

AWARD NUMBER: W81XWH-19-2-0004

TITLE: Precision Metrics for Driving Open- and Closed-Loop Resuscitation Algorithms for Enteral and IV Resuscitation in Burn Casualties

PRINCIPAL INVESTIGATOR: Dr. David Burmeister

CONTRACTING ORGANIZATION: The Geneva Foundation

REPORT DATE: Jan 2020

TYPE OF REPORT: ANNUAL

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

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE Jan 2020		2. REPORT TYPE Annual		3. DATES COVERED 12/15/2018 - 12/14/2019	
4. TITLE AND SUBTITLE Precision Metrics for Driving Open- and Closed-Loop Resuscitation Algorithms for Enteral and IV Resuscitation in Burn Casualties				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-19-2-0004	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. David Burmeister E-Mail: david.m.burmeister3.civ@mail.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation 917 Pacific Ave., Ste. 600 Tacoma, WA 98402				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Formula-driven burn resuscitation may deliver too much fluid resulting in significant co-morbidities. An alternative strategy could be the use of enteral fluid resuscitation, which has been explored for decades. In line with this, recent fluid therapy recommendations from the prolonged field care working group only mention in brief that enteral fluids have been studied in burns up to 40% TBSA. In fact, while enteral fluids have been shown to reduce the volumes of IV fluids given, there is a paucity of information regarding fluid type, volumes, and efficacy. A recent randomized controlled trial continues to advocate for oral rehydration post-burn, but this strategy has largely been forgotten by current practice. In short, the need exists for a new personalized approach that incorporates new targets and endpoints for identifying which patients respond to resuscitation (both IV and enteral) versus those that do not. Burn resuscitation is not an exact science, and experienced providers supplement UO with static physiologic measurements (e.g., blood pressure, pulmonary arterial occlusion pressure, cardiac index, etc.). For IV resuscitation, a decision support system based on burn surface area and UO was developed at USAISR and has become commercially available. Both these static measurements as well as the dynamic ones listed above (PPV, SPV, SVV) could be incorporated into existing decision support system algorithms for identifying which patients respond to both enteral and IV fluids. The current proposal will characterize burn-induced changes in functional hemodynamic variables to determine new endpoints that will guide IV and enteral resuscitation.					
15. SUBJECT TERMS Burn, prolonged field care, urine output, arterial waveforms, intravenous resuscitation, endpoints, swine, crystalloid, colloid, third spacing					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified	9	USAMRMC
					19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Changes/Problems	7
6. Products	7
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	9

1. INTRODUCTION:

Formula-driven burn resuscitation may deliver too much fluid resulting in significant co-morbidities. An alternative strategy could be the use of enteral fluid resuscitation, which has been explored for decades. In line with this, recent fluid therapy recommendations from the prolonged field care working group only mention in brief that enteral fluids have been studied in burns up to 40% TBSA. In fact, while enteral fluids have been shown to reduce the volumes of IV fluids given, there is a paucity of information regarding fluid type, volumes, and efficacy. A recent randomized controlled trial continues to advocate for oral rehydration post-burn, but this strategy has largely been forgotten by current practice. In short, the need exists for a new personalized approach that incorporates new targets and endpoints for identifying which patients respond to resuscitation (both IV and enteral) versus those that do not. Burn resuscitation is not an exact science, and experienced providers supplement UO with static physiologic measurements (e.g., blood pressure, pulmonary arterial occlusion pressure, cardiac index, etc.). For IV resuscitation, a decision support system based on burn surface area and UO was developed at USAISR and has become commercially available. Both these static measurements as well as the dynamic ones listed above (PPV, SPV, SVV) could be incorporated into existing decision support system algorithms for identifying which patients respond to both enteral and IV fluids. The current proposal will characterize burn-induced changes in functional hemodynamic variables to determine new endpoints that will guide IV and enteral resuscitation.

2. **KEYWORDS:** Burn, prolonged field care, urine output, arterial waveforms, intravenous resuscitation, endpoints, swine, crystalloid, colloid, third spacing

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Examine temporal changes in dynamic waveform and their relationships with organ (dys)function after thermal injury using a 40% TBSA pig burn model. (0-10 months)

- Objective 1a: Identify the effect of burn injury and standard of care (IV fluids) on dynamic waveforms. (0-7 months)
- Objective 1b: Dosing: Define the relationship between dynamic waveforms and MOD/AKI. (3-10 months)

Specific Aim 2: Use varying levels of enteral and IV fluids to alter organ perfusion in a 40% TBSA pig burn model to examine ensuing differences in PPV, SPV, SVV. (10-27 months)

- Objective 2a: Determine if varying levels of IV fluids increase dynamic waveform variability. (10-27 months)
- Objective 2b: Identify the efficacy of oral fluids in maintaining PPV, SVV and SPV. (10-27 months)

Specific Aim 3: Compare traditional resuscitation decision support algorithms (i.e., UO) to new algorithms containing waveform data (e.g., UO+PPV) for the ability to prevent organ damage and maintain organ perfusion in the 40% TBSA porcine burn model. (27-36 months)

- Objective 3a: Perform 12-hour in vivo experiments to compare new algorithms with UO (n=32). (27-36 months)

Deliverables:

- a. Knowledge products on how burn injury changes arterial waveform derivatives in real time over “ebb” and “flow” phases of burn shock.
- b. Identification of variables that indicate patient responsiveness to oral resuscitation can revolutionize burn care in prolonged field care scenarios
- c. Knowledge product indicating which variables will be advantageous to incorporate with decision support systems guiding burn resuscitation
- d. A refining of existing decision support to generate a personalized resuscitation approach to maximize responsiveness to fluids.
- e. More efficient burn care and improved outcomes for combat casualties.

What was accomplished under these goals?

Several model development animals have been run, with an unexpectedly high mortality rate. Several nuances to the protocol have been worked out, to include 2 more addendums that had provisions for increased model development animals. Despite these setbacks, several valuable pieces of information have been garnered, and some analyzable waveforms have been collected. Moreover, the promise of the waveform variations is shown in figure 1, wherein 1 animal displayed large increase in hemodynamic instability concurrent with waveform variations. This addresses objective 1a, wherein burn injury increases parameters such as PPV and SPV to a point, and then becomes wildly unpredictable with hemodynamic instability (i.e., burn shock and poor outcomes).

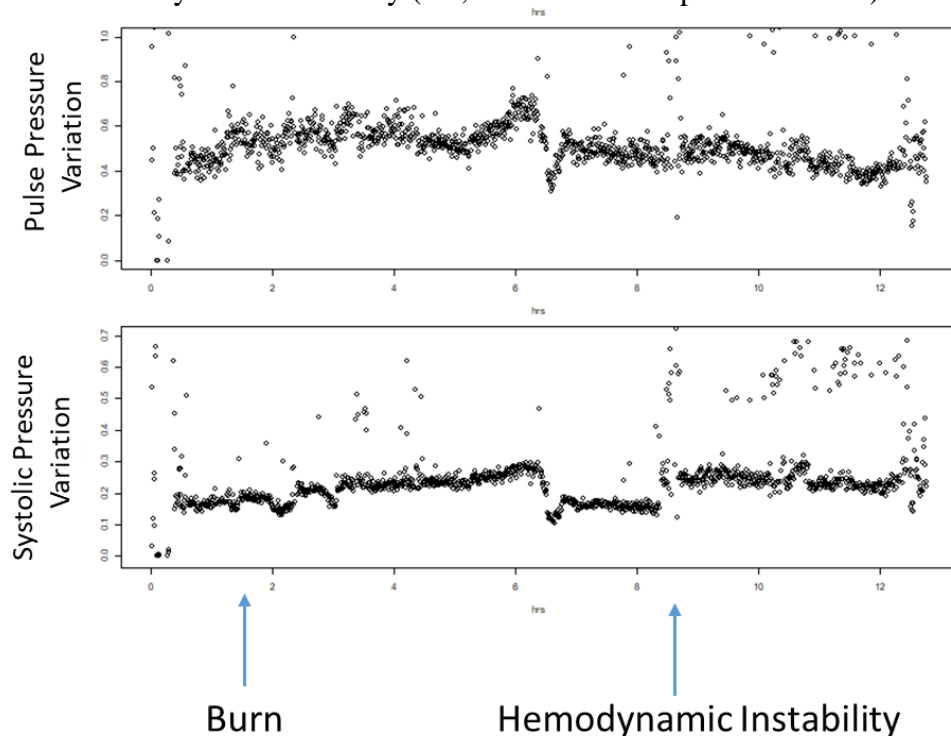


Figure 1. PPV (top) and SPV (bottom) from one animal across the 24-hour study. Increases in the amount of variation is seen progressing slowly after the burn injury, which becomes pronounced as the animal progresses into burn shock. (hemodynamic instability).

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

While this project was not intended to specifically provide training or professional development, it has allowed Dr. Burmeister to mentor a postdoctoral fellow who is new to the institute and developing a similar model for examining drugs targeting hypermetabolism. This project (if transferred) will continue to allow for training of postdoctoral fellows and residents to get involved with military-relevant research.

How were the results disseminated to communities of interest?

There have not been submitted results as an abstract to date, but an example of lactate and oxygen consumption was presented at MRDC's annual programmatic review.

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

This award is likely transferring to Uniformed Services University (USU) where Dr. Burmeister has accepted a new professorship position. As such, it is reasonable to expect there to be delays in deliverables as a new laboratory is set up, and different facilities are managed.

4. IMPACT:

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

Functional hemodynamic measurements (currently ignored in burn resuscitation evaluation) offer hope of predicting patient response to fluid. Specifically, pulse pressure variation (PPV), systolic pressure variation (SPV), and stroke volume variability (SVV) are easily obtained from the aortic waveform and are predictive of volume responsiveness perioperatively. In other patient populations, a resuscitation protocol that included SVV was compared to one that used only UO and MAP and showed decreased hospital length of stay and fewer complications. These variables likely can inform the response to fluids (both oral and IV) in the burn patient.

What was the impact on other disciplines?

While technology guiding fluid levels in other conditions is generally ahead of burns, principles found with this proposal could generally be applied to other conditions requiring fluid. As burn patients require large volumes of fluids for resuscitation purposes, the usefulness of these informative endpoints may very well be exacerbated.

What was the impact on technology transfer?

None to date, however successful implementation in burn resuscitation will be incorporated with the Burn Resuscitation Decision System-Mobile (BRDSS-M) is an Army-developed, FDA-cleared computerized fluid calculator designed to assist clinicians with fluid resuscitation for burn-injured patients. The Arcos Burn Navigator™ (NSN 6515-01-621-3571; list cost \$14,500, sell price \$12,200) is the only commercial product currently available. With the proof of concept generated within the current proposal, the most attractive variables may be easily incorporated into decision support.

What was the impact on society beyond science and technology?

If successful, this proposal has the potential to improve outcomes of severely injured warfighters. Especially considering the challenges of care in multi-domain operations, optimization of burn

resuscitation will help make triage and evacuation decisions and improve the response to injury which can accelerate return to duty rates and enhance the effectiveness of our future military.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

An altered SOW is being prepared to account for a change in cost and time for accommodation to new facilities at USU.

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

1-In the past year, a significant delay was experienced due to delays in contracting at USAMRAA for acquisition of the DSI telemetry system. Specifically, the equipment was placed on a December 17, 2018 order at USAISR, and the equipment did not arrive until June 26, 2019. Of note, Dr. Burmeister's team attempted a quick turnaround with training on the equipment having taken place on July 16, 2019.

2-Since this delay has only allowed for model development to take place, and since Dr. Burmeister is transferring agencies (as mentioned above), the tentative plan is to transfer this award to USU which will likely result in time delays.

Changes that had a significant impact on expenditures

The aforementioned transfer to USU may also impact the total cost of the award. Specifically, since animal costs are higher at USU, the enteral fluid component of the experimental design (for example) may be removed. A cost analysis is currently being performed to inform an updated SOW and budget.

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

Nothing to Report.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

Publications, conference papers, and presentations

Nothing to Report.

Journal publications.

Nothing to Report.

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

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name: David Burmeister
Project Role: PI
Nearest person month worked: 6
Contribution to Project: Dr. Burmeister is providing technical oversight and leadership of the protocol. Specifically, he will oversee regulatory approval, supervise data collection and analysis, and coordinate team meetings to review planning and execution of the study.

Name: Jamila Duarte
Project Role: Research Lab Technician III
Nearest person month worked: 6
Contribution to Project: Jamila assisted with animal procedures and processed blood/tissue samples.

Name: Tiffany Heard
Project Role: Research Lab Technician III
Nearest person month worked: 6
Contribution to Project: Tiffany is performing assays that examine mitochondria function.

Name: Joshua Little
Project Role: Private First Class
Nearest person month worked: 3
Contribution to Project: Upon availability, PFC Little runs blood Vacutainer tubes to our biochemistry core lab, and aliquots plasma for later analysis.

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

As mentioned above, Dr. Burmeister will be transitioning to USU.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS:

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: Attached

9. APPENDICES: Attached

W81XWH-19-2-0004_ISR_Decision Memo.pdf
RE PR 0011297478 (DSI Call order) (UNCLASSIFIED).msg
FW PR 0011297478 (DSI Call order) (UNCLASSIFIED).msg
DSI_order.pdf
DSI_order2.pdf
Non-DoD Source UPS Ship Notification Tracking Number 1Z5675620363360772.msg