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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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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 (ISR: US Army Institute of Surgical Research) 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, revised to 17-36 months)

- Objective 1a: Identify the effect of burn injury and standard of care (IV fluids) on dynamic waveforms. (0-7 months, revised to 17-36 months)
- Objective 1b: Dosing: Define the relationship between dynamic waveforms and MOD/AKI. (3-10 months, revised to 17-36 months)

Specific Aim 2: Use varying levels of IV fluids to alter organ perfusion in a 40% TBSA pig burn model to examine ensuing differences in PPV, SPV, SVV. (10-27 months, revised to 23-43 months)

- Objective 2a: Determine if varying levels of IV fluids increase dynamic waveform variability. (10-27 months, revised to 23-42 months)
- Objective 2b: Identify the efficacy of IV fluids in maintaining PPV, SVV and SPV. (10-27 months, revised to 23-43 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, revised to 45-48 months)

- Objective 3a: Perform 24-hour in vivo experiments to compare new algorithms with UO (n=32). (27-36 months, revised to 45-48 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 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?

The past year saw the most substantial progress and publishable results produced on this project to date. Details are given below, but highlights include:

1- Completion of in vivo experiments related to specific Aim 2.
2- Establishment of a replacement computer modeling team with subcontract execution at University of Maryland (Dr. Jin Oh-Hahn).
3- Monthly meetings with UMD modelers to analyze collected waveforms.
4- Oral presentations at the American Burn Association meeting. [1, 2]
5- Publication of findings as a manuscript in the *Journal of Burn Care and Research*. [3]

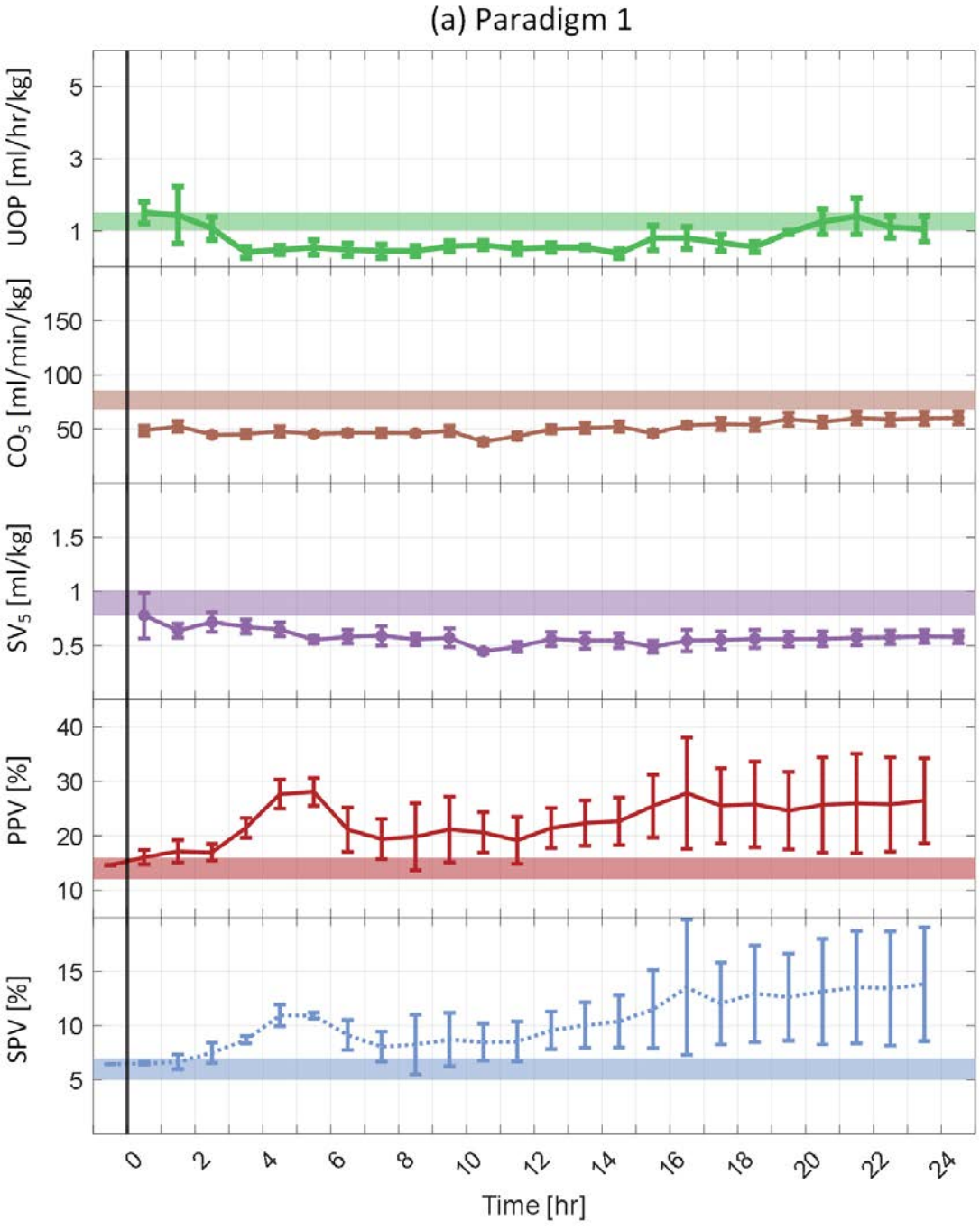
This past year started with resuming the in vivo experiments related to Specific Aim 2 with the new Geneva and Medstar personnel. Interim analyses occurred after half of each of the fluid level groups were completed (i.e., n=3-4/group) and the preliminary results were prepared for the American Burn Association (ABA) Conference. In this time, the subaward to the integral computed modelers at UMD was finalized, and the budget was retooled accordingly.

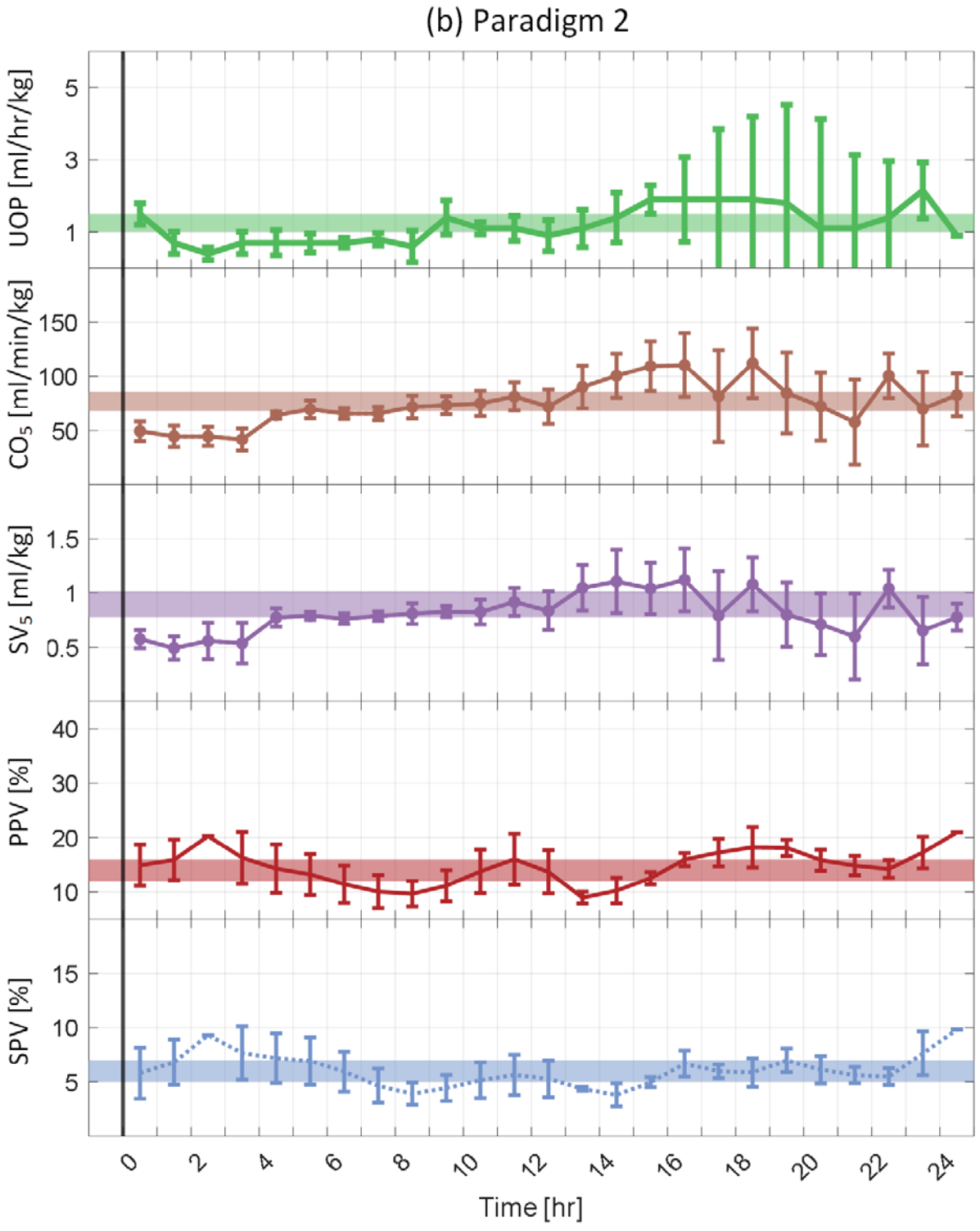
A large portion of work was completed on this award in quarter 2, which also included the dissemination of exciting results from this award at the ABA at the beginning of April. Two different oral presentations were made, which were entitled "Tracking Cardiac Output During Burn Resuscitation via Pulse Wave Analysis" and "Arterial Waveform Variations as Measures of Resuscitation Adequacy in a Porcine Model of Burn Injury". The first of these 2 was selected as a top 5 abstract, and these selections speak to the clinical relevance and excitement concerning this project.

Also during the second quarter, the Medstar group and Geneva personnel accelerated in vivo experiments a fast pace, and nearly completed all of the animals in the 3 resuscitation paradigms to fill out a sample size of 8 in each group. The remainder of these were completed early in quarter 3. On June 30, Dr. Burmeister gave a virtual in-progress review with the science officer (Dr. Erin Sanders at the time) as well as several other key stakeholders in the burn space. At this review, he presented some of the exciting data that was the focus of presentations at the ABA, and discussed how after many setbacks and roadblocks (e.g., lab relocation, COVID, animal facility delays, personnel challenges), this award was now starting to produce wonderful results.

Also in this time frame, the first knowledge product from this work was submitted an accepted for the *Journal of Burn Care and Research*. [3] One figure from that paper is presented here in Fig. 1 which shows the group-average time courses of urine output (UOP) versus best-performing cardiac output (CO) index and the corresponding stroke volume (SV) index as well as pule pressure variation (PPV) and systolic pressure variation (SPV) pertaining to 3 resuscitation paradigms. All the PWA-derived indices exhibited physiologically reasonable group-aggregated behaviors in each paradigm: (i) CO and SV indices did not change in Paradigm 1 but increased in Paradigm 2 and Paradigm 3 (and more so in Paradigm 3 than in Paradigm 2); (ii) PPV and SPV increased in Paradigm 1 (indicating that the animals became increasingly fluid responsive

toward the end of the 24 hours post burn) but decreased in Paradigm 2 and Paradigm 3 (and more so in Paradigm 3 than in Paradigm 2; indicating that the animals became less fluid responsive toward the end of the 24 hours post burn). In contrast, UOP exhibited an increasing degree of inter-individual variability toward the end of the 24 hours post burn, which made it less attractive as a metric of burn resuscitation adequacy in some animals.




(b) Paradigm 2
UOP [ml/hr/kg]
5
3
1
CO5 [ml/min/kg]
150
100
50
SV5 [ml/kg]
1.5
1
0.5
PPV [%]
40
30
20
10
SPV [%]
15
10
5
0
2
4
6
8
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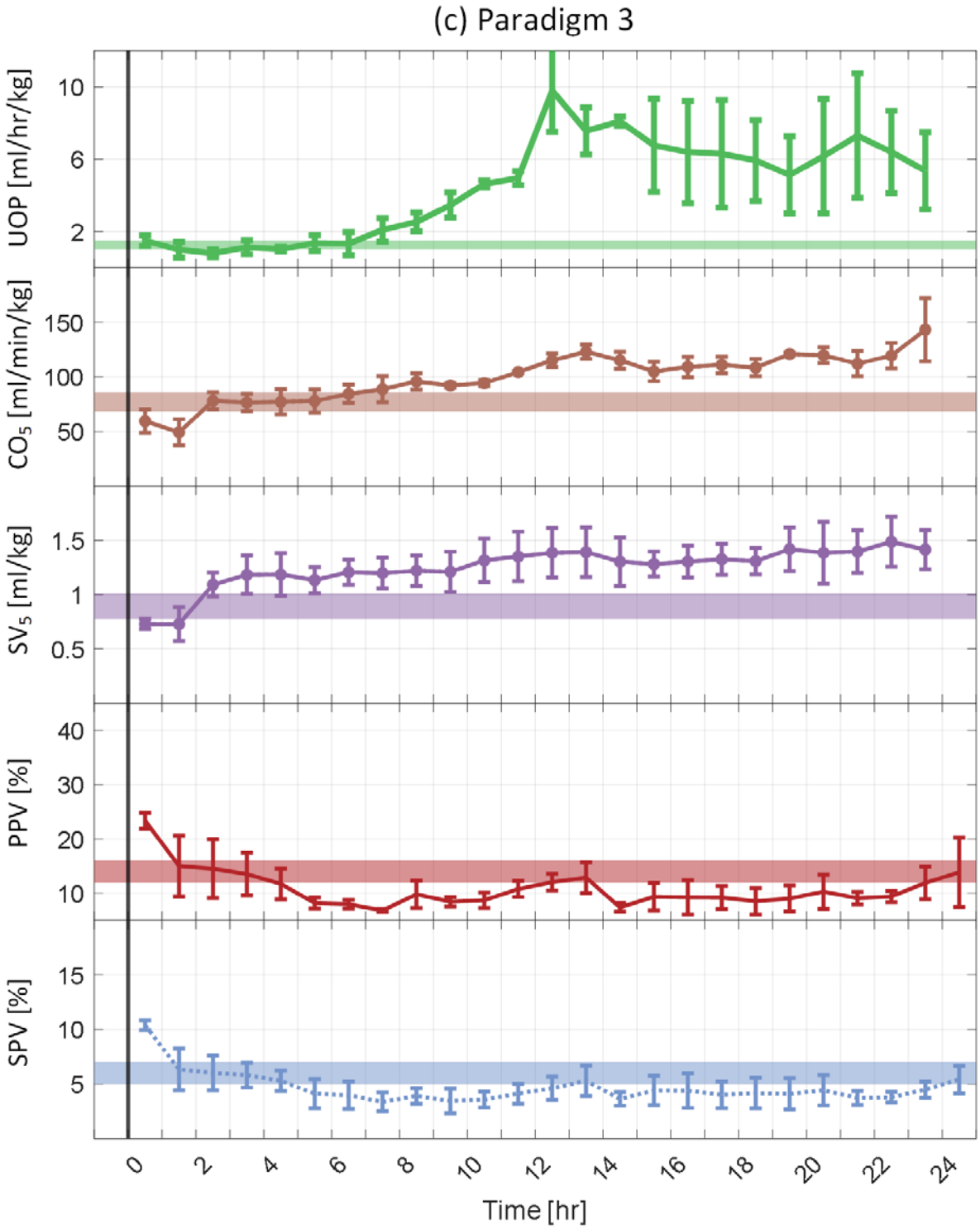

Fig. 1 Group-average time trends of UOP versus best-performing CO and SV indices as well as PPV and SPV associated with 3 resuscitation paradigms (mean+/-SE). (a) Paradigm 1: NR (no resuscitation). (b) Paradigm 2: BN (resuscitation guided by the Burn Navigator recommendation). (c) Paradigm 3: HR (resuscitation based on a high rate 500 ml/hr throughout the protocol).

Since the publication several administrative changes have happened on the award. Specifically, the Option year 2 for this award was picked up as per email sent June 23, 2022. In addition, Dr. Jonathan Monti

assumed Science Officer duties for this award. Arterial waveform data has been transferred (via DoD Safe access File Exchange) to the University of Maryland modelers for the to perform pulse wave analysis, and this data has been the subject of monthly meeting to fine tune the algorithm that is going to be used in Specific aim 3, to compare with UOP from the Burn Navigator.

Additionally, since all in vivo subjects for Aim 2 have now been completed at the Medstar Research Institute, the vast amount of samples to work with have been transferred over to USUHS for the commencement of ELISA and Western blotting analysis are underway. To date, several syndecan ELISAs (to denote endotheliopathy or vascular damage) have been attempted without specific signal. Our hypothesis is that IV fluids at a high rate would exacerbate the shedding of the glycocalyx (as has been seen in hemorrhagic shock) and thus higher syndecan levels, which have also been affected in oral resuscitation of burns [4]. . To date, we are still awaiting to confirm a specific signal in these porcine samples. Other ELISAs that are being run include Galectin-1, thrombomodulin, and inflammatory cytokines

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 a 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?
An algorithm that includes PPV is being finalized, and in the upcoming year, will be compared to UOP alone in the final head to head experiment examining the value of these waveform variations.

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.

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 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), 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?
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

1. UTILITY OF VISCOELASTIC ASSAYS FOR ASSESSING COAGULATION STATUS IN REPONSE TO VARYING IV FLUID RESUSCITATION VOLUMES AFTER EXTENSIVE BURN INJURY" Shock, October 2021.
2. 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.
3. 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.

Journal publications.

1. ArabiDarrehDor, G., et al., *The Potential of Arterial Pulse Wave Analysis in Burn Resuscitation: A Pilot In Vivo Study*. J Burn Care Res, 2022.

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:	3.6

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:	Babita Parajuli
Project Role:	Research Lab Technician III
Nearest person month worked:	12
Contribution to Project:	Babita assisted with animal procedures, tissue processing, and data analysis.

Name:	Edward Kelly
Project Role:	Resident
Nearest person month worked:	1.2
Contribution to Project:	in charge of injury pattern and ICU care

Name:	Lauren Moffatt
Project Role:	Research Director
Nearest person month worked:	0.6
Contribution to Project:	Coordination with Medstar team and facilities

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
No change to report.

What other organizations were involved as partners?
Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS:

COLLABORATIVE AWARDS: COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA) executed among THE GENEVA FOUNDATION, MEDSTAR HEALTH RESEARCH INSTITUTE, and THE UNIFORMED SERVICES UNIVERSITY OF THE HEAL TH SCIENCES (USU).

QUAD CHARTS: Attached

REFERENCES:

1. 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.
2. 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.
3. ArabiDarrehDor, G., et al., *The Potential of Arterial Pulse Wave Analysis in Burn Resuscitation: A Pilot In Vivo Study*. J Burn Care Res, 2022.
4. Gomez, B.I., et al., *Plasma and Urinary Glycosaminoglycans as Evidence for Endotheliopathy in a Swine Burn Model.* J Surg Res, 2020. **248**: p. 28-37.