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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 (I) 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, I 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 l lood infusion strategy est alances flow with safety concerns ide 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 l 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**

15. SUBJECT TERMS NONE LISTED

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a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
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TABLE OF CONTENTS

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

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).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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: 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. Although we disseminated our major findings, we have performed additional exploratory analyses and are continuing to disseminate our findings. We also 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: not complete. We are currently writing three manuscripts on the findings from Specific Aim 2 and hope to submit soon.

Milestone #6: *Knowledge product transferred to public domain.* Timeline: 16 months. Status: not complete

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. Status: complete, September 2021

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

Subtask 4: Hire Veterinary Technician Timeline: 4-10 months. Status: in progress, 50% complete. We interviewed a candidate and prepared an offer; however she had decided to take another position. We are still currently searching for a candidate to fill the position.

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: in progress, 27% complete (8/8 pilot subjects complete. Due to animal loss, the IACUC allowed us to use 10 animals total for the pilot. 7/48 main subjects complete. Overall 15/56 subjects complete for pilot and main study)

Milestone #8: *Data collection complete.* Timeline: 22-24 months. Status: not complete

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 may continue to present at additional conferences.

Subtask 6: Submit manuscript for Aim 3. Timeline: 32-36 months. Status: not complete. We are planning to begin the writing process for the pilot study soon for our target journal, *Journal of Surgical Research* (JSR).

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: not complete

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: in progress, 15% complete (7/48 complete)

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: in progress, 15% complete (7/48 complete)

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: in progress, 15% complete (7/48 complete)

Subtask 4: 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: in progress, 15% complete (7/48 complete)

Milestone #10: *Inform the relationship between IO infusion pressure and intravascular hemolysis.* Timeline: 36 months. Status: not complete

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: not complete

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: not complete

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: in progress, 15% complete (7/48 complete)

Milestone #12: *Inform the relationship between IO infusion pressure and acute occlusive pulmonary arterial fat embolism.* Timeline: 36 months. Status: not complete

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: in progress, 15% complete (7/48 complete)

Milestone #13: *Inform the relationship between IO infusion pressure and acute bony injury (Periosteal hemorrhage).* Timeline: 36 months. Status: not complete

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: in progress, 15% complete (7/48 complete)

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

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: 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?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Activities

- Manuscript acceptance and publication for Specific Aim 1 **(**Completion of Specific Aim 1)
- Presentation of Specific Aim 2 and 3 at regional and national conferences
- Worked on manuscripts for Specific Aim 2
- Completed pilot study for Specific Aim 3
- Data collection for main study of 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)
    2. User characteristics of IO needles
    3. Main study IO placement, with correlation of flow rate, pressures with IO needle placement in the bone using different IO devices (large sample size)

Specific Aim 3

- Purchased supplies
- Worked toward hiring a veterinary technician
- Completed in vivo pilot study
- Submitted to and presented findings at regional and national conferences
- Began data collection for in vivo main study

Significant Results

Specific Aim 2
Methods:
In this study, 210 infusion trials were performed utilizing two specimen types: cadaveric swine humeri and sternums. Bone density was similar to that of an average warfighter. We used five different humeral IO devices: the battery-powered EZ-IO needle and drill, along with four manual devices, the Jamshidi IO, NIO device, SAM IO manual drill and needle, and TALON humeral IO. We used two different sternal IO devices: the FASTR (PYNG) IO and TALON sternal IO. In total, there were seven different device combinations. Researchers infused 500 mL of crystalloid into the porcine bone using the 60cc syringe push-pull method.

Placement time, flow rates, and mean and maximum infusion pressures were collected for each trial, as well as subjective Likert surveys regarding IO device performance. Images were taken of the cadaveric swine specimens via CT with the IO needle intact to determine the location of the catheter tip within the bone. A model with three defined Zones of infusion was created and used to analyze position of placement in the bone as it relates to infusion pressures and flow rates.

Results:
Main results of the study were reported on in Annual Report 2020-2021. Further analyses were done to illuminate the breakdown of Zone placement for each IO device. Zone 1 and Zone 2 are considered ideal, accurate placement based on our previous findings. Zone 3 is considered non-ideal, improper placement. Results showed that the TALON and EZ-IO devices performed superiorly, with no to low rates of Zone 3 placement. The Jamshidi and NIO devices were incorrectly placed about one-third of the time (Table 1). Overall, the EZ-IO and TALON had the best performance and were also most favorably rated. Our results suggest that TALON may be a viable backup to the EZ-IO needle and drill kit, which runs on a non-replaceable battery.

Table 1. Catheter Tip Zone Placement by IO Device

	Zone1	Zone2	Zone3
TALON (Sternal)	30%	70%	0%
TALON (Humeral)	43%	50%	7%
EZ IO	60%	33%	7%
FASTR (Sternal)	23%	63%	13%
SAM IO	23%	53%	23%
Jamshidi	27%	43%	30%
NIO	23%	40%	37%

Bold < Outlined, p<.05

Specific 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.

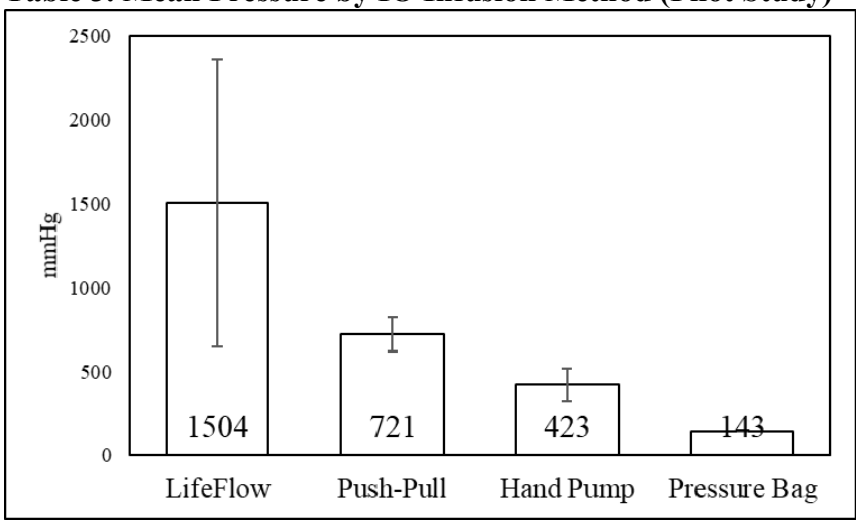
Exsanguination to achieve a MAP >20-30 was done to induce hemorrhagic shock, with blood being preserved in citrated or heparinized blood bags. Following blood loss, the animal was allowed to stabilize for a 30-minute period, with vitals recorded at ten-minute intervals. Hemolysis was assessed in the 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 LifeFlow, followed by handpump and push-pull 60cc, and pressure bag. Mean and maximum pressures also followed this trend, with pressures being highest for LifeFlow 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 2. Flow Rates by IO Infusion Method (Pilot Study)

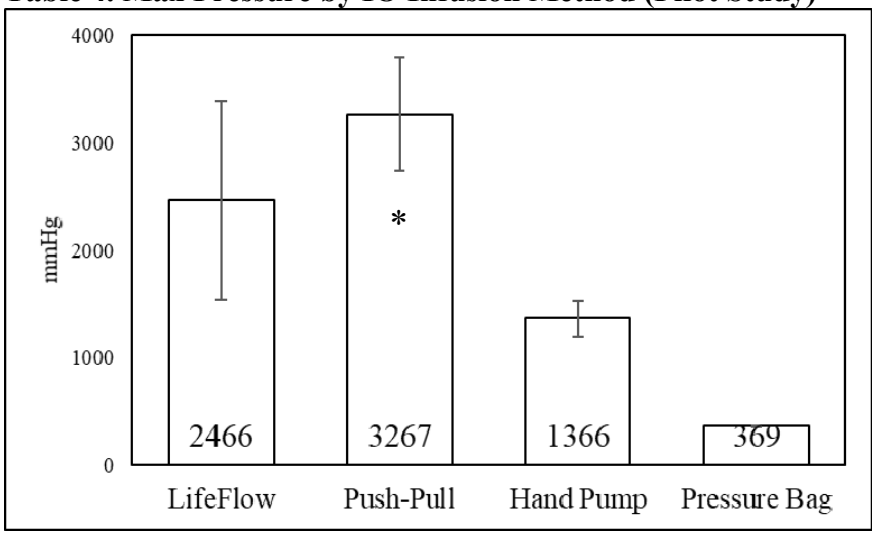
‡p<.0001 versus all others
†p<.01 versus PB
*p<.05 versus PB

Table 3. Mean Pressure by IO Infusion Method (Pilot Study)



n.s.

Table 4. Max Pressure by IO Infusion Method (Pilot Study)



*p<.05 versus Pressure Bag

Table 5. Flow Rates and Pressures between Different IO Infusion Strategies (Main Study)

Infusion Strategy	Infusion Flow Rate (mL/min)	Mean Pressure (mmHg)	Maximum Pressure (mmHg)
Pressure Bag	20.06	149.15	327.68
Hand Pump	60.99	334.56	817.75
Hand Pump	73.94	434.46	981.25
Push-Pull	44.15	537.87	2556.4
Push-Pull	44.56	481.98	1215.45
Push-Pull	86.36	263.48	939.42
LifeFlow	336.80	1693.40	3610.84

Other Achievements

Manuscript acceptance to AJEM, published in April 2022
Seven acceptances to present research findings at regional and national conferences
Received first place in Staff Research Category, Navy Medicine West ARC 2022
Received first place in Resident Research Category, Navy Medicine West ARC 2022

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. During this reporting period, a total of seven posters/presentations have been delivered at conferences, with several first-place wins.

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.

We presented our findings on IO device flow, pressure, and user characteristics (Specific Aim 2) and IO infusion methods (Specific Aim 3 pilot study). Specifically, we shared our results at the following conferences:

Specific Aim 2: AMSUS, Navy Medicine West ARC, Navy Wide ARC, MHSRS
Specific Aim 3: Navy Medicine West ARC, Navy Wide ARC, MHSRS

We also published the manuscript for Specific Aim 1 in AJEM.

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

During the next reporting period (9/15/2022-12/14/2022) 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The results of Specific Aim 2 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. Additionally, 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.

The findings of Specific Aim 3 are informing us 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. Additionally, we are continuing to highlight how important the placement within the medullary space or cancellous bone is to flow characteristics. This information is critical for first responders; it will provide them the guidance on what IO infusion method should be used to safely and effectively resuscitate critically ill and injured patients in time-sensitive situations.

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.*

Nothing to Report.

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.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

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.

The greatest change in approach over the past year was a modification to our hemorrhagic shock model. We had to modify several aspects of our IACUC protocol, including the anesthetics and medications used, due to swine sensitivity to rapid transfusion. This was a new issue that had not been experienced in previous similar studies our team performed with pigs, and we believe it is due to the new swine vendor used in this protocol. We were ultimately able to resolve the issue and carry on with the study. We hope to inform future researchers who experience these issues with the knowledge we have gained from our protocol.

Because we had to add heparin as a medication to our protocol, we had to purchase new TEG supplies with heparinase to attempt to measure blood coagulation. However, we are still unsure whether our results for this study variable will be valid due to the amount of anticoagulant the pigs are receiving. We are working with Haemonetics (TEG supplier) to try to obtain valid data despite this limitation, however if this is not feasible, we will omit coagulation data from the study.

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.

An issue that has impeded progress is the military deployment of the PI (CDR Auten) on the INDIOPACOM Expeditionary Resuscitative Surgical Team platform. He was placed on a 48 hour prepare to deploy between October 1st, 2021 and September 30th, 2022. We had other staff AIs on the protocol who were able to assist during the labs, but because they are full-time Emergency Medicine physicians, their schedules were limited. We added an additional investigator to give us more coverage at labs. With the PI now back from deployment, we have the time period between October 2022-April 2023 to finish the in vivo study.

Additionally, the veterinarian at our hospital's vivarium had orders for a new command and left June 14th, 2022. There was a delay between his leave and the new veterinarian onboarding. Because we cannot perform labs without a veterinarian present, we were not able to schedule any labs between June 15th, 2022 to late October 2022, due to the new veterinarian onboard date. Our previous veterinarian put together resources for the new veterinarian to use regarding our study in order to ensure a smooth transition when we begin labs again.

Due to this and previous issues in the pilot study, we did not complete the main protocol by our original planned date of Summer 2022. However, we are still on track to complete the main protocol within the timeline of our grant which ends in Fall 2023; we are currently targeting a Spring 2023 completion date. We would like to request a 6 month No Cost Extension (NOE) for dissemination of findings and closure report to account for CDR Auten's deployment and the absence of a veterinarian.

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

There has been a delay in hiring a veterinary technician to assist with the live animal portion of the grant. To resolve this issue, we have placed the job advertisement on the American Association for Laboratory Animal Science website to broaden our scope of applicants and spread awareness about position. This has had a significant impact on expenditures, as the veterinary technician position was funded for two years.

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

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

AMSUS 2022 (1)
Navy Medicine West ARC 2022 (2)
Navy Wide ARC 2022 (2)
MHSRS 2022 (2)

- **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.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Data

We completed the dataset for the pilot of the in vivo study and started the dataset for the main study (Specific Aim 3). We have collected the following information for each subject, each of whom was randomly assigned to one of four IO infusion strategies, during baseline, throughout exsanguination, infusion, post-infusion, and post-observation:
1) vital signs (BP, MAP, HR, RR, O2, temperature), urine output
2) TEG values
3) deoxyhemoglobin and oxyhemoglobin concentrations and tissue saturation index using NIRS (throughout entire study)
4) blood hemolysis (visual for pilot, quantified for main study)
5) mean infusion pressure (during infusion only)
6) peak infusion pressure (during infusion only)
7) flow rate (during infusion only)
8) CT scans of each IO needle position within the bone (Zone 1, 2, or 3) (collected post-mortem)
9) pathology of heart, lungs, bone (main study only) (collected post-mortem)

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

<u>Example:</u>

Name: *Mary Smith*

Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

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.

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:
<u>Organization Name:</u>
<u>Location of Organization: (if foreign location list country)</u>
<u>Partner's contribution to the project</u> (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.*