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

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CONTRACTING ORGANIZATION: The Geneva Foundation

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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 patents 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

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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 patents 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:

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?

SCIENTIFIC PROGRESS

This past year started with preparations for the final specific aim of this proposal (Specific Aim 3, SA3), which necessitated coordination with both Medstar Hospital Center and University of Maryland (UMD).

- Medstar colleagues were consulted in the beginning of 2023 to come to consensus on performance and timing of animal studies. A finalized meeting in early March clarified design and sample sizes, which was used to renew the local IACUC protocol, as well as the centralized ACURO protocol proactively in the spring.

- With UMD, many more meetings took place to discuss and optimize the algorithm that will be utilized for SA3. It was found that pulse pressure variation (PPV) had proven to be the most accurate at classifying resuscitation status in prior aims, which was presented at the American Burn Association in 2022 [1].

- Further, several algorithms were examined, including LS: Least Square, PPV10: Salinas +/- 10% via PPV values, as well as several Neural Networks with one hidden layer (NN). The neural network algorithms consistently showed the highest agreement with cardiac output (CO) and correlated best with indicators of over resuscitation (i.e., highest urine output, lowest PPV) [2].

- Several of these algorithms were used to assign suggested fluid rates to animals in the Burn Navigator group in specific aim 2 in a retrospective fashion. An example is shown if Figure 1, wherein the blue line indicates the actual fluid rate that was given to the animal, which remained high for the entire 24 hour experiment. This led to an increase in the urine output (black line) above normal values indicated by the gray box. What can be seen is that the Navigator (Salinas) algorithm in the red lines recommends an aggressive and steep increase in fluid rate (red line) as opposed to the UMD neural network algorithm shown in the yellow line. It was decided that this latter algorithm would serve as the basis for the one to be used for SA3, with important training to be done from retrospective data.

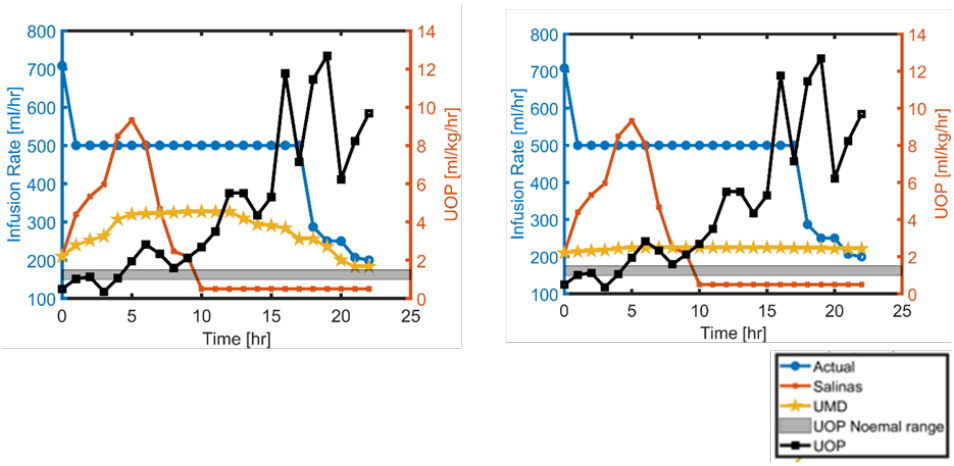

Figure 1. Comparison of Navigator algorithm (red line) and a Neural Network algorithm (yellow line) for recommended fluid rate. The actual fluids given, as well as the urine output are indicated by the blue and black lines, respectively.

- Algorithm training and optimization proceeded, and a several iterations of an excel spreadsheet that served as the basis for fluid rate recommendation, wherein PPV, TBSA, etc. are entered and a subsequent fluid rate recommendation is made.
- Medstar colleagues were able to give input on the usability of the spreadsheet, and indicated real-time measurement of the PPV was feasible. A finalized spreadsheet was shared.
- A presented graph on July 18, 2023 is seen in Figure 1. This graph shows that PPV was significantly correlated to creatinine (the clinical marker of AKI), which varied with the resuscitation strategy given. Specifically, animals that were either fluid withhold or received a high rate of IV fluid (i.e., in the extremes of resuscitation) had a positive association between PPV and AKI, while those in the adequate resuscitation group revealed a negative correlation. Not shown below is that the SVV and SPV also correlated, all of which were also correlated with blood urea nitrogen (BUN) as a secondary marker of AKI.

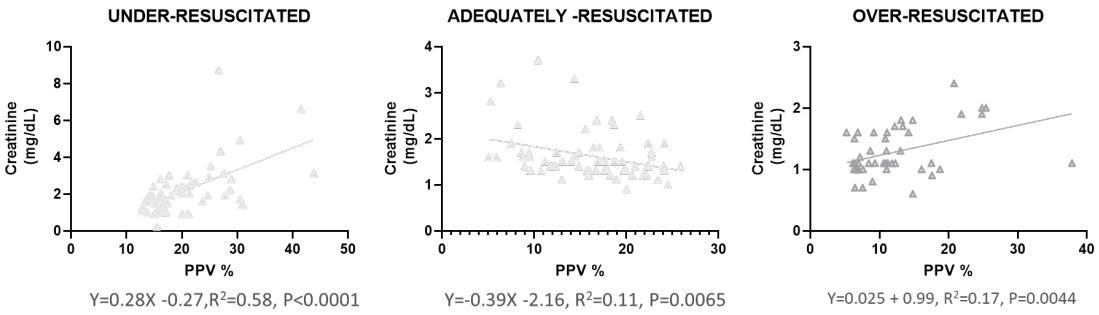

Figure 1. Individual values of creatinine plotted against PPV at any given point from the same animal in under-resuscitated animals (left) adequately-resuscitated animals (middle) and over-resuscitated animals (right). Significant positive correlations are seen at the extremely of resuscitation, with slight negative correlation showing in the Burn Navigator-driven resuscitation.

- During the first three subjects for SA3 (performed at Medstar Research Institute), it was found that PPV was actually not calculated form the existing anesthesia monitor. This provided some delays, until a working PPV monitor was brought in.
- Late in the last year, all *in vivo* experiments were completed to come up with an n of 6 in each group. Currently being explored is the tendency for the algorithm performance to lead to higher fluid levels (although, this finding was variable).

LOGISTICAL AND DISSEMINATION PROGRESS

- Regulatory action for animal protocols was required in collaboration with Medstar colleagues. An APR 13 email from the Animal Care and Use Review Office (ACURO) office was received indicating the expiration of Medstar IACUC protocol number 2020-005. Dr. Burmeister and Medstar colleagues had already addressed a renewal which included small changes such as extra model development animals to train new staff on the protocol. As such, the team was able to submit the IACUC-approved protocol to ACURI on MAY 2, and after one round of clarification, the ACURO approval was given on May 11.
- Dr. Burmeister attended the American Burn Association on May 15-19, during which he gave a breakout presentation on work that was supported with this award. The work was received very well and generated discussion surrounding the implementation of pulse waveform analyses in clinical care. Moreover, additional abstracts were presented that extended beyond the original scope of this study [3-5]. Of specific note, is how fluid resuscitation levels affected the inflammation going on in the cutaneous tissue juxtaposed to the burn.
- In print publication of the first manuscript from this award appeared in the Journal of Burn Care and Research in May [6].
- Dr. Burmeister presented at an in-progress review for the Combat Casualty Care Research Program (CCCRP) in July.
- An NCE was approved in December of 2023.

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 will allow for training of postdoctoral fellows and residents to get involved with military-relevant research.

How were the results disseminated to communities of interest?
The results have been presented as podium presentations at the American Burn Association, and as a published manuscript in the Journal of Burn Care and Research

What do you plan to do during the next reporting period to accomplish the goals?
All in vivo experiments have been done- analysis is ongoing to determine the fluid requirements when using the algorithm, amongst other readouts. This should lead to at least one other publication from this work.

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. This work has advanced the knowledge on the utility of hemodynamic pulse wave analysis (PWA)-derived indices in burn resuscitation extremes. Although more evidence is needed, our results suggest that: PWA-derived CO as well as PPV and SPV can represent fluid status during burn resuscitation and give information that is not redundant with UOP. However, preliminary evidence from the most recent studies suggest that these algorithms driven by POPV are not ready for clinical application since they have led to measurable variation in fluid requirements

What was the impact on other disciplines?
While technology guiding fluid levels in other conditions is generally ahead of burns, principles found from this research could generally be applied to other conditions requiring fluid resuscitation. As burn patients require large volumes of fluids for resuscitation purposes, the usefulness of these informative endpoints may very well be extended to other forms of shock such as distributive shock, or hypovolemic shock.

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), 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. The investigators have been using the Navigator, and have been in contact with the company throughout this award.

What was the impact on society beyond science and technology?
This research 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
None since the prior years' annual report.

Actual or anticipated problems or delays and actions or plans to resolve them
In total, a handful of delays- listed below- have impacted the overall deliverables and timelines on this award. Given these delays, it is remarkable that resilience of the investigative team has resulted in tangible and actionable findings. Additionally, with these delays in the rearview mirror, we do not expect any impediments to finishing Specific Aim 3.

1- Prior delays in equipment acquisition through USAMRAA
2- Transfer of this award to USUHS.

3- COVID 19 pandemic-related delays
4- Delays in opening the USU animal facility (pivot to Medstar facilities)
5- Personnel changes leading to inadequate technical support at the beginning of the in vivo experiments for Specific Aim 2.
6- Changes in focus of USAISR colleagues (pivot to UMD modelers).

Changes that had a significant impact on expenditures
The aforementioned transfer to USU impacted the total cost of the award, which resulted in the altered SOW. Specifically, since animal costs are higher in the D.C. area, the enteral fluid component of the experimental design was removed. This change has been made and was reported in last year's annual report.

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
N/A

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**
  - UTILITY OF VISCOELASTIC ASSAYS FOR ASSESSING COAGULATION STATUS IN REPONSE TO VARYING IV FLUID RESUSCITATION VOLUMES AFTER EXTENSIVE BURN INJURY" Shock, October 2021.
  - Kao, Y.-M., et al., T5 Tracking Cardiac Output During Burn Resuscitation via Pulse Wave Analysis. Journal of Burn Care & Research, 2022. 43(Supplement_1): p. S4-S5.
  - ArabiDarrehDor, G., et al., 97 Arterial Waveform Variations as Measures of Resuscitation Adequacy in a Porcine Model of Burn Injury. Journal of Burn Care & Research, 2022. 43(Supplement_1): p. S64-S65.
  - Kelly E, Carney B, Ziedins E, Parajuli B, Burmeister D, Moffatt L, Shupp J: 76 Resuscitation Volumes Affect Perfusion and Inflammatory Cytokine Expression in Peri-Burn Skin: Implications for Burn Conversion. Journal of Burn Care & Research 2023, 44(Supplement_2):S40-S41.
  - 4. Horseman T, Frank A, Carney B, Moffatt L, Shupp J, Nisar S, Keyloun J, Burmeister D: 102 Longitudinal Changes in Lingual and Intestinal Microbiota in a Swine Burn Model. Journal of Burn Care & Research 2023, 44(Supplement_2):S59-S59.
  - 5. Arabidarrehdor G, Kao Y-M, Hahn J-O, Burmeister D, Parajuli B, Carney B, Keyloun J, Moffatt L, Shupp J, Reese A: 103 Analysis of Arterial Blood Pressure Waveform Features in a Porcine Model of Burn and Resuscitation. Journal of Burn Care & Research 2023, 44(Supplement_2):S60-S60.

Journal publications.

- ArabiDarrehDor G, Kao YM, Oliver MA, Parajuli B, Carney BC, Keyloun JW, Moffatt LT, Shupp JW, Hahn JO, Burmeister DM: The Potential of Arterial Pulse Wave Analysis in Burn Resuscitation: A Pilot In Vivo Study. J Burn Care Res 2023, 44(3):599-609.

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:	2
Contribution to Project:	Dr. Burmeister will provide 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:	Lauren Moffatt
Project Role:	AI
Nearest person month worked:	1
Contribution to Project:	Dr. Moffatt has coordinated with Dr. Burmeister for purposes on initiating work at Medstar Research Institute. This involvement is related to the subaward agreement with MedStar rather than Geneva-hiring actions.

Name:	Babita Parajuli
Project Role:	Research Laboratory Technician

Nearest person month worked:	11.65
Contribution to Project:	Mrs. Parajuli has onboarded and will assist with all technical aspects of the protocol, to include sample setup, animal instrumentation, and ICU monitoring, as well as sample processing and running biochemical/coagulation analyses.
Name:	Edward Kelly
Project Role:	AI
Nearest person month worked:	0.6
Contribution to Project:	Dr. Kelly is responsible for animal instrumentation and ICU setting monitoring at Medstar Research Institute. This involvement is related to the subaward agreement with MedStar rather than Geneva-hiring actions.
Name:	Melissa McLawhorn
Project Role:	Research Coordinator
Nearest person month worked:	0.3
Contribution to Project:	Ms. Mclawhorn is supervisory for execution of animal fluid, analgesia, and anesthesia purposes. This involvement is related to the subaward agreement with MedStar rather than Geneva-hiring actions.
Name:	Eirks Ziedins
Project Role:	Research Technician
Nearest person month worked:	0.6
Contribution to Project:	Mr. Ziedins helps run assays during experiments, and has also written abstracts related to this award, This involvement is related to the subaward agreement with MedStar rather than Geneva-hiring actions.
Name:	Yi-Ming Kao
Project Role:	Graduate Student
Nearest person month worked:	0.3
Contribution to Project:	Mr. Kao has analyzed the arterial waveform data, and has even participated in writing abstracts. This involvement is related to the subaward agreement with UMD rather than Geneva-hiring actions.
Name:	Jin Oh Hahn
Project Role:	Associate Professor
Nearest person month worked:	0.3
Contribution to Project:	Dr. Hahn has overseen the pulse wave analysis with the raw data done from the experiments, This involvement is related to the subaward agreement with UMD rather than Geneva-hiring actions.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report

What other organizations were involved as partners?
Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A
QUAD CHARTS: Please find quad chart attached.

9. APPENDICES:

ArabiDarrehDor_JBCR.pdf

1. ArabiDarrehDor G, Kao Y-M, Oliver MA, Reese AD, Carney BC, Keyloun JW, Chung KK, Moffatt LT, Shupp JW, Hahn J-O: **97 Arterial Waveform Variations as Measures of Resuscitation Adequacy in a Porcine Model of Burn Injury**. *Journal of Burn Care & Research* 2022, **43**(Supplement_1):S64-S65.
2. Kao Y-M, ArabiDarrehDor G, Oliver MA, Reese AD, Keyloun JW, Chung KK, Moffatt LT, Shupp JW, Hahn J-O, Burmeister DM: **T5 Tracking Cardiac Output During Burn Resuscitation via Pulse Wave Analysis**. *Journal of Burn Care & Research* 2022, **43**(Supplement_1):S4-S5.
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