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

PRINCIPAL INVESTIGATOR: Victor A. Convertino

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

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Victor A. Convertino, PhD

E-mail: victor.a.convertino.civ@mail.mil

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

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:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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) 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: In an effort to provide an adequate number of waveform signals for algorithm validation testing, data collection was expanded from three to five clinical case series 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) 100 patients who underwent cardiac surgery.

100% Milestone Achieved: Data sets for cardiac surgery patients have been obtained as part of the CDMRP funding support and collaboration with the Special Purpose Processor Development Group at the Mayo Clinic, and preliminary analysis has been completed. Results are being used to update and refine the compensatory reserve measurement (CRM) algorithm. A manuscript will be written and submitted for publication as a final report.

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 completed 47 of the originally proposed 150 LBNP experiments, but the remaining 103 experiments were suspended due to laboratory shutdowns during COVID-19 and the subsequent termination of funding to the USAISR after FY21. In an effort to complete this important part of the project, the staff at the Mayo Clinic Human Physiology Laboratory under the direction of Dr. Michael Joyner obtained IRB approval to conduct LBNP experiments in which blood samples were collected on 80 volunteers using the same LBNP protocol conducted on the initial 47 subjects at USAISR. The samples are being sent from Mayo Clinic to the Medical Readiness Systems Biology Laboratory (MRSBL) at the Walter Reed Army Institute of Research (WRAIR) under a CRADA for genome analysis under the direction of Dr. Rasha Hammamieh. The combination of genome samples from the USAISR and Mayo Clinic will provide a final data set of 127 subjects, a sample size adequate for meeting the statistical requirements of the multi-omic determination of molecular signatures of blood loss tolerance. A No Cost Extension (NCE) is required for Dr. Hammamieh's lab to analyze these samples allowing for completion of work associated with more than $ of invested CDMRP funds.

Subtask 1: Submission, review, and approval for new LBNP experiments and blood collection to be conducted on healthy humans at the Mayo Clinic LBNP Laboratory have been completed by the Human Research Protection Office (HRPO).
The Office of Naval Research (ONR) HRPO conducted a review and subsequently approved the LBNP protocol to be used at the Mayo Clinic in support of the multi-omics project. As a result of conducting 80 experiments at Mayo Clinic, there is no longer a need to pursue continuing review and approval of the originally proposed LBNP experiments at USAISR.

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

Currently, experiments have been completed with the generation of 254 blood samples collected from 127 human subjects (47 subjects at USAISR and 80 subjects at Mayo Clinic). This sample size will be adequate for meeting the statistical requirements of the multi-omic determination of molecular signatures of blood loss tolerance. In order to provide approved administrative support for completion of the genomic analyses, a one-year no-cost extension (NCE) is requested.

Major Task 2: Analysis of blood samples collected during LBNP experiments.

90% Milestone Achieved: 94 blood samples collected from 47 subjects at USAISR have been analyzed by the Medical Readiness Systems Biology laboratory at the WRAIR. Blood sample analysis of 160 additional samples collected from 80 subjects who participated in Mayo Clinic LBNP experiments is required to complete Specific Aim 2 of the project.

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

90% Milestone Achieved: Ongoing pending completion of multi-omics blood sample analysis and arterial waveform feature analysis of electronic analog signals collected from cardiac surgery patients.

Major Task 3: Write manuscripts.

90% Milestones Achieved by the end of Y4Q4. The following manuscripts have been written, submitted to journals, and published (note: those publications highlighted in red were published or accepted for publication during the current reporting period):

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).

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.

100% Milestones Achieved before or by the end of Y2Q4. The proposed machine learning algorithm for measurement of the compensatory reserve (CRM) was completed. A Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) of 0.9268 (0.0059, 95% CI = 0.915–0.938) for sensitivity and specificity of the Mayo Clinic CRM algorithm was slightly higher (P = 0.104) than the 0.9164 (MSE = 0.0066, 95% CI = 0.903–0.929) ROC AUC generated from the FDA-approved Flashback Technologies CRI algorithm, indicating the successful completion for development of the CRM.

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

STATUS: 90% complete – 47 experiments were completed prior to April 2019, but further delay in execution of Specific Aim 2 at USAISR resulted due to two major events: 1) the COVID-19 pandemic that required closure of all human research activities for 2+ years; and 2) protocol revision required for review and approval by the MRDC IRB of a newly submitted LBNP Standard Operating Procedure (SOP) designed to replace the original LBNP protocol (M-10138). The new LBNP SOP protocol (USAISR Protocol #H-22-007) was submitted to the MRDC IRBO on 8 Feb 2022 with a newly drafted 'supplemental' protocol that would allow for blood samples to be collected before and immediately after LBNP exposure. Support for continuation of LBNP experiments under Specific Aim 2 has been suspended at USAISR due to unavailability of funding but was resumed with the successful completion of 80 LBNP experiments conducted at the Mayo Clinic. Final completion of Specific Aim 2 awaits approval of a NCE so that blood samples can be analyzed by the Medical Readiness System Biology laboratory at WRIAR for genetic expressions.

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

STATUS: 100% Milestone Achieved: Data obtained from 8 clinical studies are completed with the publication of 8 papers in clinical peer-reviewed journals (see references 4, 5, 7, 8, 11, 12, 13 and 16 under Specific Aim 3, Major Task 3 above).

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

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?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

- *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:** D*escribe 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 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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 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?
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. 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:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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.

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.
2) The re-opening of the USAISR LBNP laboratory did not occur until after the POP. Consequently, support for continuation of LBNP experiments under Specific Aim 2 has been suspended at USAISR due to unavailability of funding.

3) In an effort to complete Specific Aim 2, Mayo Clinic has agreed to collect blood samples for multi-omic analysis from 80 LBNP experiments conducted under their independent IRB-approved protocol (IRB Protocol Number 19-002893) using the same CDMRP project LBNP protocol profile to add to the results obtained in the initial 47 USAISR subjects.
4) Final completion of Specific Aim 2 awaits approval of a NCE so that blood samples collected at the Mayo Clinic can be sent under an approved Material Transfer Agreement (MTA #22-0328) to the Medical Readiness System Biology (MRSB) laboratory at WRIAR for analysis of genetic expressions.

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.

Potential delay in completing Specific Aim 2 for multi-omic analysis of blood samples being sent from the Mayo Clinic to the MRSB laboratory at WRAIR awaits approval of an NCE.

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.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Since there were no experiments conducted at USAISR since the laboratory closure during COVID-19 pandemic, there were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects during the reporting period.

The following details are provided for the 80 LBNP experiments conducted at Mayo Clinic during this reporting period:
IRB Protocol Number: 19-002893
HRPO Protocol Number: 19-002893
Protocol PI: Timothy B. Curry, M.D., Ph.D.
Site: Mayo Clinic
Title: Physiological Validation of Current Machine Learning Models for Hemodynamic Instability in Humans
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 3, 2021*
- *Approved by IRB, March 23, 2021*
- *Submitted to Navy HRPO: April 19, 2021*
- *Approved by Navy HRPO: April 22, 2021*

STATUS:
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*

Note: 80 LBNP experiments were conducted during Y3Q3-Y4Q1 that allowed for the collection of blood samples at rest and following LBNP that induced hemodynamic decompensation.

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:** *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. *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).*

Note: those publications highlighted in red were published or accepted for publication during the current reporting period:

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. *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, 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. *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) "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)**
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. Describe the technologies or techniques were shared.

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**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. 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.

*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**

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. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*

- *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".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Dr. Victor Convertino
Project Role:	Principal Investigator at USAISR
Researcher Identifier (e.g. ORCID ID):	0000-0001-9246-0554
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 MRSB collaborators, conducted staff training, and supervised LBNP experiments
Funding Support:	USAISR Core Funding
Name:	Ms. Denise Woods
Project Role:	BHT CHIP Lab Research Assistant at USAISR
Researcher Identifier (e.g. ORCID ID):	None
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.
Funding Support:	CDMRP Funding
Name:	Ms. Natalie Koons
Project Role:	Graduate Student Intern at USAISR
Researcher Identifier (e.g. ORCID ID):	0000-0003-1928-4632
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.
Funding Support:	CDMRP Funding
Name:	Dr. Rasha Hammamieh
Project Role:	Director, Medical Readiness Systems Biology Laboratory at WRAIR
Researcher Identifier (e.g. ORCID ID):	0000-0001-8643-6232
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. Her lab will also perform multi-omic analyses of blood samples provided by the Mayo Clinic.
Funding Support:	CDMRP Funding
Name:	Dr. Clifton Haider
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Researcher Identifier (e.g. ORCID ID):	0000-0002-5869-432X
Nearest person month worked:	3
Contribution to Project:	Dr. Haider has led the Mayo Clinic SPPDG effort to develop the CRM algorithm
Funding Support:	CDMRP Funding
Name:	Dr. David Holmes
Project Role:	Biomedical Engineer/Computer Scientist at Mayo Clinic
Researcher Identifier (e.g. ORCID ID):	Unknown
Nearest person month worked:	1
Contribution to Project:	Dr. Holmes has performed verification and validation testing on the early generations of the CRM algorithm
Funding Support:	CDMRP Funding
Name:	Dr. Michael Joyner

Project Role:	Anesthesiologist/Collaborating Investigator at Mayo Clinic
Researcher Identifier (e.g. ORCID ID):	0000-0002-7135-7643
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
Funding Support:	CDMRP Funding
Name:	Dr. Tim Curry
Project Role:	Anesthesiologist/Collaborating Investigator at Mayo Clinic
Researcher Identifier (e.g. ORCID ID):	0000-0001-5327-9525
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
Funding Support:	CDMRP Funding
Name:	Ms. Shelly Roberts
Project Role:	Research Nurse at Mayo Clinic
Researcher Identifier (e.g. ORCID ID):	None
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
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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

No change to report

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

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

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

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

CDRMPL-18-0-DM180240 / DM180240

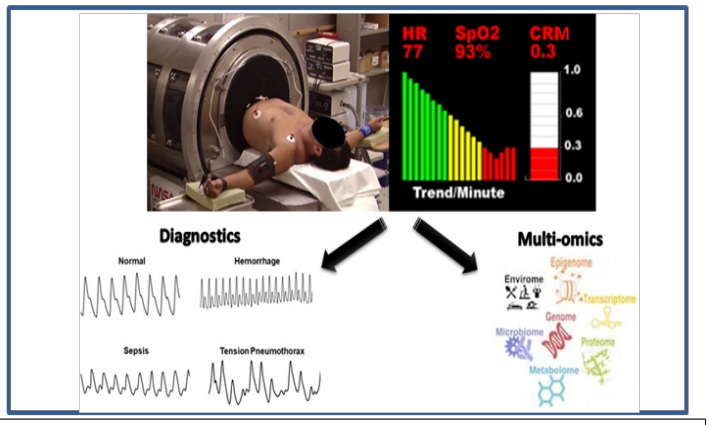
PI: Victor A. Convertino **Org:** US Army Institute of Surgical Research **Award Amount:** $2,032,601

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	0	0

Updated: 30 January 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 capabilites
- ☑ 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.*