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TITLE: Comparison of Flow Rate, Pressure, and Safety Among Pressurized Intraosseous Blood Transfusion Strategies in a Swine (Sus scrofa) Model of Hemorrhagic Shock

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SUPPLEMENTARY NOTES

14. **ABSTRACT** **Three of the top fi e pre enta le causes of attlefield death (e tremity hemorrhage, unctional hemorrhage, noncompressi le torso hemorrhage) rely on rapid ascular access to initiate Ad anced Resuscitati e Care (ARC) Current Tactical Com at Casualty Care (TCCC) guidelines stress the importance of initiating resuscitation within minutes of wounding Howe er, the massi ely hemorrhaged patient, such as dismounted comple last in uries (CBI), presents a ascular access challenge to e en the most seasoned medical teams Intraosseous (IO) catheters pro ide non collapsi le access in patients that can ser e as a ridge to therapy while preparations are made for central enous access, when peripheral access is not o taina le For this reason, IO access has een used e tensi ely o er the past decade y military first responders initiating remote damage controlled resuscitation (r CR) espite the clear importance of early ascular access in ARC for lood product transfusion, a knowledge gap e ists on which IO lood infusion strategy est alances flow with safety concerns Wide clinical aria ility e ists with infusion strategies ranging from gra ity to manual syringe infusion Both safety and efficacy concerns ha e een e pressed within the trauma critical care community that IO gra ity infusion cannot meet the demands of r CR Concern also e ists that infusion pressures a o e gra ity may lead to increased shear stresses causing intra ascular hemolysis and or displacement of marrow into the enous system leading to fat em oli Filling this knowledge gap y determining which infusion strategy possesses flow rates rapid enough to preser e life ut minimize secondary infusion pressure related complications has the long term impact of impro ing attlefield sur i al**

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1. INTRODUCTION:

Intraosseous (IO) infusion is an important vascular access technique used by military first responders to infuse fluids and blood when intravenous (IV) access is difficult or unobtainable. When seconds matter, IO infusion can be set up quickly and started faster than IV in order to rapidly initiate rapid resuscitation. Currently, the optimal IO infusion method is unknown. Unlike IV, IO must overcome the resistance within the medullary space and cancellous bone to achieve clinically meaningful flow; infusion needs to be fast enough to overcome this resistance but must not generate substantially high pressures that cause adverse clinical effects. The purpose of this project is to identify the optimal method of IO infusion to use for critically injured warfighters in the austere environment. This project is multifaceted and seeks to answer several questions regarding IO access in the prehospital environment: 1) which IO infusion technique provides the fastest flow rate, with minimal complications resulting from high pressures, 2) which IO device is objectively and subjectively best for use in the austere military environment, 3) how IO placement location affects the subsequent flow and pressures generated during infusion.

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

3. ACCOMPLISHMENTS:

Intraosseous access, intraosseous infusion, intraosseous device, intraosseous placement, IO, hemorrhage, blood transfusion, Tactical Combat Casualty Care, TCCC, prehospital care, advanced resuscitative care, remote damage control resuscitation

What were the major goals of the project?

Accomplishments: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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 – Perform a study in a cadaveric swine (Sus scrofa) forelimbs with bone density approximating the adult trauma population to describe blood infusion flow rates, mean and peak infusion pressures between eight different IO transfusion strategies.
Major Task 1 – Administrative
Subtask 1: Documents submitted for IRB approval. This subtask has been completed. The first study is IRB approved (NMCSD IRB 2019.0010). This study was deferred to the IRB from IACUC as using cadaveric specimens and not live animals. Timeline: 1-4 months. Status: complete, April 2019
Milestone #1: *IRB approval obtained. **ACURO not required as not a live animal study.* Timeline: 4 months. Status: complete, July 2019
Subtask 2: Purchase equipment and establish contracts for study conduct. Timeline: 1-8 months. Status: complete, September 2019
Subtask 3: Hire CRC. Timeline: 1-8 months. Status: complete, September 2020.

Subtask 4: Arrange 9 separate dates for infusion trials (1 day for model refinement, 10 cadaveric forelimb trials, 8 days for study execution x 30 cadaveric forelimb trials per day = 250 observations) Timeline: 6-10 months. Status: complete, November 2019
Subtask 5: Presentation of Aim 1 at regional and national conferences. Timeline: 8-12 months. Status: complete, October 2020
Subtask 6: Submit manuscript for Aim 1. Timeline: 12-14 months. Status: complete, July 2021
Milestone #2: *Knowledge product transferred to public domain.* Timeline: 14 months. Status: complete, January 2022
Major Task 2 – Intraosseous Flow
Subtask 1:
a. Intraosseous infusion of whole blood into cadaveric swine forelimbs using 8 different infusion strategies including but not limited gravity, pressure bag left at 300 mmHg, pressure bag manually maintained above 300 mmHg, 10 cc syringe with 3-way stopcock, 60cc syringe with 3-way stopcock, hand bulb transfusion without pressure bag, hand bulb transfusion with pressure bag, and the LifeFlow rapid manual transfuser. There will be 30 trials per strategy. Each strategy will use 3 infusers performing 10 trials each per strategy. These 3 infusers will remain the same with each of the different infusion strategies (3 infusers, ten trials per infuser, 8 strategies equals 240 total infusion trials).
b. We will measure flow rate (ml/min), mean infusion pressure (mmHg), and max infusion pressure (mmHg).
c. Analysis of flow rate, mean and max infusion studies will be performed via the Kruskal Wallis one way analysis of variance test. The results will lead to three infusion strategies that best balance infusion flow rate with infusion pressures being compared to pressure bag infusion maintained above 300 mmHg (most commonly used current strategy). This approach will decrease the overall requirement for live animal use during research, meeting the intent of the three R approach to research (Reuse, Reduce, Refine).
Timeline: 6-10 months. Status: complete, April 2020
Subtask 2:
a. Video the digital manometer screen during the infusion time for each of the infusion strategies, including but not limited gravity, pressure bag left at 300 mmHg, pressure bag manually maintained above 300 mmHg, 10 cc syringe with 3-way stopcock, 50 cc syringe with 3-way stopcock, hand bulb transfusion without pressure bag, hand bulb transfusion with pressure bag, and the LifeFlow rapid manual transfuser.
b. Video review in 2 second intervals to determine area under the curve for mean infusion pressures. Digital manometers automatically record the digital manometer screen during the infusion time for each of the strategies.
c. Manometer device review to record peak infusion pressures between strategies.
Timeline: 6-10 months. Status: complete, April 2020
Subtask 3: Evaluate subjective assessment of three different manual infusers (investigators). We will have infuser (end user) feedback via Likert scale questions in the form of a post infusion survey recording hand fatigue, sense of reliability for the first 20 minutes of trauma care, feasibility for use in confined or low light settings, and appropriate for corpsman and medic use. Timeline: 6-10 months. Status: complete, April 2020
Subtask 4: Compare the difference between flow (ml/min), mean infusion pressure (mmHg), and max infusion pressure (mmHg) in all 8 infusion strategies. Timeline: 6-10 months. Status: complete, April 2020
Subtask 5: Assess the difference in inter-investigator infusion between each of the selected strategies. These differences will be correlated with maximum grip strength between the three infusers. Timeline: 6-10 months. Status: complete, April 2020

Milestone #3: *Data collection and analysis complete, chose 3 pressure infusion strategies above for comparison study against a pressure bag in the in vivo model (Aim 3).* Timeline: 14 months. Status: complete, April 2020

Specific Aim 2 – To describe the practical relationship between ease of use, time, needle distortion or displacement with manual 15 gauge IO devices (including, but not limited to, SAM Manual IO, Persys Medical BIG, Teleflex Talon IO Humerus, Talon IO Sternum, Jamshidi Manual IO, and PYNG Medical FAST Sternal IO) and a battery operated drill (EZ IO).

Major Task 1 – Administrative

Subtask 1: Documents submitted for IRB approval. This subtask has been completed. This second study is IRB approved (NMCSD IRB 2020.0044). This study was also deferred to the IRB from IACUC as using cadaveric specimens and not live animals. Timeline: 1-4 months. Status: complete, June 2020

Milestone #4: *IRB approval obtained. ** ACURO not required as not a live animal study.* Timeline: 1-4 months. Status: complete, July 2020

Subtask 2: Purchase equipment and establish contracts for Aim 2 study conduct. Timeline: 1-8 months. Status: complete, March 2021

Subtask 3: Arrange 8 separate dates for infusion trials (1 day for model refinement, 10 cadaveric forelimb trials, 7 days for study execution x 30 cadaveric forelimb trials per day = 220 observations). Timeline 10-14 months. Status: complete, March 2021

Milestone #5: *Data collection complete.* Timeline: 10-12 months. Status: complete, March 2021

Subtask 4: Presentation Aim 2 at regional and national conferences. Timeline: 14-16 months. Status: complete, October 2021. We presented at the 2022 Association of Military Surgeons of the United States (AMSUS), 2022 Navy Medicine West Academic Research Competition (ARC), 2022 Navy Wide ARC, and 2022 Military Health System Research Symposium (MHSRS).

Subtask 5: Submit manuscript for Aim 2. Timeline: 14-16 months. Status: In progress (90% complete). We currently have three manuscripts on the findings from Specific Aim 2. One article has been accepted (Mil Med. Kay V, et al), one manuscripts has been submitted (Gehrz J, et al. JACEP Open) and one is still in draft phase (Accepted and Submitted Manuscripts Attached).

Milestone #6: *Knowledge product transferred to public domain.* Timeline: 16 months. Status: In Process. Findings have been relayed to TCCC Chair, CAPT Travis Deaton.

Major Task 2 – Intraosseous Catheter Placement

Subtask 1: Define the flow performance in ml/min between 7 intraosseous catheters including, but not limited to, SAM Manual IO, Persys Medical BIG, Teleflex Talon IO Humerus, Talon IO Sternum, Jamshidi Manual IO, and PYNG Medical FAST Sternal IO and a battery operated drill (EZ IO). Timeline: 10-14 months. Status: complete, April 2021

Subtask 2: Evaluate subjective assessment of three different manual catheter placement users (investigators). Timeline: 10-14 months. Status: complete, April 2021

Subtask 3: Describe needle angle of entry in relation to the medullary cavity and needle displacement as this relates to intraosseous flow, evidence of needle displacement, or cortical fracture. This will be described by external and internal objective measures. Each bone will undergo CT Scan after infusion to determine intramedullary or cortical bone placement. This zone of placement will be correlated with both mean and max infusion pressures and flow rates. This knowledge product in combination with in vivo data from Specific Aim 3 will inform the development of a pilot computational model on intraosseous infusion in a porcine (sus scrofa) proximal humerus. Timeline: 10-14 months. Status: complete, April 2021

Subtask 4: Assess the difference in inter-investigator placement between each of the 7 manual catheters. Timeline: 10-14 months. Status: complete, April 2021

Subtask 5: Assess the time to placement of each of the 7 devices as measured by location of site of insertion, deploying device, and flushing catheter. Timeline: 10-14 months. Status: complete, April 2021

Specific Aim 3 – Perform an in-vivo study to determine optimal flow rates and infusion pressures for IO blood infusion strategies in high proximal humerus bone density swine (Sus scrofa) model of hemorrhagic shock.

Major Task 1

Subtask 1: Submit documents for IACUC approval. Timeline: 6-8 months. Status: complete, February 2021

Milestone #7: *IACUC approval obtained.* Timeline: 8 months. Status: complete, March 2021

Subtask 2: Purchase equipment and establish contracts for study conduct. Timeline: 8-14 months.

Subtask 3: Hire CRC. Timeline: 1-8 months. Status: complete, September 2020

Subtask 4: Hire Veterinary Technician Timeline: 4-10 months. Status: complete, March 2023

Subtask 5: Arrange 20-24 separate dates in vivo research (Anticipate 1-3 study subjects per day over 24-28 days = 8 pilot subjects and 48 main study subjects) Timeline: 16-22 months. Status: complete, April 2023

Milestone #8: *Data collection complete.* Timeline: 22-24 months. Status: complete, April 2023

Subtask 5: Presentation Aim 3 at regional and national conferences. Timeline: 24-30 months. Status: in progress (presented results of pilot at the 2022 Navy Medicine West ARC, 2022 Navy Wide ARC, and 2022 MHSRS). We presented the results of the main study at the 2023 Navy Medicine West ARC 2023, Navy Wide ARC 2023, and Government Services Chapter American College of Emergency Physicians (GSACEP) 2023. We will be presenting results at the 2023 Naval Medical Center San Diego (NMCSD) Surgery Sturtz Conference, MHSRS 2023, and American College of Emergency Physicians (ACEP) Conference 2023.

Subtask 6: Submit manuscript for Aim 3. Timeline: 32-36 months. Status: Anticipate Manuscript Draft Submission November 2023.

Milestone #9: *Knowledge product transferred to public domain for optimal care in the prehospital or early phase of trauma care of victims of massive hemorrhage where vascular access is a challenge and resuscitation is key to survival.* Timeline: 36 months. Status: In Process, discussed results with TCCC Chair CAPT Travis Deaton and THOR Co-Director, Dr. Phillips Spinella.

Major Task 2: Define practical relationship between IO infusion flow, pressure, needle position and intravascular hemolysis

Subtask 1: Define the flow performance in ml/min between 4 intraosseous blood transfusion strategies that differ by infusion pressure at 5 mins and for total infusion volume. Timeline: 22-24 months. Status: complete, April 2023

Subtask 2: Define mean and peak infusion pressures in mmHg between 4 intraosseous blood transfusion strategies that differ by infusion pressure. [12 swine X 4 groups = 48 swine total] [12 swine X 4 groups = 48 swine total]. Timeline: 22-24 months. Status: complete, April 2023

Subtask 3: Assess the anatomic position of the intraosseous catheter within the medullary cavity as it applies to flow, pressure and bone density of the study subject. [12 swine X 4 groups = 48 swine total] Timeline: 22-24 months. Status: complete, April 2023

Subtask 4: Assess plasma free hemoglobin levels at baseline, post infusion, from collected blood, and 1 hour post infusion to determine relationship between infusion pressure and hemolysis as it applies to infusion pressure. 48 times 4 samples per subject = 192. [12 swine X 4 groups = 48 swine total]. Timeline: 22-24 months. Status: complete, April 2023.

Milestone #10: *Inform the relationship between IO infusion pressure and intravascular hemolysis.* Timeline: 36 months. Status: complete, April 2023

Milestone #11: *Inform development of a pilot computational model based on flow, pressure, and needle placement characteristics between two cadaver studies (Aim 1 and Aim 2) and this in-vivo study that will*

allow for adjustment of both needle angle, diameter of catheter, viscosity of fluid, and increasing or decreasing levels of bone density within the porcine (sus scrofa) proximal humerus model. This will allow for translational testing at theoretical higher and lower bone densities, needle positions and fluid viscosity. Based on study findings, it can also give us a predictive computational model for hemolysis based on changes to these study variables and prior research on intraosseous infusion pressure threshold. This pilot computational model could allow future research development into a human humerus computational intraosseous infusion model or intraosseous catheter device development.
Timeline: 36 months. Status: In Process, Contract with Dr. Vinals to construct the computational model is complete. Dr. Vinals has recruited a graduate student with him at University of Minnesota. No Cost Extension was approved and data has been transferred to Dr. Vinals to complete this model (Preliminary model conditions attached). Anticipate this being completed by April 2024.

Major Task 3: Define practical relationship between IO infusion pressure and acute occlusive pulmonary fat embolism
Subtask 1: After post observation period and euthanasia obtain upper, hilar, and lower lung biopsies for h/e and oil red o staining by blinded pathologist (3 samples per subject times 48 subjects – 144). Timeline: 22-24 months. Status: complete, April 2023
Milestone #12: Inform the relationship between IO infusion pressure and acute occlusive pulmonary arterial fat embolism. Timeline: 36 months. Status: complete, April 2023
Major Task 4: Define practical relationship b/w IO infusion pressure and acute bony injury
Subtask 1: Post observation obtain three bone biopsies adjacent to IO needle insertion site to assess for periosteal hemorrhage and fractures within the trabecular network of cancellous bone. 3 biopsies per subject times 48 subjects = Same site 48. Timeline: 22-24 months. Status: complete, April 2023.
Milestone #13: Inform the relationship between IO infusion pressure and acute bony injury (Periosteal hemorrhage). Timeline: 36 months. Status: Complete, April 2023.
Major Task 5: Define practical relationship between IO infusion pressure and acute cerebellar hypoxia as a surrogate for occlusive brain arterial fat emboli and intravascular hemolysis
Subtask 1: From baseline post intubation monitor rS02 via NIRS as a surrogate for evidence of cerebral hypoperfusion and hypoxia during key phases of the protocol to include post exsanguination, IO infusion, and the post IO infusion period. On necropsy subject cardiac atrial septum will be assess macroscopically for septal defects for correlation back to findings of cerebral hypoxia. Timeline: 22-24 months. Status: complete, April 2023
Milestone #14: Inform the relationship between IO infusion pressure and acute cerebral hypoxia as a surrogate for cerebral fat embolism and intravascular hemolysis. Timeline: 36 months. Status: Not complete. This data has not been analyzed. Plan to analyze after manuscript submitted for main study and submit this data as a separate manuscript. Timeline December 2023-January 2024 for analysis.
Major Task 6: Define practical relationship b/w IO infusion pressure and acute renal injury (If funding not sufficient for pathologic services this analysis will be removed. Previous research on similar model has not shown renal injury in the acute phase after intraosseous infusion)
Subtask 1: Post observation obtain upper kidney biopsies from all 48 animals to assess for evidence of acute renal injury between four infusion strategies varying by degree of pressure. Assessing for diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, or frank necrosis observed. (If the budget permits) Timeline: 22-24 months. Status: N/A – do not have the budget to perform this additional collection.
Milestone #15: Inform the relationship between IO infusion pressure and acute renal injury. (If the budget permits). Timeline: 36 months. Status: N/A – do not have the budget to perform this additional collection.

What was accomplished under these goals?

Major Activities, Specific Objectives, and Significant Results:

Major Activities

1. Performed major administrative tasks related to the grant.
    - Obtained No Cost Extension to complete computational model and in vivo work (Specific Aim 3).
    - Completed remaining research labs (Specific Aim 3).
    - Completed contract for design of computation model with Dr. Vinals at University of Minnesota (Specific Aim 3).
    - Preliminary computational model description complete, awaiting flow, pressure and anatomic variables to be added (Specific Aim 3).
2. Presented preliminary main study results to the 2023 MHSRS (Poster) and ACEP 2023 (Podium) (Specific Aim 3).
3. Accepted manuscript on end user characteristics and placement IO devices in Military Medicine (Specific Aim 2).
4. Submitted manuscript on impact of flow and pressure parameters from IO device catheter tip placement location to Journal of the American College of Emergency Medicine Open (Specific Aim 2).
5. Completed analysis of flow and pressure characteristics of different IO infusion methods (Specific Aim 3).

Specific Objectives

Specific Aim 1

- Manuscript acceptance and publication in *American Journal of Emergency Medicine* (AJEM)
- Completed Specific Aim 1

Specific Aim 2

- Presented study findings at regional and national conferences
- Began working on three manuscripts:
    1. Pilot IO placement, looking at correlation of flow rate, pressures with IO needle placement in the bone using different IO infusion methods (small sample size). Target *Journal of Special Operations Medicine (JSOM)*.
    2. User characteristics of IO needles. Published in *Journal of Military Medicine (Mil Med).*
    3. IO placement, with correlation of flow rate, pressures with IO needle placement in the bone using different IO devices (large sample size). Submitted to *Journal of American College of Emergency Physicians (JACEP Open)*.

Specific Aim 3

- Purchased supplies
- Hired a veterinary technician
- Completed in vivo pilot study
- Submitted to and presented findings at regional and national conferences
- Completed main in vivo study
- Initiated work on computational model of intraosseous flow based on in vivo data
- Began working on three manuscripts:

1. Main In In Vivo Flow study, looking at correlation of flow rate, pressures with IO needle placement in the bone using different IO infusion methods and effect on clinical complications like intravascular hemolysis, pulmonary or coronary marrow emboli, or damage to trabecular bone). Target *Transfusion THOR supplement.*
2. Study of effects of intraosseous flow on cerebral perfusion utilizing intracranial NIRS monitoring. Target *Journal of Surgical Research (JSR)*.
3. In Vivo Pilot Model development highlighting challenges of using CDPA for rapid infusion and effects of local hypocalcemia and resultant dysrhythmias and pulmonary hypertension. Target *Journal of Surgical Research (JSR)*.

Significant Results:

Computational Model Pilot Construct Completed (Aim 3):

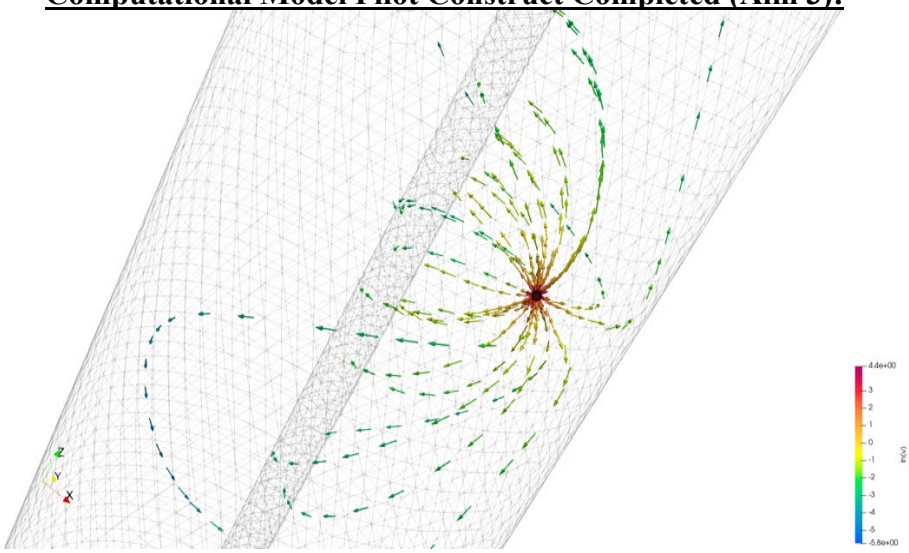


Figure 1: Columnar Skeleton of IO Infusion Model with potential exits via emissary veins

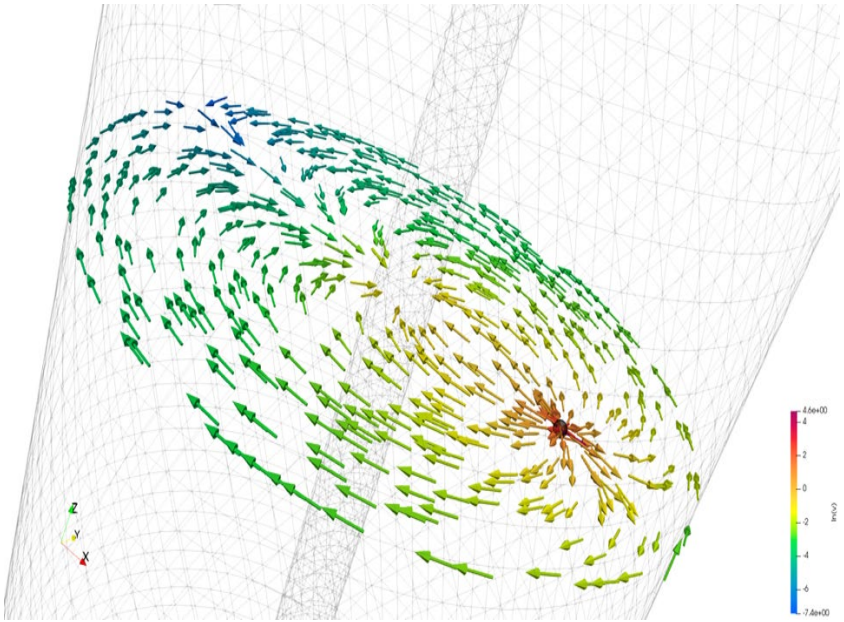
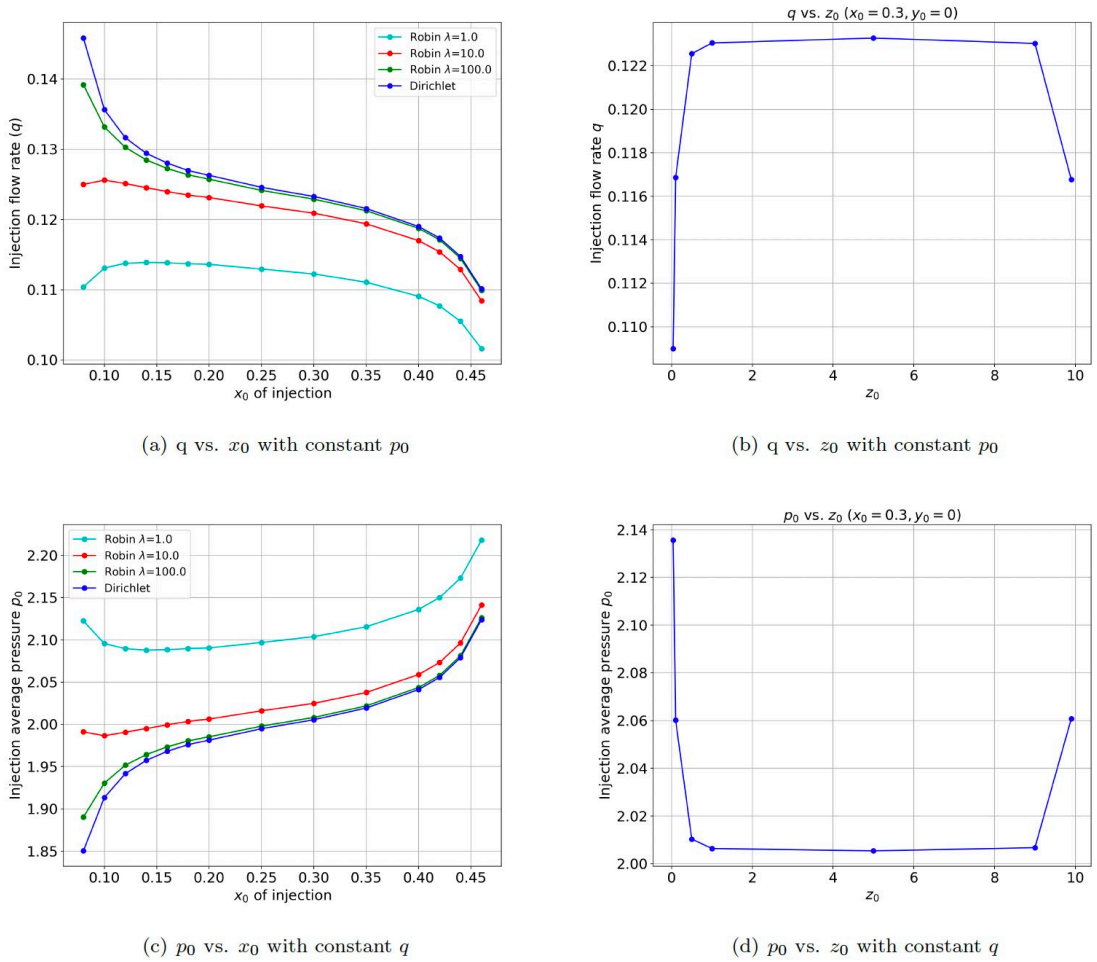


Figure 2: Intrinsic Centripetal and Centrifugal flow patterns within the Medullary Space



(a) q vs. x_0 with constant p_0

(b) q vs. z_0 with constant p_0

(c) p_0 vs. x_0 with constant q

(d) p_0 vs. z_0 with constant q

Figure 3: Injection flow rate q and average injection pressure p_0 for varing injection locations and λ. $z_0 = 5.0$ and $y_0 = 0$ in (a),(c).

Abstracts Submitted for MHSRS 23 (Poster) and ACEP 23 (Podium) Presentations (Aim 3):

Methods:

Prior to beginning the experiment, the animal was intubated, and surgical procedures were performed to obtain vascular access. The near infrared spectroscopy (NIRS) monitor was set up to measure brain oxygen levels throughout the experiment. Baseline vitals and labs (hemolysis, thromboelastography (TEG), blood chemistry) were taken following procedures.

Exsanguination to achieve a MAP ~30 was done to induce hemorrhagic shock, with blood being preserved in heparinized blood bags. Following blood loss, the animal was allowed to stabilize for a 30-minute period, with vitals recorded at ten-minute intervals. Hemolysis was assessed in the blood bag prior to infusion. After the observation period, labs were redrawn. Infusion strategy (pressure bag, push-pull with a 60cc syringe, handpump, LifeFlow®) was randomly assigned for an investigator to perform. In the pilot study, both single-site and double-site IO infusion was

tested. An autologous transfusion (~10-15% of blood volume) was then given intraosseously based on the random assignment. Flow rates and in-line pressures were recorded. Following infusion, labs were taken again. The animal was then observed for a one-hour observation period, and final labs were performed. Vitals were collected throughout the infusion and observation period. The animal was euthanized, and the humerus was removed and taken to computed tomography (CT) for scanning to locate the position of the IO needle. The heart was inspected for atrial or ventricular septal abnormalities with methylene blue. Heart, lung, and bone pathology specimens were collected post-mortem and sent to a veterinary pathologist for analysis.

Results:

The following are our flow rate, mean/max pressures, and hemolysis (presence of plasma free hemoglobin in blood) results.

Figure 1. Flow Rates by Method

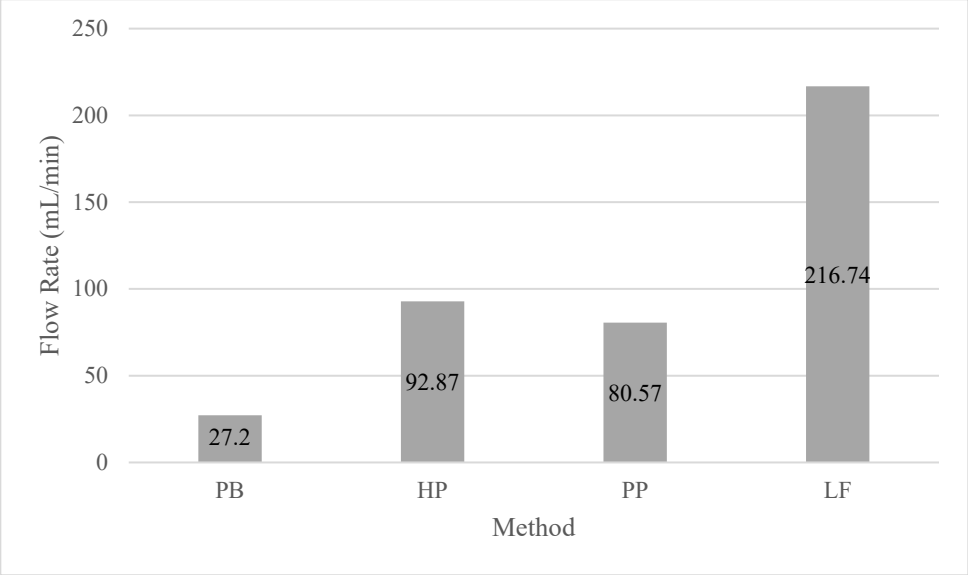


Figure 2. Mean Infusion Pressures by Method

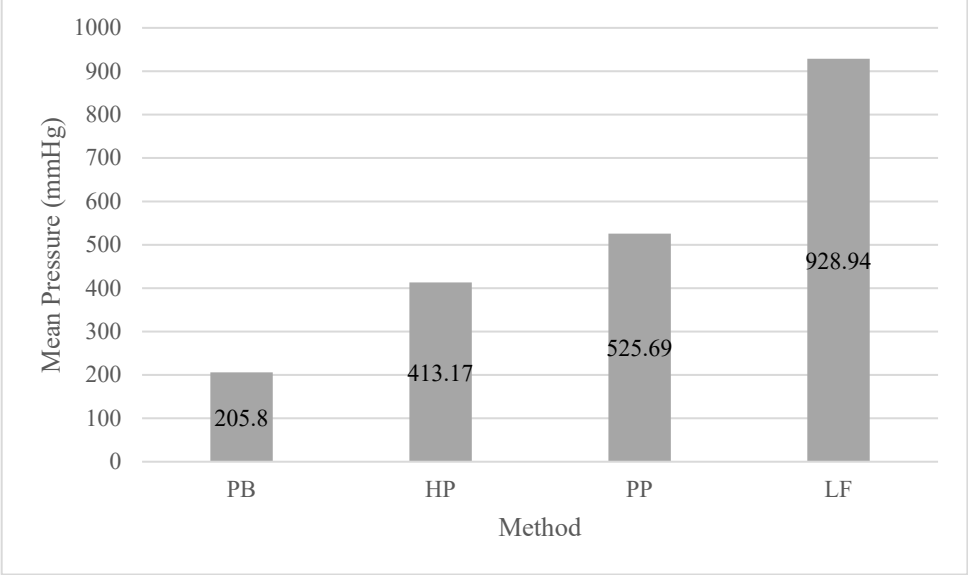


Figure 3. Max Infusion Pressures by Method

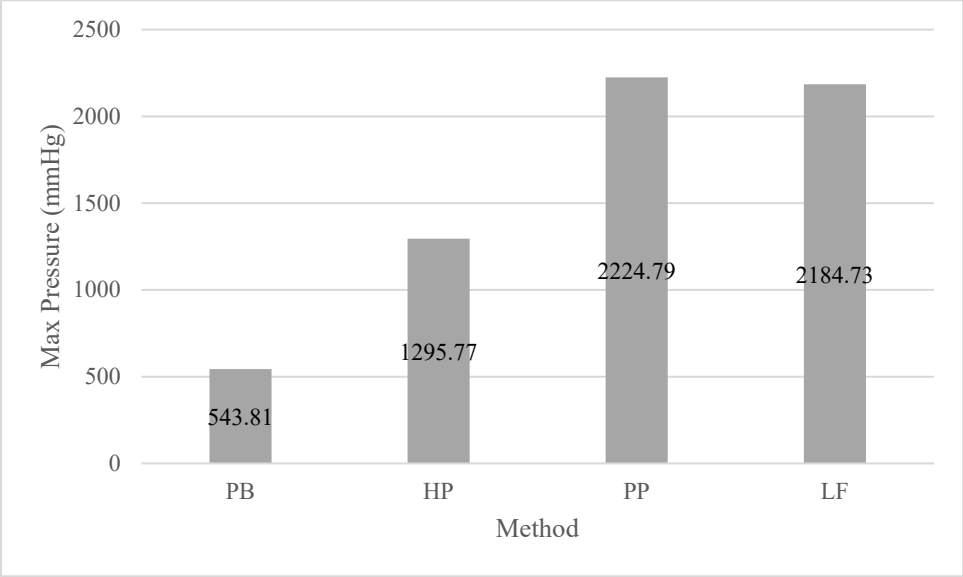
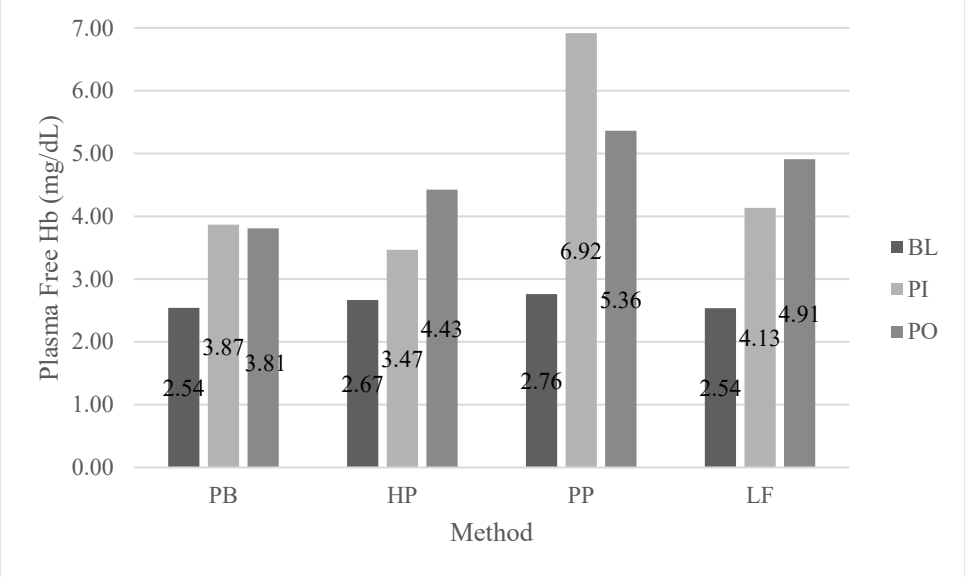


Figure 4. Plasma Free Hb by Method



Consistent with our cadaveric swine model results, the pressure bag had the lowest flow rates. LifeFlow offered high flow rates, but at the cost of high mean and max pressures. The handpump exhibited similar flow rates to push-pull with a 60cc syringe. However, the handpump had significantly lower pressures than the push-pull method. There was no occlusive fat emboli

identified on oil red o staining of pulmonary or coronary artery biopsies of any of the four methods. There was also no damage noted to the trabecular bone adjacent to infusion zone with any of the methods (ACEP and MHSRS presentations attached).

The remaining data (NIRS, CT placement), including flow rate, pressure, and hemolysis data with statistical analysis complete is awaiting final analysis by our data analyst and will have a draft of the manuscript with this data included in the winter 2024 quarterly report.

In Vivo Pilot Model Development (Aim 3):

Methods:

Prior to beginning the experiment, the animal was intubated, and surgical procedures were performed to obtain vascular access. The near infrared spectroscopy (NIRS) monitor was set up to measure brain oxygen levels throughout the experiment. Baseline vitals and labs (hemolysis, thromboelastography (TEG), blood chemistry) were taken following procedures.

Exsanguination to achieve a MAP >20-30 was done to induce hemorrhagic shock, with blood being preserved in citrated or heparinized blood bags. Following blood loss, the animal was allowed to stabilize for a 30-minute period, with vitals recorded at ten-minute intervals. Hemolysis was assessed in the blood bag prior to infusion. After the observation period, labs were redrawn. Infusion strategy (pressure bag, push-pull 60cc, handpump, LifeFlow) was randomly assigned for an investigator to perform. In the pilot study, both single-site and double-site IO infusion was tested. An autologous transfusion (~10-15% of blood volume) was then given intraosseously based on the random assignment. Flow rates and in-line pressures were recorded. Following infusion, labs were taken again. The animal was then observed for a one-hour observation period, and final labs were performed. Vitals were collected throughout the infusion and observation period. The animal was euthanized, and the humerus/humeri was removed and taken to computed tomography (CT) for scanning to locate the position of the IO needle. The heart was inspected for atrial or ventricular septal abnormalities with methylene blue. Heart, lung, and bone pathology specimens were collected post-mortem and sent to a veterinary pathologist for analysis (main study only).

Results:

Infusion results followed a similar trend to study results from Specific Aim 1; generally, infusions rates were fastest using Life Flow, followed by handpump and push-pull 60cc, and pressure bag. Mean and maximum pressures also followed this trend, with pressures being highest for Life Flow and lowest for pressure bag. In the pilot, double-site transfusion for the handpump was predictably faster than single-site. Interestingly the pressure bag double-site was outperformed by the single site, which we believe is due to catheter tip placement. Evidence of hemolysis was absent in all specimens. Interpretation of TEG, NIRS, and pathology results is ongoing. A comprehensive analysis of all study variables will be included within the pilot and main study manuscripts.

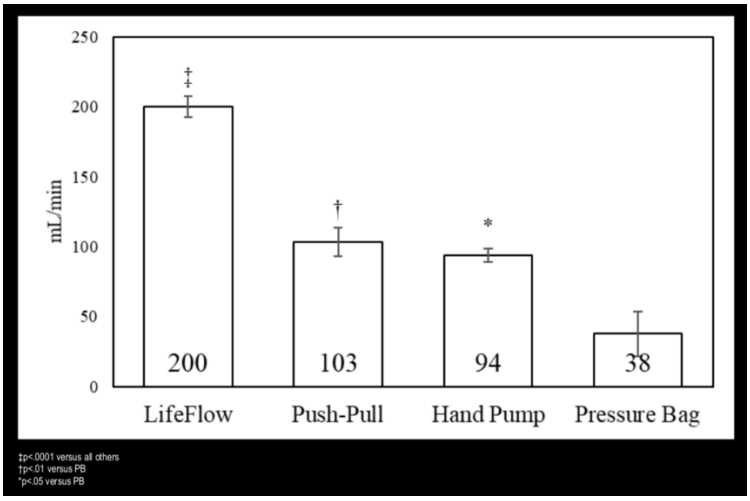


Table 1: IO Infusion Flow Rates By Strategy

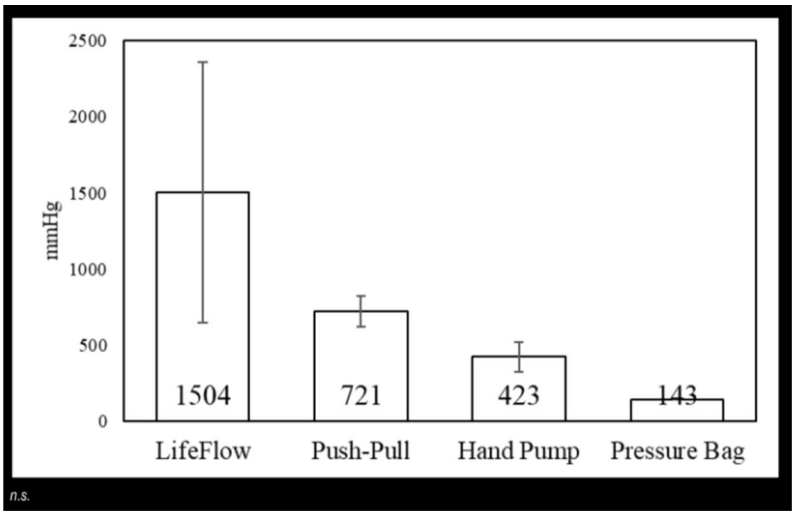


Table 2: IO Infusion Pressures (Mean) By Strategy

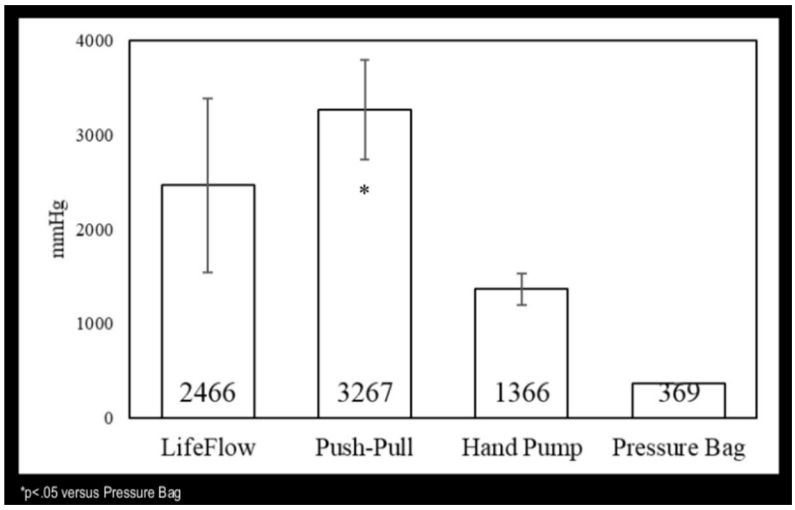


Table 3: IO Infusion Pressures (Maximum) By Strategy

Additional Achievements Included in Appendices:

1.) Mil Med Publication (IO Placement – Aim 2)
2.) ACEP Presentation (In Vivo Flow – Aim 3)
3.) MHSRS Presentation (In Vivo Flow – Aim 3)
4.) JCACEP Open Manuscript Submission (IO Placement – Aim 2)
5.) Computational Pilot Model Mathematical Fundamental Design (Computational Model – Aim 3)
6.) TCCC Vascular Access Module Update (All Aims)

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.

Training activities during this year included one-on-one mentoring of Emergency Medicine residents in preparation for conference abstract submissions and presentations, as well as manuscript preparation. Resident physicians on the project also received in-depth, hands-on training for different IO infusion strategies and hemorrhagic shock animal model techniques. In general, the residents involved in these studies have become more familiar with the research process, giving them the tools they need to formulate their own research questions and studies as they move forward in their medical career.

Professional development during this year primarily occurred in the form of conferences. Residents were able to participate in the animal research labs and make conclusions based on study results, leading them to create quality presentations and disseminate the findings to a wide variety of research conferences.

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.

The results of our project were disseminated to both Military Medicine and Emergency Medicine communities in the form of conference posters and presentations. Results were also disseminated to the committee on TCCC leadership. This can be seen in the form of TCCC Module 8 (Vascular Access) update.

We presented our findings on IO device flow, pressure, and user characteristics (Specific Aim 1 and 2) and IO infusion methods (Specific Aim 3). We have shared our results at the following venues:

Specific Aim 1 in AJEM (PMID – 35123236)
Specific Aim 2: AMSUS 2022, Navy Medicine West ARC 2022, Navy Wide ARC 2022, MHSRS 2022
Specific Aim 3: Navy Medicine West ARC 2023, Navy Wide ARC 2023, MHSRS 2023, ACEP 2023

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

During the next reporting period (10/16/2023-1/15/2024) we plan to have submitted our manuscripts for Specific Aim 2 and Specific Aim 3 (pilot study) and have made additional progress on data collection for Specific Aim 3, now that we have a veterinarian present at our research facility. We will continue to submit our findings to additional research conferences.

In particular, we plan to:
-Continue searching for and hire a veterinary technician
-Submit manuscripts on Specific Aim 2 findings (3 total; IO placement pilot to *Journal of Special Operations Medicine*, IO device user characteristics to *Military Medicine*, IO placement to *Annals of Emergency Medicine*)
-Submit manuscript on findings of pilot in vivo study for submission to JSR (Specific Aim 3)
-Begin working on abstracts and planning submission to 2023 research conferences
-Make progress in data collection for in vivo main study (Specific Aim 3)

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?

The results of Specific Aim 1-3 will expand the base of knowledge and research on IO devices and infusion methods for TCCC in order to treat critically injured soldiers that require IO infusion during a near peer conflict in traditional or maritime environments. We have tested nearly every available IO device on the market on both humeral and sternal sites and assessed time to placement, flow rate, mean and peak pressure, and operator opinion of ease of use, comfort with device, device efficacy, and hand fatigue. The findings have given us insight on which IO devices may be best for corpsmen and medics to carry with them in the field. We also reviewed the placement location in the bone by device and found that some devices were more likely to have a placement in optimal conditions than others. This information will inform TCCC on the best devices to use for patients in the field to obtain quick and accurate IO placement when minutes matter. This information has been published in AJEM and Mil Med and passed to TCCC leadership for incorporation into training guidelines.

The findings of Specific Aim 3 have informed which IO infusion methods generate the greatest flow rates while also minimizing extreme pressures, providing an optimal flow while minimizing potential negative clinical complications associated with high pressures within the bone marrow in a dynamic live model. The Hand Bulb technique minimizes infusion pressures while providing significantly faster flow rates than the pressure bag. The Life Flow device generated the highest infusion speeds with the highest infusion pressures. The only infusion technique where low grade (pfHgb <25 mg/dl) was noted was with the push pull technique.

Additionally, the findings highlight in an in vivo model the impact IO catheter tip placement plays on infusion pressure and flow rates. This data is being analyzed currently with plans to publish in manuscript form this winter. The in vivo data has also allowed us to work with the University of Minnesota collaborator, Dr. Jorge Vinals to create a computational model pilot of IO flow. The pilot could utilized additional data from human humerus and sternal anatomy to create representative computational models of IO flow in this common human infusion sites. The pilot computational model once further developed could lead to novel catheter device development in civilian-military partnerships.

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.

In addition to the primary purpose of informing military first responders and TCCC, the findings of this study will also impact civilian prehospital care, emergency medicine, trauma care, and critical care. There are many similarities between the prehospital environment and austere field conditions; patients are often critically ill and require rapid transfusion, but IV access may be difficult in these cases due to loss of fluids and/or blood. Difficult vascular access is also a challenge within trauma surgery, emergency medicine, and critical care practice environments. The findings on best IO infusion strategies and devices, as well as the effect of placement on flow rate, can improve quality of IO infusion for all of these disciplines. Our findings are revealing the fastest and safest way to infuse blood in these conditions, the IO device that performs most optimally, and the optimal catheter tip placement location for IO device users.

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 computational pilot model will be further development in future grant funded efforts. The pilot model will be applied in future research efforts to human humeral and sternal models. This knowledge product could lead to future device development and transfer to technology. The computational pilot will be available to DARPA or other government research agencies.

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 knowledge products from this study can better inform care delivered in a Distributed Maritime Operations environment where Independent Duty Corpsman and General Medical Officers are likely to be the providers in charge of delivering care. These providers are more likely to use IO catheters than central venous catheters and this better understanding of best transfusion techniques will likely improve overall survivability on these platforms.

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.

a. Actual Problems or delays and actions to resolve them

Due to the previous issues we have experienced as outlined in prior reports, including issues in the pilot study, military deployment of the PI (CDR Auten) on the INDIOPACOM Expeditionary Resuscitative Surgical Team platform, where he was placed on a 48 hour prepare to deploy between October 1st, 2021 and September 30th, 2022, and the absence of a veterinarian at our command from June-October 2022, we completed data collection for Specific Aim 3 later than expected. The No Cost Extension was approved for dissemination of findings and closure to report to account for these issues that have impeded completion.

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.

a. Anticipated Problems/Issues

No anticipated problems/issues. The No Cost Extension will allow us to complete the computational model, submit the manuscript for Aim 3 to peer review and complete analysis on cerebral blood flow during intraosseous infusion.

Changes that had a significant impact on expenditures:

N/A

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

We submitted one amendment related to the swine animal subjects under the IACUC during this reporting period: we increased the acceptable weight range of the swine, modified the anesthesia protocol, and added IV heparin to the protocol.

Both changes were approved by the IACUC.

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).*

Lee KJ, McGuire MM, Harvey WC, Bianchi WD, Emerling AD, Reilly ER, Bebarta VS, Lopez JJ, Zarow GJ, Auten JD. Performance comparison of intraosseous devices and setups for infusion of whole blood in a cadaveric swine bone model. Am J Emerg Med. 2022 Apr;54:58-64. doi: 10.1016/j.ajem.2022.01.039. Epub 2022 Jan 25. PMID: 35123236. Status of Publication: accepted Acknowledgement of federal support: Yes

Kay VC, Gehrz JA, Grady DW, Emerling AD, McGowan A, Reilly ER, Bebarta VS, Nassiri J, Vinals J, Schrader A, Zarow GJ, Auten JD. Application Times, Placement Accuracy, and User Ratings of Commercially Available Manual and Battery Powered Intraosseous Catheters in a High Bone Density Cadaveric Swine Model. Mil Med. 2023. In press. PMID: Pending. Status of Publication: accepted. Acknowledgement of federal support: Yes

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).*

Butler F, Auten, J. Tactical Combat Casualty Care Module 8: Vascular Access.

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.*

Navy Medicine West ARC 2023 (2)
Navy Wide ARC 2023 (1)
MHSRS 2022 (1)
ACEP (1)

- **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.

We identified an effective technique to minimize hypocalcemia in swine receiving rapid transfusion, by replacing citrate in blood bags with heparin. We plan to disseminate this technique in future publications in Journal of Surgical Research.

We identified an optimal IO infusion technique (Hand Bulb) that provides minimal infusion pressures (<1000mmHG) with significantly improved flow rates when compared to pressure bag infusion. Also showed that the LifeFlow could safely be used for IO infusion and achieved flow rates 3 times higher than any other technique. This was shared with TCCC Chair, CAPT Travis Deaton and THOR Co-Director Dr. Phillip Spinella and will be submitted for publication in Transfusion.

- **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. Anticipate novel computational pilot model of IO flow will submit to DHA IP for review.

- **Other Products**

We are in process of developing a pilot computational model for IO flow. Mathematical basis and columnar framework are attached as an appendices.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jonathan Auten
No change.

Name: Benjamin Walrath
No change.

Name: William Bianchi
No change.

Name: Andrew McGowan
No change.

Name: Vik Bebarta
No change.

Name: Erin Reilly
No change.

Name: Jorge Vinals
Project Role: *Subject Matter Expert for Computational Model Development*
Researcher Identifier: SCOPUS ID - 7006012672
Nearest person month worked: *1 month on Contract*
Contribution to Project: *Dr. Vinals is beginning the construct of the computational model and has developed a columnar model of which to build off of with our study data*

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://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.*

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.