlies monitoring patients and combat casualties with severe blood loss due to traumatic injury. The results from this CDMRP funded project delivered the first and only breakthrough medical monitoring technology capable of providing early prediction that a bleeding patient is about to experience circulatory shock. This technology resulted in 50% less time required by combat medics to recognize a bleeding casualty [see publication #2], a result that demonstrates life-saving potential of this monitoring capability. When applied to patients who suffer from low circulating blood volume, this new monitoring technology outperformed all currently used standard monitoring methods with greater accuracy. With the completion of the multi-omic blood sample analysis, we will be the first to be able to identify individuals who are at greatest risk for experiencing the onset of circulatory shock by their genetic profile.

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 a variety of clinical disciplines. This breakthrough technology can enhance skills of emergency medical personnel to prioritize triage and save lives by having access to a capability that provides earlier and more accurate identification of a bleeding patient. 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*
- *Masimo 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*
- *Oak Ridge Institute for Science and Education (ORISE)*
- *University of Pittsburg Center for Military Medicine Research*
- *Institute of Electrical and Electronic Engineers*
- *Wake Forest School of Medicine Summer Intern Career Program*
- *East Central Mississippi Trauma Care Region*

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. Also, as a result of this project, the PI is a joint patent owner with full government purpose rights to work with ZOLL Medical Corporation engineers under a CRADA to integrate the CRM algorithm onto the ZOLL commercially available Propaq® M vital signs monitor which is 510(k) FDA cleared (K180482) in the U.S. The Propaq® M currently provides all the capabilities required to deliver a comprehensive hypovolemia detection solution by integrating the CRM algorithm software into the base monitor. Rugged & lightweight, the Propaq® M is specifically designed for the rigors of military and aeromedical operations, which opens the door for implementing the CRM algorithm on approximately 7,000 existing Propaq-deployed devices by the Government in Roles 2 through 5 environments through

a software upgrade; no hardware modifications are required. Integration of the CRM algorithm will be submitted as a software update to the FDA for 510(k) clearance. Once approved, the Government may purchase and use the device for its purposes with eventual marketing to the civilian sector.

What was the impact on society beyond science and technology?

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. Most significantly, the PI has presented numerous in-service lectures on a national level 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:

Changes in approach and reasons for change

1) Although significant progress has been made in the execution of the project, the number of USAISR LBNP experiments conducted in Y1Q1 through Y4Q4 has been dramatically reduced from the target number of 150 to completion of only 47 experiments, putting both the LBNP and multi-omic analysis of blood samples portions of the project significantly behind schedule. This situation is the direct result of the closing of all laboratory facilities at the USAISR due to the COVID-19 pandemic. However, the collaborative work conducted at the Mayo Clinic resulted in an additional 80 human experiments that will provide an adequate sample size to allow for completion of the multi-omic work.

2) Although a new LBNP Standard Operating Procedure (SOP) protocol for LBNP experiments to be conducted at the USAISR has been completed, the plans for execution of further LBNP studies have been abandoned given the LBNP experiments and blood samples collected at Mayo Clinic.

3) A supplemental protocol to allow for analysis of blood samples collected at the Mayo Clinic has been submitted to the WRAIR IRB for review and approval. It is anticipated that this review process may require 3 to 4 weelks (i.e., fourth quarter of FY23). Once approved, sample analysis for genetic identification of individuals with high and low tolerance to reduced central blood volume similar to hemorrhage (Specific Aim 2) can be continued and completed.

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

Pending WRAIR IRB approval of the protocol that will allow blood samples to be received from Mayo Clinic, no further problems that might impede completion of the project are anticipated.

Changes that had a significant impact on expenditures

The USAISR has undergone a significant re-organization of the Research Directorate under a new Research Director. Although these changes are designed to improve the overall personnel and function of the BHT CHIP human physiology research laboratory that is instrumental in supporting this project, these changes have created significant delay in the ability to execute any new experiments to meet the updated target completion date of Y4Q4 followed by a 1-year NCE. This situation has been confounded by the expiration of CDMRP funding at the end of FY21 in the absence of replacement funding. Finally, the continued closing of all human research activities at the USAISR from Y1Q3 through Y3Q3 due to the COVID-19 pandemic has significantly delayed the completion of the project past the projected end of Y4Q4 (i.e., end of FY22). As such, a no-cost extension for FY23 is required to allow for completion of the project.

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

TOTAL PROTOCOL(S): Two (2) human subject research protocols will be required to complete the Statement of Work.

PROTOCOL (1 of 2 total):
IRB Protocol Number: Standard Operating Procedure (M-10973)
HRPO Protocol Number: Not assigned.
Protocol PI: Victor A. Convertino, Ph.D.
Site: US Army Institute of Surgical Research
Title: Reference Protocol to Support using Lower Body Negative Pressure to Study the Physiology of the Compensatory Stage of Progressive Hemorrhage to the Point of Hemodynamic Instability in Humans

SUBMITTED TO AND APPROVED BY:

- With the annual continuing review, the MRDC IRB recommended approval with a revision of the previously approved protocol (M-10138) as a new SOP protocol reviewed by USAMRDC IRBO on 10 May 2022. Final IRB approval by USAMRDC HRPO has been granted as a result of SOP completion.
- A protocol to allow for analysis of the 160 blood samples collected from 80 human subjects by the Mayo Clinic has been submitted to the WRAIR IRB by Dr. Hammamieh and is currently undergoing review for approval.

STATUS:

(i) *Report progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed:*

- Number of subjects recruited/original planned target: 47/150
- Number of subjects screened/original planned target: 47/150
- Number of patients enrolled/original planned target: 47/150
- Number of patients completed/original planned target: 47/150

Note: no progress has been made during Y4Q1 through Y4Q4 due to the re-review and approval process for MRDC Protocol M-10973. Principal investigator responses to the MRDC IRB audit for a LBNP protocol deviation of M-10138 has been completed and accepted by the MRDC IRB. The BHT CHIP laboratory is currently being prepared to re-open for continued experimentation. In order to complete all experimentation, a request for a new no-cost extension for completion of Specific Aims 2 and 3 has been submitted.

(ii) *Report amendments submitted to the IRB and USAMRDC HRPO for review: 14 since the initial submission in 2011. Eight since the initiation of the current project.*

(iii) *Report any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: NONE*

PROTOCOL (2 of 2 total):
IRB Protocol Number: 19-002695
HRPO Protocol Number: Contract # N0001419C2017, PR # 1300758814
Protocol PI: Timothy B. Curry, M.D., Ph.D.
Site: Mayo Clinic
Title: Physiology of the Early Stage of Hemorrhage and Early Identification of Progression toward Hemodynamic Instability in Humans for Validation of Current Machine Learning Models
Target required for clinical significance: 80
Target approved for clinical significance: 80

SUBMITTED TO AND APPROVED BY:

- Protocol status: IRB Approved
- Submitted to IRB for review: March 23, 2018
- Approved by IRB, 5 November 2018
- Submitted to ONR HRPO: April 19, 2021
- Approved by ONR HRPO: April 22, 2021

STATUS:

(i) *Report progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed:*

- Number of subjects screened/original planned target: 80/80
- Number of patients enrollment/original planned target: 80/80
- Number of patients completed/original planned target: 80/80

(ii) *Report amendments submitted to the IRB for review:*

- N/A.

(iii) *Report any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:*

- N/A.

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. *Convertino VA, Schauer SG, Weitzel EK, Cardin S, Stackle ME, Talley MJ, Sawka MN, Inan OT. Wearable sensors integrated with compensatory reserve monitoring in critically injured trauma patients. Sensors 20(22): 6463, 2020*
2. *Koons NJ, Owens GA, Parsons DL, Schauer SG, Buller JL, Convertino VA. Combat medic testing of a novel monitoring capability for early detection of hemorrhage. J Trauma Acute Care Surg. 89:S146-S152, 2020*
3. *Koons NJ, Nguyen B, Suresh MR, Hinojosa-Laborde C, Convertino VA. Tracking DO_2 with compensatory reserve during whole blood resuscitation following controlled hemorrhage in baboons. Shock 53:327-334, 2020*
4. *Benov A, Brand A, Rosenblat T, Antebi B, Ben-Ari A, Amir-Keret R, Nadler R, Chen J, Chung KK, Convertino VA, Paran H. Evaluation of sepsis using compensatory reserve measurement: a prospective clinical trial. J. Trauma Acute Care Surg. 89:S153-S160, 2020*
5. *Convertino VA**,** Wampler MR, Johnson MC, Alarhayem A, Le TD, Nicholson S, Myers JG, Chung KK, Struck KR, Cuenca C, Eastridge BJ. Validating clinical threshold values for a dashboard view of the compensatory reserve measurement for hemorrhage detection. J. Trauma Acute Care Surg. 89:S169-S174, 2020*
6. *Convertino VA, Koons NJ, Suresh M. Physiology of human hemorrhage and compensation. Compr. Physiol. 11:1531-1574, 2021*
7. *Schauer SG, April MD, Arana AA, Maddry JK, Escandon MA, Linscomb C, Rodriguez D, Convertino VA. Efficacy of the compensatory reserve measurement in an emergency department trauma population. Transfusion 61:S174-S182, 2021*
8. *Convertino VA, Johnson MC, Alarhayem A, Nicholson SE, Chung KK, DeRosa M, Eastridge BJ. 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 61:S167-S173, 2021*
9. *Convertino VA, Techentin RW, Poole RJ, Dacy AC, Carlson AN, Cardin S, Haider CR, Holmes III DR, Wiggins CC, Joyner MJ, Curry TB, Inan OT. AI-enabled advanced development for assessing low circulating blood volume for emergency medical care: comparison of compensatory reserve machine-learning algorithms. Sensors 22, 2642, 2022*
10. *Koons NJ, Moses CD, Thompson P, Strandenes G, Convertino VA. Identifying critical DO_2 with compensatory reserve during simulated hemorrhage in humans. Transfusion 62:S122-S129, 2022*
11. *Ciaraglia AV, Convertino VA, Johnson MC, Nicholson SE, DeRosa M, Eastridge BJ. Compensatory reserve and pulse character: enhanced potential to predict urgency for transfusion and other life-saving injuries after traumatic injury. Transfusion 62:S130-S138, 2022*
12. *Convertino VA, Cardin S. Advanced medical monitoring for the battlefield: a report on clinical data that verify compensatory reserve measurements for early*

and accurate hemorrhage detection. J Trauma Acute Care Surg. 93:S147-S154, 2022

13. *Convertino VA, Wagner A, Akers KS, VanFosson CA, Cancio LC. Early identification of sepsis in burn patients using compensatory reserve measurement: a case series pilot study. Burns 6:137-145, 2022*
14. *Gupta JF, Telfer BA, Convertino VA. Importance of feature analysis for compensatory reserve measurement to predict hemorrhagic shock. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. 2022:1747-1752, 2022*
15. *Gupta JF, Arshad SH, Telfer BA, Snider EJ, Convertino VA. Noninvasive monitoring of simulated hemorrhage and whole blood resuscitation. Biosensors 22, 2642, 2022*
16. *Ciaraglia AV, Convertino VA, Wang H, Cigarroa F, Thomas E, Fritze D, Nicholson SE, Stewart R, Eastridge BJ. Intraoperative use of compensatory reserve measurement (CRM) in orthotopic liver transplant: improved predictor for hypovolemic events. Milit Med. 2023 (in press).*

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

Convertino VA, Inan OT, Cardin S (editors). AI-enabled Sensor-related Technologies for Physiological Monitoring Designed to Advance Emergency Medical Care. Biosensors (ISSN 2079-6374)/Sensors (ISSN 1424-8220) Special Issue. Basel, Switzerland: MDPI Publishers, 2022 (published; federal support acknowledged - no).
https://www.mdpi.com/topics/AI_Sens_phy_emer

Convertino VA, Koons NJ. Autonomic response to hypovolemic shock. In: Biaggioni I, Browning K, Fink G, Jordan J, Low PA, Paton JFR (eds.). Primer on the Autonomic Nervous System, Fourth Edition. Chapter 55. San Diego: Elsevier Inc./Academic Press, 2023, pp. 309-314 (published; federal support acknowledged - yes).

Other publications, conference papers and presentations.

*1) "Identifying critical DO_2 with compensatory reserve during simulated hemorrhage in humans." Poster presented at the Experimental Biology Annual Meeting, Philadelphia, Pennsylvania, 2022 (international meeting) **

*2) "Identifying critical DO_2 with compensatory reserve during simulated hemorrhage in humans." Podium talk presented at the Military Health and Science Research Symposium, Kissimmee, Florida, 2022 (military meeting) **

3) "DOD needs for AI in Healthcare." Panel talk presented at the AI/ML in Healthcare Symposium hosted by the University of Pittsburg Center for Military Medicine Research, Pittsburgh, Pennsylvania, May (military meeting) 2022

4) "Career Paths in Translational Medicine: Recognizing and Leveraging Unique Career Opportunities." Virtual Keynote Speech presented at the Oak Ridge Institute for Science and Education (ORISE) Career Fair, January 2023 (national meeting)

*5) "Superiority of compensatory reserve measurement compared to the shock index for early and accurate detection of reduced central blood volume status". Poster presented at the American Physiology Society Summit, Long Beach, California, 2023 (international meeting) **

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

This CDMRP funded project resulted in a novel breakthrough medical monitoring technology that provides for the first time a clinical technique that leads to early prediction of the onset of circulatory shock in a bleeding patient based on continuous moment-to-moment analysis of arterial waveform features that can be obtained noninvasively from a simple pulse oximeter.

- **Inventions, patent applications, and/or licenses**

*Development of the CRM algorithm has resulted in US Patent Application No. 16/934,805 entitled "Systems, Methods and Media for Estimating Compensatory Reserve and Predicting Hemodynamic Decompensation Using Physiological Data". Techentin RW, Curry TB, Joyner MJ, **Convertino VA**, Holmes DR III, Haider CR, Felton CL, Gilbert BK, Van Dorn CS, Carey WA are listed as co-inventors.*

- **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 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?

Name:	Dr. Victor Convertino
Project Role:	Principal Investigator at USAISR
Nearest person month worked:	3
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:	Dr. Taylor Schlotman
Project Role:	Co-Investigator at USAISR

Nearest person month worked:	3
Contribution to Project:	Dr. Schlotman served as the assigned operator of the LBNP system for execution of the 47 LBNP experiments in which blood samples were collected from the 47 subjects who participated in the multi-omics experiments. She also was responsible for preparation of all methodologies for data collection in the USAISR BHT CHIP laboratory.
Name:	Ms. Natalie Koons
Project Role:	Graduate Student Intern at USAISR
Nearest person month worked:	1
Contribution to Project:	Ms. Koons has contributed to the development and practice of the LBNP protocol and assisted with preparation of methodologies for data collection. Although currently attending medical school, she has continued to contribute to data analysis, interpretation of results, and writing of manuscripts.
Name:	Dr. Rasha Hammamieh
Project Role:	Director, Systems Biology Group at USACEHR
Nearest person month worked:	0
Contribution to Project:	Dr. Hammamieh's laboratory is currently performing the comprehensive multi-omic analyses of blood samples collected during the LBNP experiments conducted at USAISR and Mayo Clinic.
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. David Holmes
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Nearest person month worked:	1
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. She was also responsible to oversight of blood sampling before and after LBNP.
Funding Support:	CDMRP Funding

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 change to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

Updated Quad Chart is also included as a separate PowerPoint file.

9. APPENDICES:

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

CDRMPL-18-0-DM180240 / DM180240

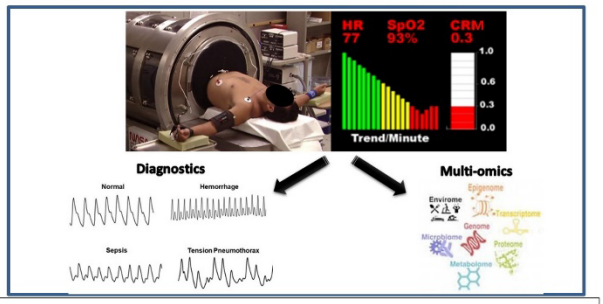
PI: Victor A. Convertino **Org:** US Army Institute of Surgical Research **Award Amount:** $2,032,601

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	22	23
Algorithm Development & Testing						
Experimental Data Collection & Multi-omics Analysis						
Clinical Data Collection & Analysis						
Complete data collection & analysis, Interpret/publish findings						
Estimated Budget ($K)		760	705	568	NCE	NCE

Updated: 31 Oct 2023

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 data on patients for algorithm clinical validation
- ☑ 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; Validate CRM algorithm for triage capabilities

FY22-23 Goals–Continue data collection and analysis, interpret/publish findings

- ☐ Complete multi-omics blood sample analyses
- ☐ Analyze findings and publish results

Budget Expenditure to Date

Projected Expenditure: $2,032,601 Actual Expenditure: $2,032,601