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ORIGINAL RESEARCH

Trauma

The relationship between intraosseous catheter tip placement, flow rates, and infusion pressures in a high bone density cadaveric swine (*Sus scrofa*) model

Joseph A. Gehrz MD ^{1,2,3} \bigcirc y Victoria C. Kay MD ^{1,2} Derek W. Grady MD ⁴	
Alec D. Emerling MD ^{1,2,3} Andrew McGowan MD ^{1,2,3} Erin R. Reilly MPH ^{1,2}	I
Vikhyat S. Bebarta MD ^{5,6} Joshua Nassiri MD ^{1,4,3} Jorge Viñals PhD ⁷	
Gregory J. Zarow PhD ^{1,8} Jonathan D. Auten DO ^{1,2,3}	

¹Combat Trauma Research Group, Clinical Investigations Department, Naval Medical Center San Diego, San Diego, California, USA

²Department of Emergency Medicine, Naval Medical Center San Diego, San Diego, California, USA

³Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

⁴Department of Radiology, Naval Medical Center San Diego, San Diego, California, USA

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⁵Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA

⁶Department of Emergency Medicine, Center for COMBAT Research, University of Colorado School of Medicine, Aurora, Colorado, USA

⁷School of Physics and Astronomy, University of Minnesota, Minneapolis, Minnesota, USA

⁸The Emergency Statistician, Idyllwild, California, USA

Correspondence

Joseph A. Gehrz, Department of Emergency Medicine, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134, USA. Email: joegehrz@gmail.com

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Abstract

Background: Intraosseous (IO) infusion is a life-preserving technique when intravenous access is unobtainable. Successful IO infusion requires sufficiently high flow rates to preserve life but at low enough pressures to avoid complications. However, IO catheter tips are often misplaced, and the relative flow rates and pressures between IO catheter tips placed in medullary, trabecular, and cortical bone are not well described, which has important implications for clinical practice.

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Objectives: We developed the Zone Theory of IO Catheter Tip Placement based on bone density and proximity to the venous central sinus and then tested the influence of catheter tip placement locations on flow rates and pressures in a cadaveric swine model.

Methods: Three cross-trained participants infused 500 mL of crystalloid fluid into cadaveric swine humerus and sternum (N = 210 trials total) using a push-pull method with a 60 cm³ syringe. Computed tomography scans were scored by radiologists and categorized as zone 1 (medullary space), zone 2 (trabecular bone), or zone 3 (cortical

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bone) catheter tip placements. Differences between zones in flow rates, mean pressures, and peak pressures were assessed using analysis of variance and analysis of covariance to account for participant and site differences at the p < 0.05 threshold. **Results:** Zone 1 and zone 2 placements were essentially identical in flow rates, mean pressures, and peak pressures (each p > 0.05). Zone 1 and zone 2 placements were significantly higher in flow rates and lower in pressures than zone 3 placements (each p < 0.05 or less).

Conclusion: Within the limitations of an unpressurized cadaveric swine model, the present findings suggest that IO catheter tip placements need not be perfect to acquire high flow rates at low pressures, only accurate enough to avoid the dense cortical bone of zone 3. Future research using in vivo animal and human models is needed to better define the clinical impact of IO catheter placement on infusion flow rates and pressures.

1 | INTRODUCTION

1.1 | Background

Difficult intravenous access is a common challenge encountered in emergency departments and prehospital settings.¹⁻³ When peripheral venous access is not quickly established in critically ill or injured patients, intraosseous (IO) catheters play an important role in the administration of blood, fluids, and medications during initial resuscitation.⁴⁻⁶ Driving fluids directly into the bone marrow through anatomic, landmark-based placement of IO catheters as a bridge to definitive vascular access is endorsed by major resuscitation trainings.⁷⁻¹⁰ Successful IO infusion requires a balance between flow rates and pressures, as infusion flow rates must be sufficiently high for effective treatment but at pressures low enough to avoid complications, including shear stresses from excessive infusion pressures causing intravascular hemolysis or fat embolism.^{11,12} However, the clinical impact of proper placement of the IO catheter tip within the medullary space versus the denser trabecular or cortical bone was unclear.

IO catheterization reportedly has high first-attempt insertion success rates.^{13,14} However, IO access confirmation is currently guided only by the return of blood and the ease of saline flush without evidence of surrounding extravasation.¹⁵ Published reports in the adult and pediatric literature indicate that a significant proportion of landmark-based IO catheter placements are suboptimal.¹⁶⁻²² Variation in IO catheter tip placement might explain, at least in part, why flow rates vary greatly within IO studies.^{23,24}

We therefore developed the Zone Theory of IO Catheter Tip Placement to measure the clinical significance of IO tip placement location. Zones are distinguished based on two factors: relative bone density (porosity) and proximity to the venous central sinus. Zone 1 is the medullary space, where high flow rates and low infusion pressures might be expected because of high bone porosity and immediate proximity to the sinus. Zone 2 is the trabecular space, where intermediate flow and pressure performance might be expected because the cancellous bone is further from the sinus and less porous than the medullary cavity. Zone 3 is the cortical space, where poorest flow and pressure performance might be expected because of low bone porosity and furthest distance from the sinus. The present study was specifically designed to assess differences between zones in infusion flow rates and pressures to better inform prehospital and emergency medicine providers on the clinical importance of accurate IO catheter tip placement.

1.2 | Importance

Studying the role of catheter tip placement on IO flow rates and pressures is of great importance toward reducing morbidity and mortality in critically ill and injured patients. Optimizing IO catheter performance can improve the efficacy of therapies delivered in the initial moments of resuscitation. Prior research has established that IO catheters are inconsistently placed in humans,^{17,20–22,25} but whether IO catheter tip placement variability translates to systematic differences in infusion flows and pressures was unclear. The present study represents the first step in filling this important gap.

1.3 Goals of this investigation

The goal of this investigation was to put the Zone Theory of IO Tip Placement to an empirical test by contrasting flow rates, mean pressures, and peak pressures in zone 1, zone 2, and zone 3 in a translational cadaveric swine humerus and sternal model with bone densities approximating adult humans. Our null hypotheses were that the flow rates, mean pressures, and peak pressures would not significantly vary based on the zone location of IO catheter tips.

2 | MATERIALS AND METHODS

2.1 Study design and setting

This study employed a prospective design to contrast flow rates, mean infusion pressures, and peak infusion pressures between catheter tips placed in the three zones. This study was conducted in a translational research laboratory at Naval Medical Center San Diego (NMCSD). The NMCSD Institutional Review Board (IRB #NMCSD.2020.0044) approved this study pursuant to Federal Policy for the Protection of Human Subjects (the Common Rule) and the revised Common Rule, effective January 21, 2019, HHS 45 CFR 46.102, and DoD 32 CFR 219.101. The protocol was also reviewed by the NMCSD Institutional Animal Care and Use Committee and was determined to not fall under the category of live animal research. All activities were conducted in compliance with the Department of Defense regulations.

2.2 Model selection and preparation

Cadaveric swine (*Sus scrofa*) in the 70–90 kg range were selected because their proximal humerus bone density (>1 g/cm²) approximates that of an average 20–40-year-old male trauma patient.^{11,26–28} We utilized recently euthanized cadaveric swine samples to foster the "Refine, Reduce, Reuse" principle of animal research^{29,30} and because cadaveric swine models have demonstrated great utility in previous investigations of IO infusion.^{31,32} In this translational model, we chose one long bone (proximal humerus) and one non-load-bearing bone (sternum) to test the relationship between catheter tip location, flow rates, and infusion pressure. Proximal humerus and sternal samples were chosen because these sites have previously demonstrated the highest transfusion rates among potential anatomic locations.^{23,33}

Specimens were acquired from a third-party vendor (Sierra Medical) that specializes in biologic tissue procurement for the research and development industry. The proximal humeri and sternums were harvested and chilled after euthanasia, and then any fascia or muscle remnants were carefully removed prior to the study to prevent obstruction of emissary vessels on the surface of the bone. Bones with apparent damaged cortex from harvesting were excluded. A new swine proximal humerus or sternum was used for each trial.

As part of a larger study, we utilized 15-gauge IO catheters from commercially available IO access devices: EZ-IO (Teleflex Medical, Co.), Jamshidi IO (Becton Dickinson), PerSys NIO2 (PerSys Medical), SAM IO (SAM Medical), TALON (Teleflex Medical, Co.), and PYNG IO (Teleflex Medical, Co.). All devices except for PYNG were used on humeri, with TALON and PYNG used on sternums (30 each, 210 total). The catheters from these IO access devices are essentially identical, so the access devices are not further considered here because the present study focused exclusively on the impact of catheter tip placement location.

The Bottom Line

Intraosseous (IO) catheter tip placement can significantly influence infusion flow rates and pressure. In this prospective cadaveric study, IO catheters placed into or near cortical bone were associated with 30% lower flow rates and 15%-25% higher pressures. Training programs should emphasize proper technique to avoid IO placement into cortical bone.

2.3 Study participants

IO infusion trials were performed by a male fourth-year resident (A.E.), a male third-year resident (J.G.), and a female second-year resident (V.K.). All participants had prior experience using IO catheters. An educational session including demonstrations was performed prior to the study and participants were cross-trained so that they would be as identical as possible in IO infusion.

2.4 Interventions

IO catheters were inserted either into the greater tubercle of the proximal humerus at a 45° angle or into the sternum at a 90° angle. Successful placement was confirmed by flushing 10 mL of crystalloid fluid and observing adequate flow out of at least three emissary vessels on the surface of the bone. To ensure that samples accurately mimicked clinical parameters, those without fluid flowing out of at least three emissary vessels were excluded.

We utilized a push-pull infusion technique with a 60 mL syringe because prior research has demonstrated that pressure rarely exceeds 4000 mmHg with this technique and because this technique is currently used by a variety of prehospital medical teams.^{30,34}

After IO insertion and confirmation, intravenous tubing was attached with a calibrated in-line digital pressure gauge (Ashcroft Inc.) three inches proximal to the IO insertion site. A three-way high-flow stopcock with rotating Leur (ICU Medical) was then attached three inches proximal to the pressure gauge. On the in-line end of the threeway stopcock, 80-in. Y-type blood tubing was connected to a crystalloid bag. An empty 60 mL BD Luer-lok Tip syringe (Becton, Dickerson, and Co.) was attached to the 90° inflow port (Figure 1). The entire line was flushed with crystalloid and the pressure gauge was zeroed prior to each trial.

For each trial, 500 mL of crystalloid was manually infused through the IO catheter with continuous in-line pressure monitoring. This was accomplished by rotating the three-way stopcock to the 90° setting and then pulling back the plunger to fill the 60 mL syringe from the crystalloid bag. The stopcock was then toggled to the in-line setting, and fluid was driven into the bone by depressing the plunger of the filled syringe. This process was repeated until 500 mL of crystalloid was

FIGURE 1 Line set-up for demonstration only. A 60 mL syringe (right) attached to intravenous line via three-way stopcock, with in-line pressure monitor (center).

infused. Infusion time began after the set-up was complete and ended when the crystalloid bag was empty or until 15 min elapsed.

After infusion trials were completed, bone specimens were carefully placed in a single layer in a box, with each IO catheter facing up, and then hand-carried to an on-site radiology suite to minimize any risk of catheter movement. Imaging was performed to localize the catheter tip using a Siemens SOMATOM Definition Edge 128 slice computed tomography (CT) scanner. Axial images were acquired at a thickness of 0.5 mm with volumetric coronal and sagittal reconstructions.

2.5 | Outcomes

The outcomes included flow rate (mL/min), mean pressure (mmHg), and peak pressure (mmHg). The flow rate was calculated as the total volume infused divided by the infusion time. The mean and peak pressures were calculated via Stork solutions pressure transducer software (Stork).

2.6 | Intraosseous catheter tip location and the Zone Theory of IO Catheter Tip Placement

In collaboration with a fluid physicist (J.V.), we developed the Zone Theory of IO Tip Placement based on the principles of fluid dynamics,



FIGURE 2 Computed tomography (CT) scans of catheter tip placement in zone 1 (left), zone 2 (center), and zone 3 (right) of swine humerus.

including Darcy's law, Hele-Shaw flows, an understanding of the centrifugal nature of IO arterial flow, and the role of the central medullary venous sinus in venous outflow. Neumann (no flow) boundary conditions were applied to the outer surface of the bone model in two dimensions, while Dirichlet conditions were applied to the central venous sinus to model constant hydrostatic pressure (Appendix 1). The central medullary venous sinus was considered midline and a planar wall was assumed between the sinus and the outer bony cortex. In dimensionless units of length (domain between 0 and 1), zone 1 was the region most proximally located to the central medullary sinus (0-0.33). Zone 2 was the region of trabecular bone, including branches of the medullary sinus (0.34–0.66). Zone 3 was the most peripheral trabecular and cortical bone (0.67–1.00). Catheter tips in proximity to the cortex or physis superior to the humerus (≤ 6 mm) or sternum (≤ 2 mm) were also considered to be in zone 3. Using the CT images, IO catheters were rated as being placed into zone 1, zone 2, or zone 3 by one of two radiologists (D.G. or J.N.), who were trained in the task but were blinded to the purpose of the study.³⁵ Figure 2 displays CT scans of catheter tips placed into zone 1, zone 2, and zone 3.

2.7 Data analysis

Tests of power using G*Power software (version 3.1)³⁶ found that, assuming a 95% confidence interval and an effect size of f = 0.25 for omnibus testing, statistically significant differences would be realized on 80% of opportunities (power = 0.80), with as few as 159 trials total. Therefore, to ensure adequate power, this study included 210 trials. Two trials were excluded due to machine malfunction, so the sample size for statistical analysis was N = 208.

Normality was assessed using the Shapiro–Wilk test. The peak infusion pressures were normally distributed (SW = 0.99, p = 0.58), and the mean pressures and flow rates were not normally distributed (each SW = 0.97, p = 0.001). However, analysis of variance (ANOVA) statistics are robust against violations of normality, such that type I and type II error rates remain stable regardless of the shape of the raw data when sample sizes are greater than 25 per condition, as in the present study.³⁷

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Hypotheses were tested using ANOVA and analysis of covariance (ANCOVA) to adjust for possible participant differences and site differences (humerus vs. sternum), with pairwise comparisons to localize statistically significant differences. Each ANOVA result was confirmed using a non-parametric equivalent, Kruskal–Wallis for omnibus testing and Mann–Whitney *U*-test for pairwise testing. The confirmatory non-parametric findings were substantively similar to the parametric findings, so for simplicity, only the parametric ANOVA and ANCOVA *p*values are provided in the results section. Because of the importance of not missing real differences (type II error) by making it more difficult to commit type I error in this novel area of research, differences were considered statistically significant at the *p* < 0.05 threshold without correction for multiple comparisons.³⁸

The results are expressed as the mean (M) \pm standard deviation (SD) in text and as the mean \pm standard error of the mean (SEM) in figures. All analyses were conducted with SPSS statistical software (version 23, IBM Corp.).

3 | RESULTS

3.1 Characteristics of bone samples and IO placements

Each study participant (A.E., J.G., and V.K.) placed 70 IO catheters for a total sample size of 210 catheters, with 150 placed in the humerus and 60 placed in the sternum. Two humeral catheters were excluded due to mechanical malfunction of the placement device, so the total sample size for statistical analysis was N = 208. Of these, 69 (33%) catheter tips were placed in zone 1, 104 (50%) in zone 2, and 35 (17%) in zone 3.

3.2 | Flow rates

The flow rates for catheter tips placed in zone 1 (medullary space, M = 146 mL/min, SD = 47) and zone 2 (inner trabecular bone, M = 151, SD = 50) were statistically similar to each other (p = 0.48). Catheter tip placement in both zone 1 and zone 2 had >30% higher flow rates than those placed into zone 3 (cortical and outer trabecular bone, M = 107, SD = 38, each p < 0.001). Figure 3 shows that this pattern remained substantively identical after adjusting for site and participant (p = 0.49 for zone 1 vs. zone 2, p < 0.001 for zone 1 and zone 2 vs. zone 3).

3.3 | Mean infusion pressures

The mean infusion pressures of catheter tips placed into zone 1 (M = 635 mL/min, SD = 240) and zone 2 (M = 657, SD = 251) were statistically similar to each other (p = 0.56) and ~25% lower than those of catheter tips placed into zone 3 (M = 814, SD = 42, each p < 0.001). Figure 4 shows that this pattern remained substantively

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***p<0.001 versus Zone 1 and Zone 2





***p<0.001 versus Zone 1 and Zone 2

FIGURE 4 Mean pressure by zone.

identical after adjusting for site and participant (p = 0.74 for zone 1 vs. zone 2, p = 0.003 for zone 1 vs. zone 3, p = 0.005 for zone 2 vs. zone 3).

3.4 Peak infusion pressures

The peak infusion pressures for catheter tips placed into zone 1 (M = 2284 mL/min, SD = 533) and zone 2 (M = 2308, SD = 624) were statistically similar to each other (p = 0.51) and 10%–15% lower than those of catheter tips placed into zone 3 (M = 2527, SD = 88, p = 0.004 and 0.005, respectively). Figure 5 shows that, after adjusting for site and participant, zone 1 and zone 2 remained statistically similar (p = 0.52), and zone 3 remained significantly higher than zone 1 (p = 0.03) but only trended higher than zone 2 (p = 0.07).

4 | LIMITATIONS

The present study was limited by the cadaveric swine model, which was chosen to balance model fidelity with the ethical concerns of





*p<0.05 versus Zone 1

**p<0.01 versus Zone 1 and Zone 2

FIGURE 5 Peak pressure by zone.

studying 210 total trials while adhering to "Reduce, Reuse, and Refine" principles by utilizing a model similar to previously published IO research.^{11,29,30} Although swine anatomy does not directly translate to human anatomy, porcine bone was intentionally chosen because it has been shown to be an excellent translational model for transfusion research.^{19,28,31,32} While the present cadaveric model lacked the realism of skin and the challenges of identifying appropriate IO sites based on anatomical landmarks, we chose samples from swine with bone density closely approximating a young adult population.

Cadaveric swine are not the same as pressurized in vivo preparations, and postmortem collection of study samples may have led to slower flow rates due to some IO emissary vessels became occluded after procurement. Despite this limitation, pressure measurements were consistent with infusion parameters from prior in vivo IO studies and allowed for comparative assessments.^{11,28,39,40} Furthermore, previous animal studies have demonstrated that IO hydrostatic pressure is proportional to arterial pressure.⁴¹ This is important, because the present study was designed to contrast flow and pressure relative to zones of catheter tip placement, not to acquire absolute flow and pressure values, which somewhat ameliorates the limitations of using a cadaveric model rather than a pressurized in vivo model. Regardless, these findings should only be generalized with appropriate caution pending replication with in vivo animal and human studies. Furthermore, the in vitro model precluded assessment of intravascular hemolysis or pulmonary histology from possible damage created by shear stresses from pressurized IO. Clinical case studies and animal studies have reported the potential for these complications, so further investigations using in vivo models are warranted.^{42,43} We only used proximal humerus and sternal sites, with infusion of isotonic crystalloid using a push-pull method. The use of blood products, different anatomic sites, and different infusion techniques may confer different results.^{23,28}

This study was limited by the modest number of study participants, who were each emergency medicine residents. This limitation was mitigated by cross-training participants prior to commencement of the study.

5 | DISCUSSION

Difficult intravenous access is encountered in up to 11% of patients in the emergency department.^{1,2} When this occurs in critically ill or injured patients, IO catheters offer an important bridge to vascular access.^{4,44–46} Consensus guidelines suggest that landmark-based placement into the medullary space should be confirmed through aspiration of marrow.^{7-9,42} However, training on anatomic-based placement in resuscitation and prehospital medicine courses is often brief, with low-fidelity static mannequins and no placement feedback.⁷⁻¹⁰ Retrospective reviews have demonstrated that landmark-based placement of IO catheters can vary significantly in trauma care settings.^{16,17} The clinical impact of suboptimal or errant placements of IO catheters is poorly understood, but the limited published evidence suggests that there may be a link between IO catheter tip location, complications, and overall infusion performance.^{11,12,47,48} For these reasons, the present study was designed to determine whether there might be systematic differences in IO flow rates depending on catheter tip placement. If the location of the IO catheter tip affects clinical performance, then future resuscitation and prehospital education should focus on the importance of anatomic placement and the development of higher fidelity IO procedural training tools.

Based upon our Zone Theory of IO Tip Placement, we expected to find the highest flow rates and lowest infusion pressures in zone 1, with intermediate flow rates and pressures in zone 2, and the lowest flow rates and highest pressures in zone 3. This theory was based on bone density/porosity and proximity to the venous central sinus. That is, lower flow rates and higher pressures would be expected when bone density is higher. Second, the more peripheral the IO catheter tip is located from the central sinus of the intramedullary space, the higher the infusion pressures required to maintain forward flow.

Consistent with our theory, zone 3 IO placements were associated with 30% lower flow rates and 15%–25% higher mean and peak pressures than zone 1 or zone 2 IO tip placements. These observations were consistent with the principles of Darcy's law, prior observations of IO infusion, and theoretical fluid dynamics. First, the physical distance from the central venous sinus confers a greater length over which infused fluids must travel before exiting the IO environment and entering the peripheral circulation. Second, the presence of the IO catheter tip in or near cortical bone requires that infused fluids traverse through the medullary sinuses and return to the central venous sinus via centripetal (rather than linear) flow before exiting the bone through the emissary veins.^{49,50} Finally, the higher surrounding density of cortical bone requires higher pressure to produce the same flow rate.⁵¹

In contrast to our theory, zone 1 and zone 2 IO catheter tip placements were essentially identical in terms of flow rates, mean pressures, and peak pressures. We hypothesize two possible explanations for this observation. First, zone 1 and zone 2 may be effectively indistinguishable because the venous sinus extends off the central medullary canal. Second, it is possible that the in vitro model concealed significant differences between zone 1 and zone 2. Zone 1 catheter tips have the advantage of immediate access to the central venous sinus, which directly flows into emissary veins that exit the bone and enter the peripheral circulation. Zone 2 catheter tips, present within the trabecular bone, access an area that is rich in medullary sinuses and hemopoietic niches. These tributaries eventually return to the central venous sinus through centripetal flow.^{50,52} Overall, this result implies that IO catheters need not be placed perfectly in zone 1 to achieve optimal infusion performance, but should avoid the cortical and peripheral cancellous bone of zone 3.

The present findings offer clarity regarding two previous studies on IO hypertonic saline infusion that provided contradictory findings. Alam et al. utilized clinical confirmation of landmark-based IO catheter placement with ease of flush prior to infusing hypertonic saline. That study utilized a Sur-Fast IO (Cook Critical Care) that required manual placement and had infusion ports on the lateral aspects of the catheter and a closed catheter tip. Overall, 80% of their subjects developed osteonecrosis or soft tissue necrosis, and the investigators noted fluid extravasation into muscle compartments during their pressurized infusion. The design of the IO catheter and atypical method of confirmation (no marrow aspiration) in that study increased the risk for placement of the catheter tip in the peripheral cancellous bone or outside the cortex.⁴⁷ Bebarta et al. utilized fluoroscopic placement into the intramedullary space with the EZ IO catheter (EZ-IO, Teleflex Medical) with a standard catheter tip open to infusion. They found no evidence of myonecrosis or osteonecrosis after infusion of hypertonic saline.⁴⁸ Our present findings correlate with these two studies and suggest that IO catheter tip placement may have a substantial impact on infusion performance and decrease rates of complications. More specifically, placement into or near the cortical bone leads to significantly lower flow rates and higher infusion pressures and should therefore be avoided. Although it is thought that aspiration of marrow confirms adequate placement of catheters into the medullary space. the reliability of this qualitative measure is unclear and more research in this area is required.⁴² The implications of present findings could inform resuscitation courses to highlight the importance of accurate anatomic-based placement in line with the medullary sinus. In addition, the lower flow rates and increased pressures in the more peripheral bone could be utilized in development of higher fidelity simulation training devices for IO insertion.

Prior research on IO pressurized infusion utilizing push–pull infusion and the Belmont Rapid Infuser (Belmont Medical) also suggested that catheter tip location may be related to infusion performance.¹¹ This is clinically significant because lower flow rates slow the administration of critical interventions, such as blood transfusion or delivery of medications. If optimization of catheter tip positioning can positively impact the performance of IO infusion, this would be of great importance in the resuscitation of the critically ill or injured patients whose outcomes are impacted by the timeliness and effectiveness of medical intervention.^{7,42,53} The present study makes a novel contribution by demonstrating systematic differences in flow rates and infusion pressures based on cortical bone (zone 3) versus medullary (zone 1) or trabecular (zone 2) IO catheter tip placements.

Future research is vital for determining the clinical impact of these findings. The present study should be replicated with larger number of participants with various levels of experience. We only utilized the push–pull pressurized infusion technique, so it is important to test the Zone Theory of IO Catheter Tip Placement with other pressurized infusion techniques, such as in-line hand pumps, manual rapid infusers, and pressure bag, for example.³⁰ In addition to assessing sternum and proximal humerus, it is equally important to test other IO locations, such as proximal tibia, pelvis, and medial malleoli. Most importantly, it is crucial to challenge the present cadaveric swine findings with replication using pressurized in vivo animal models with assessment of intravascular hemolysis or pulmonary histology from possible damage caused by shear stresses from pressurized IO, and ultimately, to investigate the Zone Theory of IO Tip Placement in human subjects.

In conclusion, IO catheter tip placement can significantly influence infusion flow rates and pressure. Although this study was limited by the use of a cadaveric swine model rather than a pressurized in vivo model, present findings suggest that IO catheter tips do not need to be perfectly placed in the medullary space (zone 1) to confer high infusion flow rates and low pressures, but merely accurate enough to avoid denser, more peripheral cancellous or cortical bone (zone 3). Taken together, these results have important implications for prehospital and emergency medicine providers who use IO catheters to preserve life.

AUTHOR CONTRIBUTIONS

Jonathan D. Auten, Joshua Nassiri, Vikhyat S. Bebarta, Jorge Viñals, and Gregory J. Zarow designed this study. All authors contributed to the literature search. Jonathan D. Auten, Joseph A. Gehrz, Andrew McGowan, and Erin R. Reilly managed institutional review board submission. Victoria C. Kay, Alec D. Emerling, Joseph A. Gehrz, Andrew McGowan, Derek W. Grady, and Erin R. Reilly collected data. Gregory J. Zarow conducted the data analysis. Jonathan D. Auten, Joseph A. Gehrz, Alec D. Emerling, Derek W. Grady, Gregory J. Zarow, and Vikhyat S. Bebarta interpreted the data. All authors contributed to manuscript preparation and revision.

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CONFLICT OF INTEREST STATEMENT

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ORCID

Joseph A. Gehrz MD ^(D) https://orcid.org/0000-0002-3576-7178

TWITTER

Joseph A. Gehrz MD y https://twitter.com/JGehrz

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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AUTHOR BIOGRAPHY

Joseph A. Gehrz, MD, is an Assistant Professor of Military and Emergency Medicine at the Uniformed Services University of the Health Sciences (USUHS) and researcher with experience in prehospital resuscitative interventions. He is a principal investigator for the Combat Trauma Research Group-West and serves as Core Academic Faculty at Naval Medical Center San Diego. His research interests include optimizing the performance of intraosseous infusion strategies and the logistics of whole blood transfusion.