AWARD NUMBER: CDMRPL-16-0-DM167102

TITLE: Evaluation of Hypotensive Resuscitation +/- Aeromedical Evacuation and the Effects of Oxygen Therapeutics During Prolonged Field Care in a Swine Polytrauma Model

PRINCIPAL INVESTIGATOR: Dr. Anke H. Scultetus

CONTRACTING ORGANIZATION: Naval Medical Research Center Grant
Silver Spring, MD 20910

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6. AUTHOR(S)
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503 Robert Grant Avenue

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In light of the potential for future conflicts in parts of the world where immediate evacuation of combat casualties might not be possible, research is needed to address knowledge gaps during prolonged field care and its effects on subsequent long range patient transport to definitive care. For example, there is no data available about the impact of prolonged hypotensive resuscitation on vital organ function in TBI and polytrauma patients. Novel resuscitation fluids that might provide efficient oxygenation to vital tissue beds in the PFC environment need to be assessed for efficacy, as they may improve pre-hospital care and subsequent outcome of combat casualties. The knowledge gained will be used to optimize care provided to our wounded service members as they are moved through the en route system. The proposed research will provide needed data on the impact of prolonged hypotensive resuscitation for 72 hours on neurotrauma and polytrauma casualties and identify possible safety risks associated with aero-medical evacuation of patients. It also assesses whether or not hypotensive resuscitation is actually the best modality (compared with normotensive) in this PFC scenario. This study will directly address improvement of combat casualty safety, morbidity and mortality.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified		

TABLE OF CONTENTS

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

The objective of this study is to confirm our hypotheses related to the possible adverse effects of Prolonged Field Care (PFC) and aeromedical evacuation (AE) on polytrauma patients, and to evaluate if the use of an Oxygen Therapeutic (OT) during PFC can improve oxygenation and outcomes. We will test this hypothesis in a swine polytrauma model. Data from this study could potentially aid in the improvement of safety recommendations for prolonged field care, en route care, and aeromedical evacuation of combat casualties.
Specific aims:
This study aims at addressing the following research questions:
1) How does prolonged hypotensive resuscitation over 72 hours affect physiology and neurophysiology in polytrauma casualties?
2) What are the effects of transport/aeromedical evacuation after prolonged hypotensive resuscitation on physiology and neurophysiology in polytrauma casualties?
3) Does an OT improve systemic and cerebral oxygen delivery under conditions of prolonged hypotension in polytrauma patients?

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

Prolonged field care; hypotensive resuscitation; hemorrhagic shock; aeromedical evacuation; oxygen therapeutics

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.

	Timeline	**NMRC Status**	**USUHS Status**
1) Specific Aim 1: Determine effects of 72-h prolonged hypotensive resuscitation (PHR) on physiology/ neurophysiology in swine polytrauma model.			
Major Task 1: Obtain regulatory approvals (IACUC/ACURO) [for all 3 Phases]	Months		
Subtask 1: write/submit/obtain approval - IACUC protocol	1-2	Complete	-
Subtask 2: Submit animal protocol to ACURO and obtain approval	2-3	Complete	-
Milestone(s) Achieved: obtained IACUC and ACURO approvals	*3*	Complete	

	Timeline	NMRC Status	USUHS Status
Major Task 2: Perform pilot study – optimize PHR swine model			
Subtask 1: determine optimal PHR experimental conditions for 77-h swine study	4-8	Complete	-
Subtask 2: prepare team for prolonged experiments	4-8	Complete	-
Subtask 3: Phase 1 histopathology & immunohistopathology preparation/analysis	4-10	Ongoing	
Milestone(s) Achieved: Swine model optimized.	*10*	Complete	
Major Task 3: Perform Phase 1 experiments – determine safety/efficacy of PHR vs prolonged hypotensive			
Subtask 1: perform Phase 1 in-life experiments	8-18	ongoing	-
Subtask 2: Phase 1 histopathology & immunohistopathology	8-20	ongoing	
Milestone(s) Achieved: completed Phase 1 experiments.	*20*	ongoing	
2) Specific Aim 2: Determine effects of aeromedical			
Major Task 4: Perform Phase 2 experiments – determine safety/efficacy of AE following PHR/PNR.			
Subtask 1: perform Phase 2 in-life experiments	18-26		-
Subtask 2: Phase 2 histopathology & immunohistopathology preparation/analysis	18-28	-	
Milestone(s) Achieved: completed Phase 2 experiments.	*28*		
3) Specific Aim 3: Determine effects of adding an oxygen therapeutic (OT) to PHR regimen on physiology/and neurophysiology in swine polytrauma model.			
Major Task 4: Perform Phase 3 experiments – determine safety/efficacy of including OT in PHR/PNR.			
Subtask 1: perform Phase 3 in-life experiments	26-32		-
Subtask 2: Phase 3 histopathology & immunohistopathology preparation/analysis	26-34	-	
Milestone(s) Achieved: completed Phase 3 experiments.	*34*		
Major Task 5: Final data analysis and writing Final Report and manuscripts for peer-review.			
Subtask 1: analyze data	8-36		
Subtask 1: write/submit Final Report	32-36		
Subtask 1: prepare/submit manuscripts	32-36		
Milestone(s) Achieved: completed data analysis, submitted Final Report, and prepared manuscripts	*36*		

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.

During this reporting period animal use protocol was approved by the WRAIR/NMRC institutional IACUC (08AUG2018, 17-OUMD23LS) and by ACURO (06SEP2018). We completed the pilot study to optimize the prolonged field care model and set up of the new invasive, continuous and remote blood pressure monitoring system (Transonic). We were able to validate this system against our state-of-the art invasive measurement system and non-invasive blood pressure measurement and initiated the actual experiment work on this project:

1) Initial experiments consisted in gaining knowledge on the software and data acquisition of the Transonic device. The placement of the probes and inplant inside the animal was delayed due to early defective probes. We were then able to establish a reliable probe and implant setting with calibrated material. We used a total of 6 animals for this phase.

2) Once this was achieved, we launched a pilot experiment in order to obtain hypotension after bleeding.

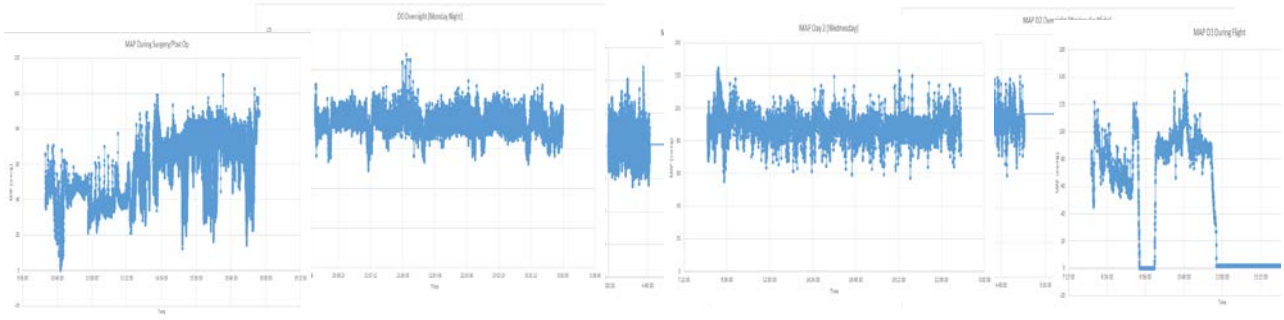
    a. A bleeding protocol was designed and an initial arterial hemorrhage of 30% estimated blood volume (EBV) fast bleed followed by a second venous bleed for slow hemorrhage of 20% EBV was tested for this protocol.
    b. The resuscitation consisted of one time 250 ml bolus of VetStarch (Hextend) 30 min after injury.
    c. On the third day, some animals underwent simulated trasnport at ground level (normobaria) or at 8000 ft (hypobaria).

    A series of 5 animals were used in this group.

3) The goal was to compare the Transonic probe reading for mean arterial pressure (MAP) with MAP measured with a non-invasive monitor and an invasive catheter in the femoral artery.

4) Results

a. Example of transonic data acquisition
b. Data were aquired every 400 sec, collected and transferred to an excel chart.

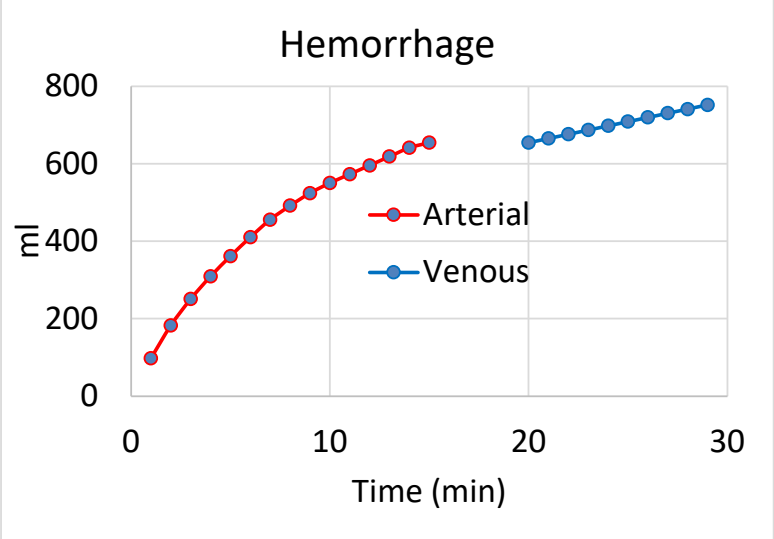


During Surgery Day 1 overnight Day 2 overnight During flight

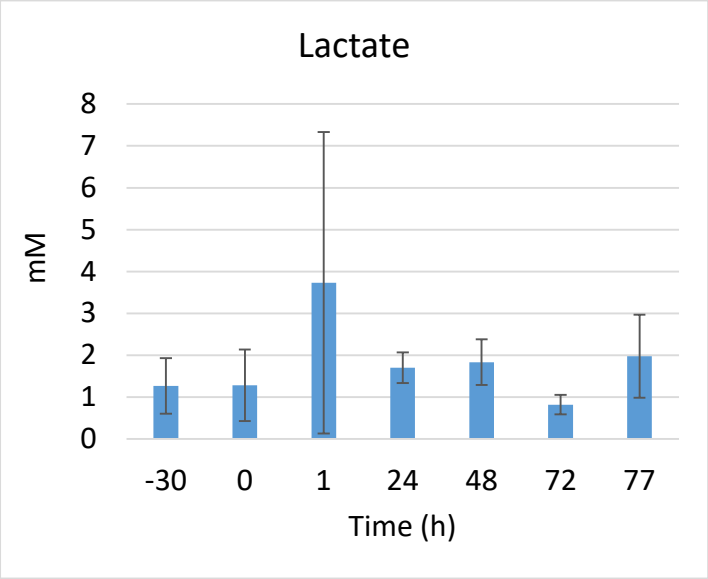
MAP decreased to ~25 mmHg and recovered to ~80 mmHg the following days.

During flight MAP initialy decreased during take off and stabilzed therafter.

c. Pattern of hemorrhage regimen

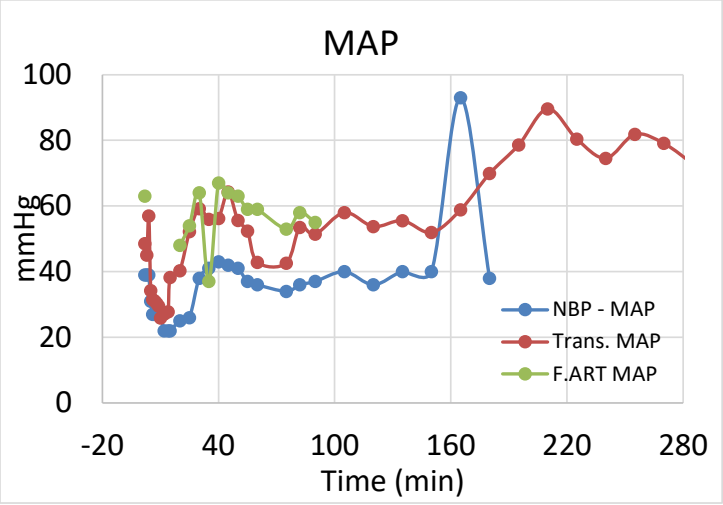


This regimen simulates an initial arterial fast bleed of 30% EBV followed by a continuous slow venous bleed of another 20% EBV. This was deemed to achieve a sustainable hypotensive MAP.

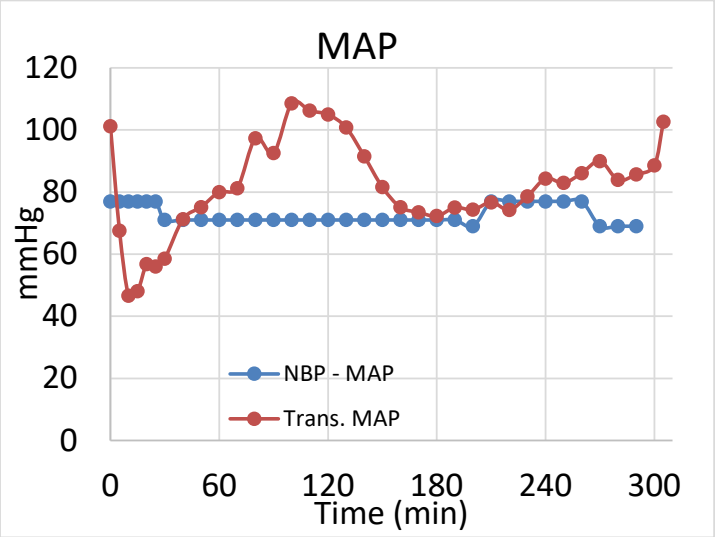


Example of lactate over time.

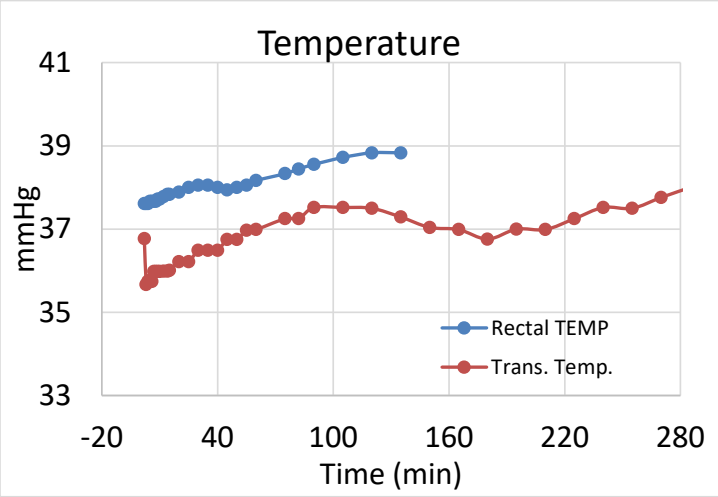
d. Comparison of MAP across different devices



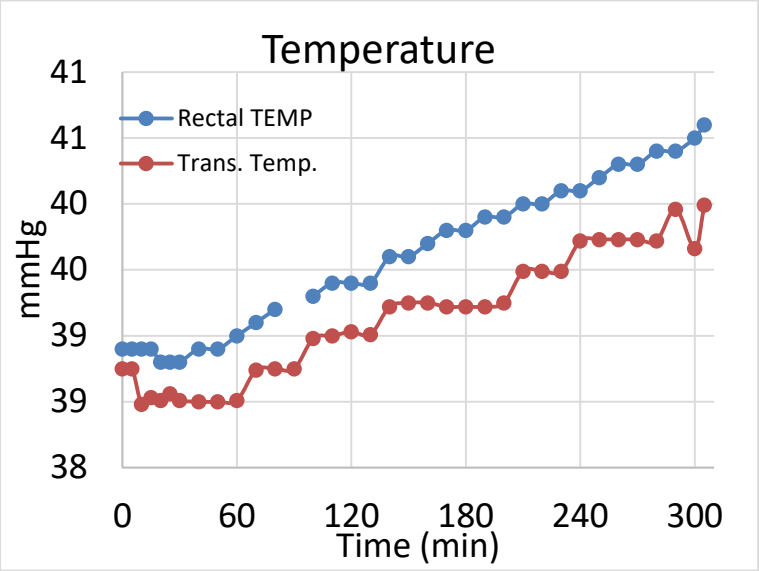
Example of MAP measured by non-invasive cuff (NBP - MAP), invasive femoral artery (F. ART MAP) and Transonic (Trans. MAP) during surgery. The actual MAP varies from devices and location but overall they indicated the same pattern when an event occurred.



Example of MAP measured by different devices during flight.



Example of Temperature measured at different locations during surgery. There was also a differential between temperature measured by a rectal probe and Transonic. Variation may account for the location of the probes (rectal vs vascular) and also the temperature at which the Transonic probe was calibrated.



Example of Temperature measured at different location during flight.

Conclusion: We have got familiar with the Transonic system and the pilots experiments seem to indicate that hypotension can be obtained only during the surgery phase. Intervention on the animal at a later may not be practical and should be limited to suboptimal conditions under prolonged field care.

Future experiments:

We will focus on further optimizing the hemorrhage and resuscitation regimen in austere/prolonged field acre conditions.

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.

This project so far provided several one-on-one training activities for new employees who will work as junior scientists or research assistants on this project. Through literature search and regular discussion groups within our team we were able to significantly increase their knowledge platform in regards to battlefield care, physiology and damage control resuscitation.

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.

Nothing to report.

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.

- Continue animal experiments

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).

Nothing to report.

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.

Nothing to report.

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.*

This project will likely have an impact on revisiting current practices in prolonged field care and possibly result in adoption of new practices. There is a dearth of knowledge on the feasibility and impact of prolonged hypotensive resuscitation for up to 72 hours and this study will provide much needed information to plan for future patient care scenarios.

- *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.*

Nothing to Report.

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:*

Nothing to report.

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.

N/A

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.

There was a delay in the animal protocol approval process in addition to an unanticipated personnel turnover. This did not result in any changes to the project. We will increase our weekly work load for the next reporting period.

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.

There were no changes that impacted expenditure during this reporting period.

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

N/A

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

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).*

Nothing to report.

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).*

Nothing to report.

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.*

Nothing to report.

- **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.

Nothing to report.

- **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.

Nothing to report.

- **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*
  - *other.*

Nothing to report.

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".

Personnel	Role	Person month worked
Dr. Anke Scultetus	PI	1
Col Debra Malone	AI	1
Noemy Carballo	Senior Research Assistant: animal	3
Dr. Francoise Arnaud	Scientist: project management	2
Dr. Yaron Dayani	Research Associate: data analysis	3
Kevin Flores-Castillo	Research Assistant: animal, data	2
Jordan Hubbell	Research Assistant: animal, data	2
Joel Duberstein	Research Assistant: animal, data	2
Michael Hammett	Research Assistant: hematology	2
William Porter	Chamber Operator	2
Andrea White	Research Assistant: animal, data	2
Fang Zhou Yang	Research Assistant: animal, data	2
Alexander Connor	Research Assistant: animal, data	2
Dr. Ye Chen	Scientist: molecular biology	2

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.

Nothing 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://ers.amedd.army.mil*** *for each unique award.*

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

Evaluation of hypotensive resuscitation ± aeromedical evacuation and the effects of oxygen therapeutics during prolonged field care in a swine polytrauma model

Prolonged Field Care Research Award Log Number: DM167102

PI: Anke H. Scultetus, M.D. **Org:** Naval Medial Research Center **Award Amount: $2,834K**

Study Aims

This proposal aims to:

- evaluate the effects of prolonged hypotensive resuscitation up to 72 hours during prolonged field care (PFC).
- evaluate the effects of aeromedical evacuation (AE) after PFC.
- evaluate the effects of oxygen therapeutics (OTs) on oxygen delivery to vital tissues.

Approach

We propose to investigate the clinical implications of PFC and hypotensive resuscitation and test next-generation resuscitation methods. Swine will undergo initial traumatic brain injury and hemorrhagic shock. They will then be kept under prolonged hypotensive resuscitation (PHT) for 72 h. In one study arm, animals will then also undergo aeromedical transportation in a hypobaric chamber to evaluate the effects of transport after PFC. Ina third arm, we will test the efficacy of an oxygen therapeutic on oxygen delivery to vital tissues during 72 h of PFC.

Rapid evacuation of combat casualties to CONUS is current standard. However, future conflicts might require prolonged field care for up to 72 h before casualties can be transported to a higher level of care.

Timeline and Cost

Activities	Y1	Y2	Y3
IACUC/ACURO approval			
Swine polytrauma PHR experiments			
Swine polytrauma PHR + AE experiments			
Swine polytrauma PHR + OT experiments			
Data analysis/manuscript/final report			
Estimated Budget ($K)	**991**	**907**	**937**

Updated: 09/09/2019

Goals/Milestones

Y1 Goals

X IACUC/ACURO protocol written, submitted and approved

X Initiate swine polytrauma experiments

Y2 Goals

X Continue swine polytrauma experiments

Y3 Goals

☐ Complete swine experiments

☐ Data analysis

☐ Manuscript preparation

☐ Final study report

Comments/Challenges/Issues/Concerns

- N/A

Budget Expenditure to Date

Projected Expenditure: $1898K

Actual Expenditure: $1898K

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.*