AWARD NUMBER: W81XWH-20-2-0033

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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REPORT DATE: October 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
OCTOBER 2021	ANNUAL	15SEPT2020 - 14SEPT2021

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-20-2-0033

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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E-Mail:

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

SUPPLEMENTARY NOTES

14. **ABSTRACT: Three of the top five preventable causes of battlefield death (extremity hemorrhage, junctional hemorrhage, noncompressible torso hemorrhage) rely on rapid vascular access to initiate Advanced Resuscitative Care (ARC). Current Tactical Combat Casualty Care (TCCC) guidelines stress the importance of initiating resuscitation within 30 minutes of wounding. However, the massively hemorrhaged patient, such as dismounted complex blast injuries (DCBI), presents a vascular access challenge to even the most seasoned medical teams. Intraosseous (IO) catheters provide non-collapsible access in patients that can serve as a bridge to therapy while preparations are made for central venous access, when peripheral access is not obtainable. For this reason, IO access has been used extensively over the past decade by military first responders initiating remote damage-controlled resuscitation (rDCR). Despite the clear importance of early vascular access in ARC for blood product transfusion, a knowledge gap exists on which IO blood infusion strategy best balances flow with safety concerns. Wide clinical variability exists with infusion strategies ranging from gravity to manual syringe infusion. Both safety and efficacy concerns have been expressed within the trauma/critical care community that IO gravity infusion cannot meet the demands of rDCR. Concern also exists that infusion pressures above gravity may lead to increased shear stresses causing intravascular hemolysis and/or displacement of marrow into the venous system leading to fat emboli. Filling this knowledge gap by determining which infusion strategy possesses flow rates rapid enough to preserve life but minimize secondary infusion pressure related complications has the long-term impact of improving battlefield survival.**

15. SUBJECT TERMS NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	29	**19b. TELEPHONE NUMBER** *(include area code)*

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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. 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 for critically injured warfighters in the austere environment. This project is multifaceted and seeks to answer several questions regarding IO in the prehospital environment: 1) which IO infusion technique provides the fastest flow rate, while also minimizing potential complications resulting from high pressures, 2) which IO device is objectively and subjectively rated best for use in the austere military environment, 3) how IO placement affects the subsequent flow and pressures generated during infusion.

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

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

2. **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: not complete

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: in progress [4/6 presentations complete – 67%]

Subtask 5: Submit manuscript for Aim 2. Timeline: 14-16 months. Status: not complete

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: in progress (95%)
Subtask 3: Hire CRC. Timeline: 1-8 months. Status: complete, September 2020
Subtask 4: Hire Veterinary Technician Timeline: 4-10 months. Status: in progress, 25% complete
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, 4% complete (2/8 pilot subjects)
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: not complete
Subtask 6: Submit manuscript for Aim 3. Timeline: 32-36 months. Status: not complete
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: not 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: not 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, not 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: not complete
Milestone #10: *Inform the relationship between IO infusion pressure and intravascular hemolysis.* 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: not 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: not 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: not 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: not complete

Milestone #15: *Inform the relationship between IO infusion pressure and acute renal injury. (If the budget permits).* Timeline: 36 months. Status: not complete

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:

- Completion of Specific Aim 1 and 2 studies
- Presentation of Specific Aim 1 and 2 at regional and national conferences
- Manuscript preparation and submission for Specific Aim 1
- Started data collection for Specific Aim 3

Specific Objectives:

Specific Aim 1

- Received IRB approval
- Hired CRC for the project
- Purchased equipment and supplies, established contract with porcine humeri supplier
- Arranged and completed all IO infusion lab dates
- Completed data collection, manometer video review, and data analysis
- Presented at regional and national conferences
- Manuscript submission to American Journal of Emergency Medicine (AJEM)
- Selected the four best strategies for the follow-on in-vivo study based on study results

Specific Aim 2

- Received IRB approval
- Purchased all equipment and supplies
- Arranged and completed all IO placement/infusion lab dates
- Completed data collection, analysis
- Presented at regional and national conferences
- Assessed differences between IO devices and made conclusions on the best devices for use in the field
- Developed zone placement model and correlated placement with pressures and flow rates

Specific Aim 3

- Received IACUC and ACURO approval
- Purchased equipment and supplies, worked toward establishing contracts with swine supplier and veterinary pathology
- In process of hiring a veterinary technician
- Began in vivo pilot study, data collection

Significant Results:

Specific Aim 1

Methods Overview:

- This study was an in-vitro, randomized experimental design which compared whole blood flow rate and mean and peak pressure of eight different IO infusion strategies in cadaveric porcine humeri with similar bone density to the average male soldier.
- The eight strategies used were as follows: 1) gravity, 2) pressure bag set to 300 mmHg and allowed to deflate (PB), 4) pressure bag maintained at or above 300 mmHg throughout the entirety of the experiment (PB 300), 4) push-pull with a 10cc syringe (PP 10mL), 5) push-pull with a 60cc syringe (PP 60mL), 6) handpump tubing (HP), 7) handpump tubing with a pressure bag (HB 300), 8) LifeFlow manual rapid infuser (manual RI).
- An IO needle was placed in the cadaveric porcine humerus using the Arrow EZ-IO system. The randomly assigned transfusion strategy was then set-up by the transfuser.
- Set-up times were recorded for each trial. Pressures were measured for the first minute of the transfusion and were used to calculate average mean and peak pressure. Flow rate was determined based on time of infusion and volume of blood transfused.
- Following each transfusion, a Likert scale survey was filled out assessing user feedback on set-up and hand fatigue, comfort with using the infusion method, efficacy of method to control hemorrhage, comfort with using in a space confined setting, comfort with a corpsman/medic using the method, device failure/malfunction, and trust in resuscitating within 10-15 minutes after arrival or injury.

Main Results:

- Set-up times varied by method. All strategies on took on average two minutes or less to set up. The fastest methods were gravity and HP strategies, while the most time-consuming strategies to set up were those involving a pressure bag.
- Flow rate was highest for the manual RI, followed by PP 60mL, PP 10mL, HP 300, HP, PB, PB 300, and gravity.
- Mean infusion pressure followed a similar trend to the flow rate results.
- Peak infusion pressure was lowest for gravity and pressure bag strategies, intermediate for HP strategies, and highest for the manual RI, PP 10mL, and PP 60mL. The peak pressure for HP 300 was higher than HP alone.
- The manual RI received the most favorable ratings for easy set-up, minimal hand fatigue, and use in confined settings. Additionally, it was trusted to meet the demands of damage control resuscitation, can be effectively used by corpsmen, and initiating damage control within the first 15 minutes of arrival. PP 60mL ranked second for use in confined settings, meeting demands of damage control resuscitation, and can be successfully used by corpsmen; however, it ranked low in set-up and hand fatigue. Both the PP and HP 300 methods received poor scores for set-up and hand fatigue. PB 300 was rated highest for potential to initiate damage control but low in potential to meet demands of damage control resuscitation in first 15 minutes of injury or casualty arrival. PB methods scored well for lack of failure/malfunction, but poorly for comfort in use, use in confined settings, and can be effectively used by corpsmen. Gravity had good scores for easy set-up, minimal hand fatigue, and lack of failures or malfunctions, but scored lowest for use in confined settings, can effectively be used by corpsmen, initiating damage control, and meeting demands of damage control resuscitation.
- For a more detailed overview of the results, please see attached presentations and manuscript submission. Figures (1-3) can be found in the appendix.

Specific Aim 2

Methods Overview (Pilot):

- A pilot study was performed to allow for participants to practice on the swine model and with equipment used in the study.
- In the pilot study, researchers performed ten infusion trials utilizing three main IO infusion methods (handpump tubing, push-pull technique with a 10mL, 20mL, and 60mL syringe, and LifeFlow manual rapid infuser) and infused 500 mL of saline solution into a cadaveric swine humerus using an Arrow EZ-IO catheter.
- Flow rate and mean and maximum infusion pressures were collected for each trial. Images were taken of the cadaveric swine specimens via computed tomography (CT) with the IO needle intact in order to determine placement location within the bone.

Main Results (Pilot):

- Mean flow rates varied significantly by infusion strategy, with the manual RI achieving the highest mean flow rate (216 mL/min) and mean pressure (1562 mmHg).
- Infusion by push-pull with a 10mL syringe achieved the highest maximum pressure (3868 mmHg) but achieved a lower flow rate (105 mL/min).
- Samples within Zone 1 generally showed higher infusion pressures and lower flow rates than Zone 2 or 3.

Methods Overview (Main):

- In the main study, 210 infusion trials were performed utilizing two specimen types: cadaveric swine humeri and sternums. Bone density was similar to that of an average male warfighter.
- We used five different humeral IO devices: Arrow EZ-IO needle and drill, along with four manual devices: Jamshidi IO, Persys NIO, SAM IO manual drill and needle, and T.A.L.O.N. humeral IO. We used two different sternal IO devices: FAST1 IO and T.A.L.O.N. sternal IO. In total, there were seven different device combinations.
- Researchers infused 500 mL of saline solution into the porcine bone using the 60mL syringe push-pull method.
- Placement time, flow rate, and mean and maximum infusion pressure were collected for each trial, as well as subjective Likert scale surveys regarding IO device performance.
- Images were taken of the cadaveric swine specimens via CT with the IO needle intact in order to determine placement location 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.

Main Results (Main):

- Results for the three different placement Zones:
    - Flow rates for Zone 3 were significantly lower than Zone 1 and 2.
    - Mean pressure for Zone 3 was significantly higher than Zone 1 and 2.
    - Peak pressure for Zone 3 was significantly higher than Zone 1 and 2.

- Results regarding different IO devices:
    - There was no significant difference between flow rates and pressures for the humeral IO devices.
    - There was a significant difference between flow rates and mean and peak pressures for the sternum IO devices. The T.A.L.O.N. IO device had significantly higher flow rates and lower mean and peak pressures in comparison to the FAST1 IO device.
    - The T.A.L.O.N. IO device had significantly higher flow rates and lower pressures than all other devices.
    - EZ-IO device received the highest average scores on subjective Likert scale surveys, while SAM IO received the lowest average scores on subjective Likert scale surveys.

For a more detailed overview of the results, please see attached abstracts and presentations. Figures (4-11) can be found in the appendix.

Specific Aim 3

Methods Overview:

- 90-120 kg swine (*Sus scrofa*) were exsanguinated and given autologous transfusion via one of four infusion strategies: 1) pressure bag, 2) handpump tubing, 3) push-pull 60mL, and 4) LifeFlow manual rapid infuser. These four strategies were determined based on results of Specific Aim 1. Each strategy will be done with single and double site IO.
- Vital signs, biochemistry, thromboelastography (TEG), and near infrared spectroscopy (NIRS) results were taken at baseline, post-exsanguination, post-infusion, and following a 60-minute post-infusion observation period (post-observation). Visual hemolysis testing was done at baseline, during exsanguination (from blood bag), post-infusion, and post-observation.
- During the infusion period, flow rate and mean and peak pressures were recorded.

Main Results:

Main results of the pilot are still pending, as we have not completed trials on all subjects. Preliminary results show:

- There was no evidence of hemolysis with pressure bag and handpump strategies.
- Flow rate is greater for infusion with handpump than with pressure bag.
- Infusion pressures are higher for handpump than pressure bag.
- Push pull 60mL and manual RI methods have not yet been performed in this pilot.

Other Achievements:

- Received first place in Resident Research Category, SOMSA 2020
- Received first place in Staff Research Category, Navy Medicine West ARC 2020
- Received second place in Staff Research Category, Navy Wide ARC 2020
- Received first place in Resident Research Category, Navy Medicine West ARC 2021
- Received first place in Resident Research Category, Navy Wide ARC 2021
- Research findings highlighted in Tactical Combat Casualty Care (TCCC) Tactical Field Care: Vascular Access Module 2021

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. Residents on the project received in-depth, hands-on training for different IO devices and infusion strategies. 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 career.

Professional development during this year primarily occurred in the form of conferences. Residents were able to participate in the labs and make conclusions based on 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 nine abstracts were submitted to research conferences. So far, six 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 and integrated into current and upcoming updates on the vascular access module.

We presented our findings for Specific Aim 1: a comparison of eight IO infusion methods and Specific Aim 2: pilot study IO infusion/placement location, main study IO placement location, and IO device comparison. Specifically, we shared our results at the following conferences:
Specific Aim 1: Navy Medicine West ARC, Navy Wide ARC, JSSEM, SOMSA
Specific Aim 2: Navy Medicine West ARC, Navy Wide ARC, MHSRS

We have submitted the manuscript for Specific Aim 1 to AJEM and hope to disseminate the major results of our findings there.

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

During the next reporting period, we plan to have an accepted publication on the findings of Specific Aim 1. Additionally, we plan to have completed the pilot study for Specific Aim 3. We will continue to present our findings from Specific Aim 2 and begin the manuscripts to publish our results.

In particular, we plan to:
-Hire a veterinary technician
-Have an accepted publication for Specific Aim 1 findings
-Present findings at ACEP (2) (Specific Aim 2)
-Draft manuscripts on Specific Aim 2 findings (3; IO infusion pilot, IO devices, IO placement)
-Complete pilot study (8 subjects) (Specific Aim 3)
-Begin abstracts to present pilot study findings for spring conferences (Specific Aim 3)
-Have main study dates planned and ready for execution (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 1 and 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.

We have learned which 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. Perhaps most importantly we have highlighted how important the placement within the medullary space or cancellous bone is to flow characteristics. These findings will be tested in a live animal research model for Specific Aim 3.

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 haven given us insight on which IO devices may be best for corpsmen and medics to carry with them in the field.

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 impact 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 infusion, but IV access may be difficult 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.

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 results of Specific Aim 1 have been transferred to TCCC Tactical Field Care: IV/IO Access Module. These recommendations on IO access will be taught to all medical military personnel and will impact the care they provide in the field.

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.

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.

Nothing to Report.

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.

We have a hiring staff delay for a veterinary technician. We had identified a candidate, but she had a family emergency to attend to and could no longer take the position. We are resolving the delay by re-advertising the position.

Changes that had a significant impact on expenditures
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.

We have a hiring staff delay for a veterinary technician. We had identified a candidate, but she had a family emergency to attend to and could no longer take the position. We are in the process of identifying a new candidate now.

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 two amendments under the IACUC during this reporting period: 1) to add a suprapubic catheter procedure for male swine and 2) to add a surgical incision to allow the NIRS monitor to be placed closer to the brain in order to capture oxyhemoglobin and deoxyhemoglobin levels in the brain throughout the experiment. Both changes were approved by the IACUC; both of these procedures will be done under anesthesia.

Significant changes in use of biohazards and/or select agents

N/A

5. 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).*

Nothing to Report.

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.*

Navy Medicine West ARC 2020
Navy Wide ARC 2020
JSSEM 2020
SOMSA 2020
Navy Medicine West ARC 2021
Navy Wide ARC 2021
MHSRS 2021

- **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 developed a novel cadaveric porcine model for studying IO insertion and infusion. This model is described in out submission to the AJEM and will be available to future researchers that either wish to replicate or build off of this work. No formal technology transfer required.

- **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 started the dataset for the pilot portion of our in vivo 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
4) blood hemolysis
5) mean infusion pressure
6) peak infusion pressure
7) flow rate
8) CT scans of each IO needle position within the bone (Zone 1, 2, or 3)

6. 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".

Example:

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.

7. 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.*

8. 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.

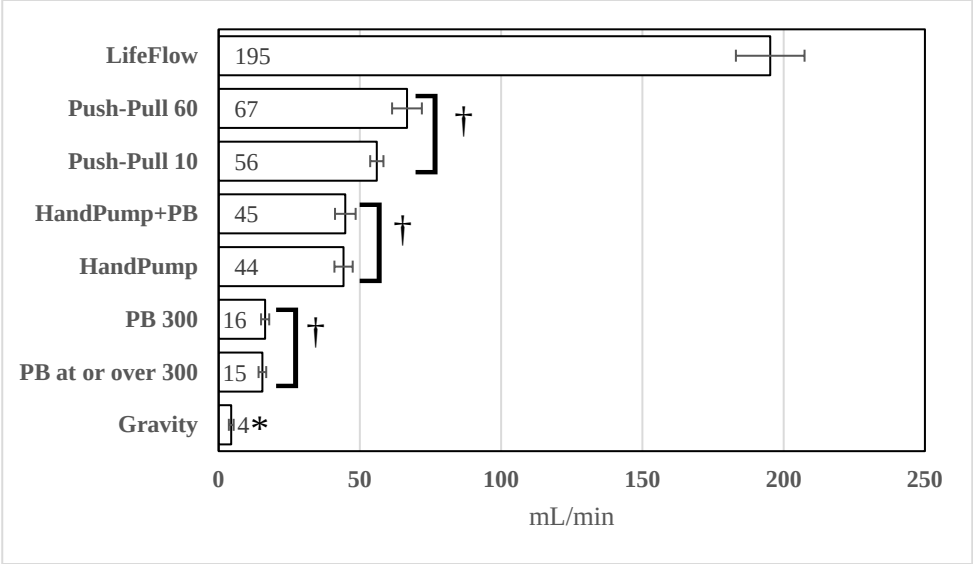

Figure 1. Flow rates (mL/min) for each infusion strategy.

*p<0.05 versus next higher flow rate.
†p<0.001 versus next higher flow rate.

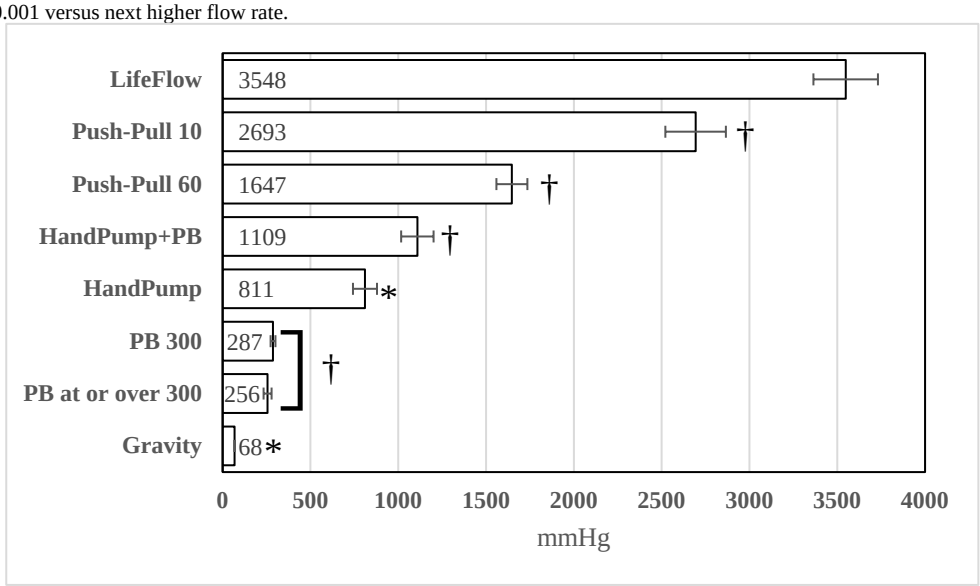

Figure 2. Mean pressures (mmHg) for each infusion strategy.

*p<0.05 versus next higher mean pressure.
**p<0.01 versus next higher mean pressure.
†p<0.001 versus next higher mean pressure.

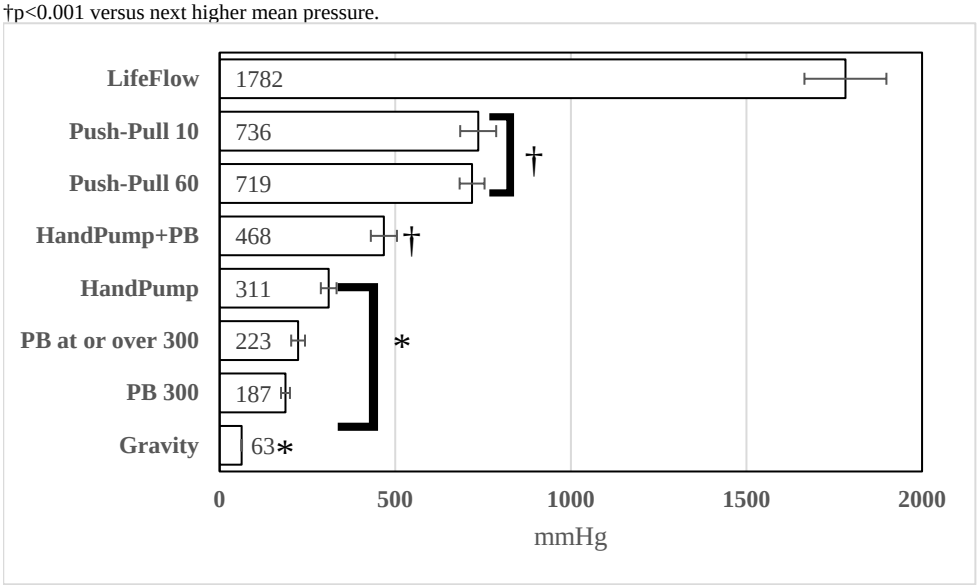

Figure 3. Peak pressures (mmHg) for each infusion strategy.

*p<0.05 versus next higher peak pressure.
**p<0.01 versus next higher peak pressure.
†p<0.001 versus next higher peak pressure.

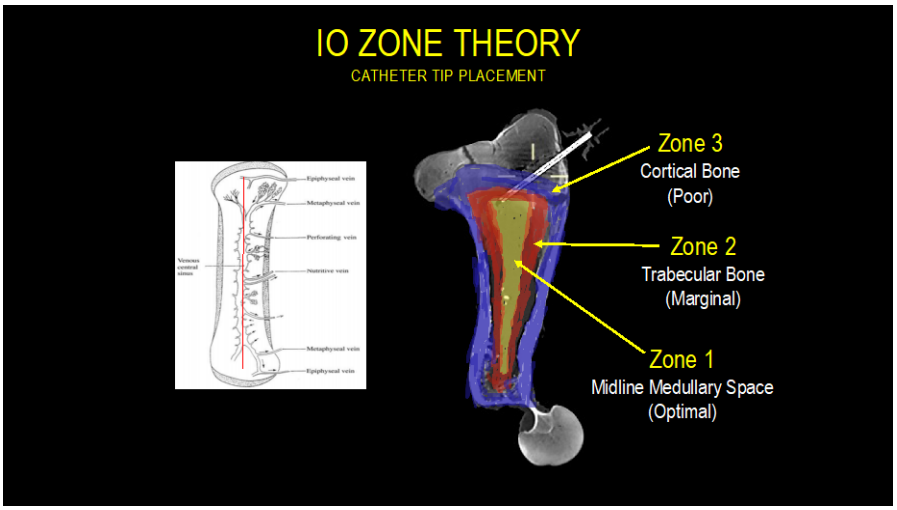

Figure 4. IO Zone Model with Three Defined Zones

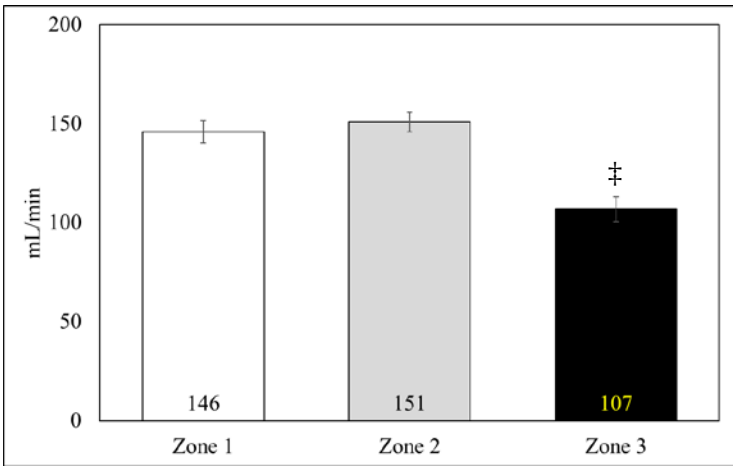

Figure 5. Flow Rates by Zone

‡p<.00001 versus Zone 1, Zone 2

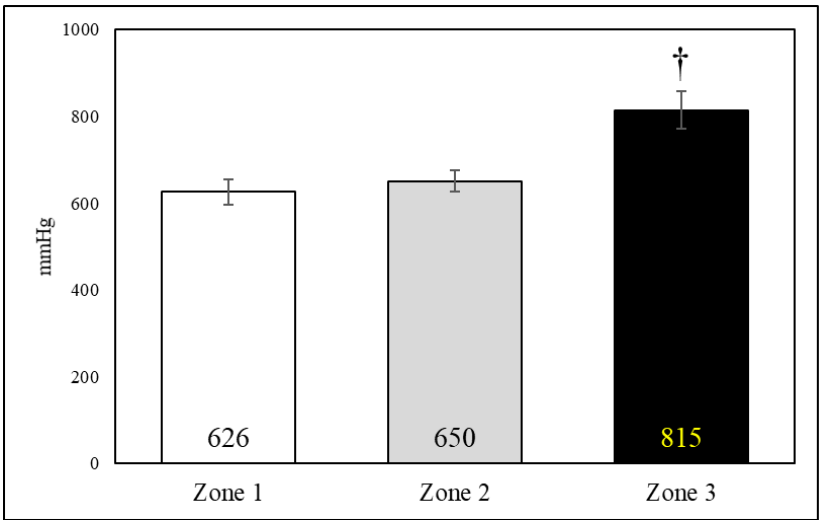

Figure 6. Mean Pressure by Zone
†p<.0001 versus Zone 1, Zone 2

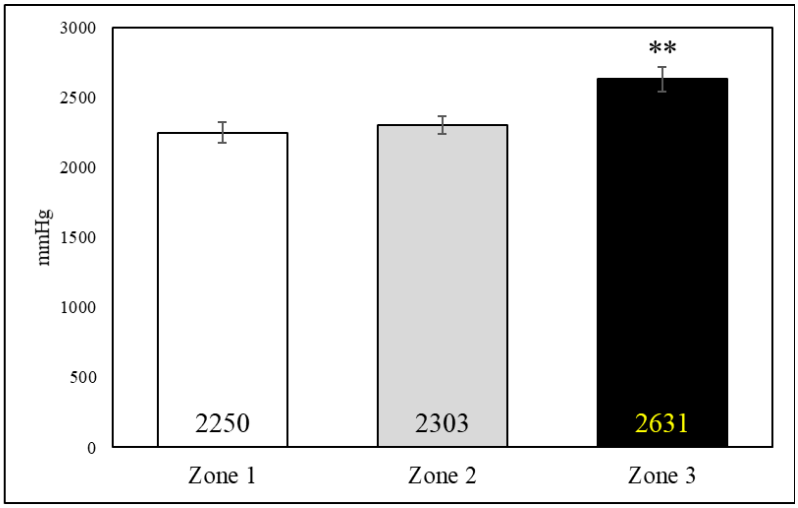

Figure 7. Peak Pressure by Zone
**p<.01 versus Zone 1, Zone 2

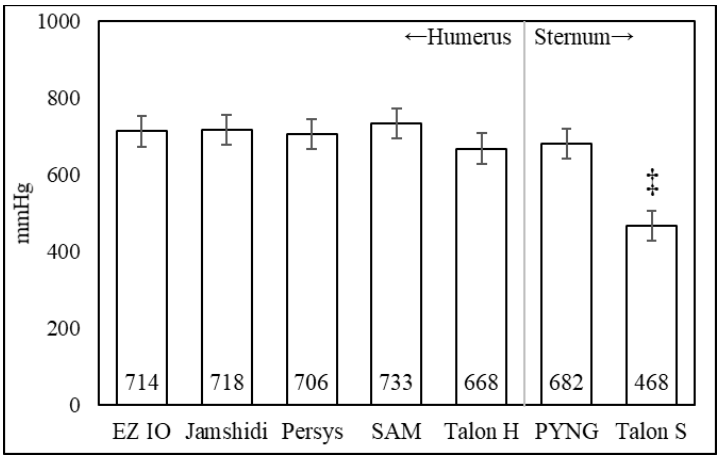

Figure 8. Mean Pressure by Device
‡p<.0001 versus all others

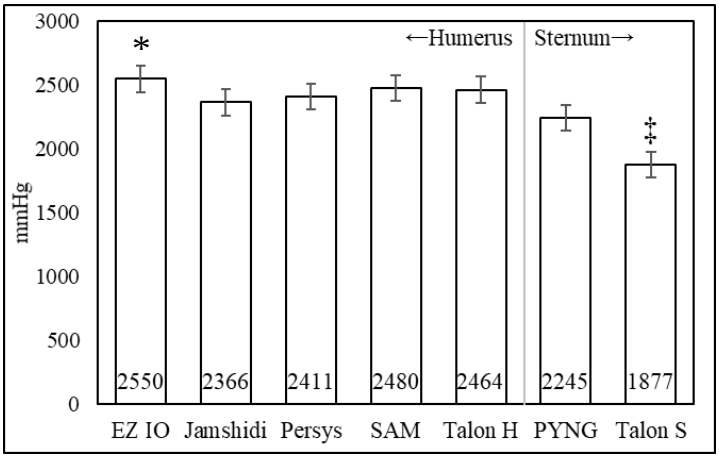

Figure 9. Peak Pressure by Device
*p<.05 versus PYNG
‡p<.0001 versus all others

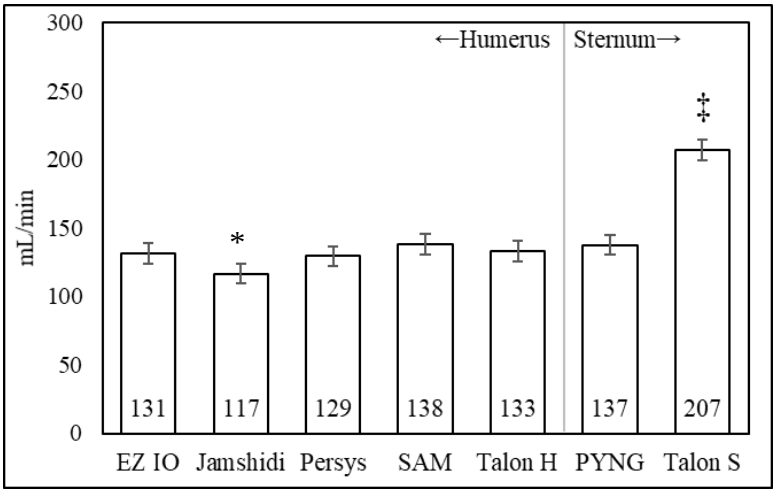

Figure 10. Flow Rate by Device
*p<.05 versus Persys, SAM
‡p<.0001 versus all others

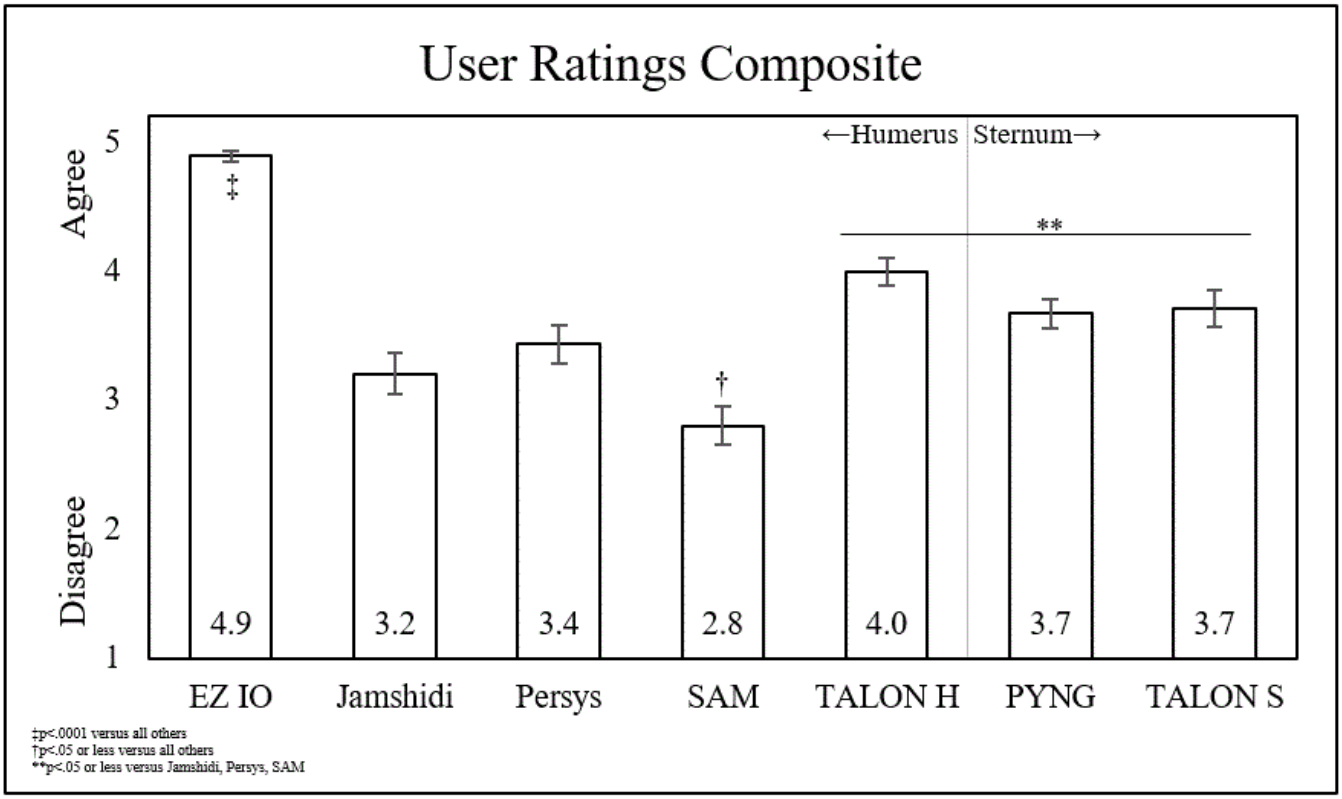

Figure 11. User Ratings Composite Score by Device