The purpose of this study was to determine and compare the maximum concentration (Cmax) and time to maximum concentration (Tmax) of epinephrine administered via tibial intraosseous (IO), sternal IO, and intravenous (IV) routes in a porcine model of cardiac arrest during cardiopulmonary resuscitation. Five pigs each were randomly assigned to 3 groups: tibial IO, sternal IO, and IV. Cardiac arrest was induced with IV potassium chloride. After 2 minutes, cardiopulmonary resuscitation was initiated. Epinephrine was administered to each animal, and serial blood samples were collected over the next 3 minutes. Enzyme-linked immunosorbent assay was used to determine the epinephrine concentration. Multivariate analysis of variance helped determine if there were statistically significant differences between groups. There were significant differences in Cmax between the sternal IO and IV (P = .009) and tibial IO and IV (P = .03) groups but no significant difference between tibial and sternal IO groups (P = .75). Significant differences existed in Tmax between the tibial IO and IV (P = .04) and between tibial IO and sternal IO (P = .02) groups but no difference between the sternal IO and IV groups (P = .56). Intravenous administration of 1 mg of epinephrine resulted in a serum concentration 5.87 and 2.86 times greater than for the tibial and sternal routes, respectively.

**Keywords:** Advanced Cardiac Life Support, cardiac arrest, epinephrine, intraosseous.

Cardiac arrest remains one of the leading causes of mortality, with more than 900 occurrences daily in the United States. When a patient experiences cardiac arrest, it is critical to rapidly establish vascular access to administer lifesaving drugs. Given that the patient is in a state of cardiovascular compromise, vascular access procedures become difficult and time-consuming. The difficulty and delay in establishing vascular access may be magnified during mass casualty scenarios or a situation such as when multiple limbs are traumatically amputated in the same patient. These factors can contribute to excessive delay in obtaining vascular access, with resultant loss of life.

Although there are limited data, the American Heart Association, American Academy of Pediatrics, and the American College of Surgeons recommend that if intravenous (IV) access cannot be attained, drugs should be administered by the intraosseous (IO) route. In both civilian and military medicine, IO infusion is an accepted practice. The technique is taught in both adult and pediatric Advanced Trauma Life Support and Advanced Life Support provider courses. Additionally, IO infusion is used in special operations medicine by all military branches. The IO method possesses the advantages of ease and speed of placement, allowing rapid access to the circulatory system. Furthermore, IO allows the safe administration of fluids and drugs with the potential for bioequivalence with IV-administered drugs. However, it has not been determined if the anatomic location of the IO device has an impact on drug bioavailability. Nor has it been determined if there are differences between the IO and IV concentrations of epinephrine when administered during cardiac arrest.

The purpose of this study was to compare and determine the maximum concentration (Cmax) and time to maximum concentration (Tmax) of epinephrine ad-
ministered via tibial IO, sternal IO, and IV routes in a porcine model of cardiac arrest during cardiopulmonary resuscitation (CPR). The research questions that guided the study were as follows:

1. Are there statistically significant differences in the Cmax of epinephrine in the heart when the drug is administered via tibial IO, sternal IO, and IV routes in a cardiac arrest scenario during CPR?

2. Are there statistically significant differences in the Tmax of epinephrine in the heart when the drug is administered via tibial IO, sternal IO, and IV routes in a cardiac arrest scenario during CPR?

Physiologic and pharmacodynamic effects of fluids and medications administered through the IO route have been studied and documented for decades. Studies have compared the pharmacokinetics of medications administered via the IO route compared with the IV route. Tobias and Nichols reported the use of succinylcholine using the tibial IO route in a pediatric patient and found that with a dose of 1 mg/kg, adequate intubating conditions were obtained in 45 seconds.

The results from several animal studies suggest the IO route is equivalent to the IV route for a wide variety of medications. Jaimovich et al compared IO and IV administration of an anticonvulsant in a porcine model. In another study, Jaimovich and colleagues evaluated IO vs IV administration of antibiotics. Brickman et al compared the 2 approaches in the administration of diazepam and phenobarbital in dogs. Similarly, Cameron and associates compared the times between IO and IV injection using a radionucleotide technique in normovolemic and hypovolemic canines. Goldstein et al examined the pharmacokinetics of ampicillin administered by IV and IO in kittens. Other authors investigated the effect of route of administration on the pharmacokinetics of amikacin administered by IV and IO routes in 3- and 5-day-old foals.

Chastagner et al examined antibiotic administration via a permanent IO device in swine. In all of the aforementioned studies, there were no statistically significant differences between the 2 routes of administration.

Dubick and colleagues evaluated hemodynamic variables and electrolyte concentrations in euvoletic swine infused with a bolus of 4 mL/kg of 6% hetastarch via the sternal IO or IV route. Furthermore, they looked for evidence of histologic abnormality in the sternum and lung tissue. There were virtually identical responses in hemodynamic variables, plasma volume expansion, changes in plasma protein concentrations, hematocrit, and plasma electrolytes when evaluated during the initial 120 minutes after infusion. No histologic changes or emboli were found during necropsy. Similarly, rapid restoration of hemodynamic values was reported in hemorrhaged, conscious sheep after 6% hetastarch infusion via a sternal IO device. Other investigators have reported the effectiveness of IO infusion of hypertonic saline in resuscitating animals from hemorrhagic hypotension.

Spivey et al investigated the administration of sodium bicarbonate infusion via the IO route and stated that the IO route is equivalent to peripheral IV.

To date, only one study in human subjects has compared the pharmacokinetics of drugs administered by the 2 routes. Von Hoff and colleagues found no statistically significant differences between IO and IV administration of morphine sulfate in adults. The authors emphasized that the major limitation of this study was that they evaluated only morphine sulfate and the findings may not apply to other classes of drugs. Another limitation they indicated was that the IO administration of morphine might not be generalized to IO administration of medications in emergency situations or through other IO devices designed for emergency use. They recommended future studies of other drugs and other IO devices. Specifically, those medications used in emergencies must be investigated.

There are limited studies evaluating drug delivery during cardiac arrest. Recent studies by Hoskins et al compared IO and IV routes of administration during CPR after cardiac arrest. These studies showed that tibial IO delivery was slower than but as effective as IV delivery and that humeral head IO delivery was as effective as either IV or sternal IO. In these studies, labeled epinephrine was found to be equivalent between the IO and IV routes based on the appearance of tracers in central circulation. However, these studies did not quantify the Cmax and Tmax of epinephrine in the circulation, as we did in the current study.

**Materials and Methods**

This study was a prospective, experimental mixed (between and within subjects) design. Computer-generated numbers were used to randomly assign 15 Yorkshire-cross swine weighing between 50 and 70 kg to 3 groups: tibial IO (n = 5), sternal IO (n = 5), or peripheral IV (n = 5). The swine were purchased from the same vendor, were of equal size, were the same sex, and came from the same lot number to minimize variability. Male swine were used to avoid potential hormonal effects.

The swine were fed a standard diet and observed for 3 days to ensure a good state of health. The subjects had nothing by mouth after midnight the day before the experiment. Buprenorphine (0.01 mg/kg) was administered intramuscularly 30 minutes before anesthetic induction for preemptive analgesia. Each animal was sedated, anesthetized, and mechanically ventilated 30 minutes before instrumentation. Anesthesia was induced with an intramuscular injection (5 mg/kg) of tiletamine hydrochloride/zolazepam hydrochloride (a mixed drug consisting of a dissociative similar to ketamine and a benzodiazepine) and inhaled 4% to 5% isoflurane. Following endotracheal intubation, the isoflurane concentration was reduced...
to a maintenance dose of 2% to 3% for the remainder of the experiment. The animals were ventilated at a tidal volume of 8 to 10 mL/kg and a respiratory rate of 10/min to 14/min (Fabius GS anesthesia machine, Dräger Medical Systems, Telford, Pennsylvania). The swine were monitored continuously during the entire experiment for heart rate, arterial blood pressure, oxygen saturation, end-tidal carbon dioxide, and temperature (using an Infinity Delta XL monitor, Dräger Medical Systems, Telford, Pennsylvania). Peripheral IV access was placed in the left ear of all subjects. Normal saline (NS, 0.9%) was administered at 100 mL/h to maintain patency. Normothermia was maintained in each animal by the use of a forced-air warming blanket (Bair Hugger Model 505, Arizant Inc, Eden Prairie, Minnesota) to sustain body temperature greater than 36.0°C. An 8.5F, 10-cm central venous catheter (Cordis, Arrow International Inc, Reading, Pennsylvania) was inserted in the right subclavian vein of all animals using the modified Seldinger technique, for the purpose of blood specimen collection from the right atrium.

Animals in the tibial IO group had a 2.5-cm IO needle (EZ-IO AD, Vidacare Inc, San Antonio, Texas) placed in the proximal medial aspect of the left tibia. Animals in the sternal IO group had the same model of 2.5-cm needle placed in the upper sternum. Placement confirmation in both IO groups consisted of aspiration of bone marrow and rapid infusion of 10 mL of 0.9% NS according to the manufacturer’s recommendation. Sternal IO needle placement was guided by live fluoroscopy (GE OEC 9600, Salt Lake City, Utah) because of the unique segmented anatomy of the porcine sternum. Fluoroscopy prevented insertion of the IO needle in a poorly perfused cartilaginous region of the sternum or into the mediastinum. Fluoroscopy is unnecessary in humans, as the sternum ossifies following embryologic development. Following sternal IO device placement, we injected iohexol contrast solution (GE Healthcare Inc, Princeton, New Jersey), 300 mg/mL, through the IO needle using an injector (Mark V ProVis, Medrad Inc, Indianola, Pennsylvania) to confirm successful access to the circulation. The animals were allowed to stabilize for 15 minutes following IO device placement.

After stabilization, we induced cardiac arrest with IV potassium chloride, 20 mg/kg, and flushed with 10 mL of 0.9% NS. The electrocardiographic waveform was observed, and asystole was confirmed in 2 leads before discontinuation of anesthesia. A stopwatch was used to time an elapsed time of 2 minutes following confirmation of asystole. After the 2-minute period, external chest compressions were delivered by a continuous-compression mechanical CPR device (Thumper Model 1007CC, Michigan Instruments Inc, Grand Rapids, Michigan). This device compressed the sternum at a predetermined depth of 3.8 cm (1.5 in) and at a rate of 100/min according to American Heart Association guidelines. It was used to ensure the rate and depth of compressions delivered were consistent over time and were reproducible from animal to animal. Manual ventilations were delivered via the anesthesia circuit at a ratio of 2:30 compressions.

After 1 minute of CPR, a baseline blood specimen was collected via the large-diameter central venous catheter, followed by a 10-mL 0.9% NS flush in all groups. Epinephrine at a dose of 1 mg was rapidly administered by IV, tibial IO, or sternal IO push, followed by 10 mL of 0.9% NS. Blood specimens were collected via the central venous catheter every 30 seconds following administration of epinephrine for 3 minutes, for a total of 7 specimens including the baseline, as timed by a stopwatch. Before each specimen collection, the researchers aspirated and discarded 5 mL of blood and fluid from the catheter to avoid dilution of the specimen. External chest compressions were continued in each animal throughout the 3-minute specimen collection. Adequacy of compressions was confirmed by palpation of femoral pulse and the presence of an arterial blood pressure waveform measured on the vital signs monitor. All blood samples were collected in labeled heparinized tubes and were immediately centrifuged. The concentration of epinephrine in plasma was determined by use of enzyme-linked immunosorbent assay (ELISA).

Results
The minimum number of animals was used to obtain a statistically valid result. The determination of effect size for this experiment was based on previous work. Using the data reported in those studies, it was calculated that the treatment group had a moderate effect size of 0.6. Using statistical power analysis software (G*Power 3.00 for Windows), an effect size of 0.6, a power of 0.80, 2-sided testing, and an α of 0.05, we determined that a sample size of 5 swine per group would be needed for the study.

A multivariate analysis of variance (MANOVA) was used to determine if there were significant differences in the groups. A Wilks Λ indicated there were significant differences between the groups (P = .01). A Tukey post hoc analysis was used to determine where the significance was. Pigs of similar size and weight were used in all 3 groups; there were no significant differences in the weights of the pigs by group (P > .05). It was anticipated that the stress of anesthesia, instrumentation, and CPR would generate the release of endogenous epinephrine. The amount of endogenous epinephrine secreted should be relatively the same in all groups. To validate this assumption, we compared the baseline concentration of epinephrine across the 3 groups. There were no significant differences in the baseline data (P > .05).

The Cmax was compared across the 3 groups (Figure 1). The Cmax for the tibial IO group ranged from 1,038
to 5,260 ng/mL, with a mean (±SD) of 3,371 ± 1,561 ng/mL, the Cmax for the sternal IO group ranged from 3,314 to 18,617 ng/mL (mean, 6,924 ± 6,551), and the Cmax for the IV group ranged from 8,579 to 38,768 ng/mL (mean, 19,810 ± 12,323). There were significant differences in Cmax between the sternal IO and IV groups (P = .009) and tibial IO and IV groups (P = .03) but no significant difference between the tibial and sternal IO groups (P = .75). The IV administration of 1 mg of epinephrine resulted in a serum concentration 5.87 and 2.86 times greater than for the tibial and sternal routes of administration, respectively.

The Tmax was also compared across the 3 groups (Figure 2). The Tmax for the tibial IO group ranged from 150 to 180 seconds (mean, 156 ± 13 seconds); for the sternal IO group, from 30 to 120 seconds (mean, 60 ± 42 seconds); and for the IV group, from 30 to 180 seconds (mean, 78 ± 69 seconds). There were significant differences in Tmax between the tibial IO and IV (P = .04) and between the tibial IO and sternal IO (P = .02) groups but no difference between the sternal IO and IV groups (P = .56).

Discussion

Previous studies have clearly demonstrated the efficacy and equivalence of IO drug delivery in both normovolemic and hypovolemic states. However, this study suggests that during cardiac arrest with ongoing CPR, the Cmax of epinephrine is higher when administered through a peripheral IV compared with both tibial and sternal IO routes. This may be a result of impaired bone marrow perfusion during cardiac arrest. There may also be a relationship between the anatomical location of the IO device and serum drug concentrations; the more distal the IO infusion site is from the sampling site, the longer concentrations of drug take to rise. Another possible explanation is a local vasoconstrictive effect of epinephrine in the bone marrow circulation impairing drug delivery to the systemic circulation. Epinephrine delivery may differ substantially from other drugs that have not yet been studied in a cardiac arrest scenario.

The Advanced Cardiac Life Support (ACLS) recommendation for the endotracheal administration of epinephrine is 2 to 2.5 times the IV dose. The Pediatric Advanced Life Support (PALS) recommendation for endotracheal epinephrine is 10 times the IV dose. Whereas no studies were used to establish these dosage guidelines, it has been demonstrated that equivalent doses of endotracheal epinephrine are less effective than IV epinephrine.21 However, the current guidelines for administration of epinephrine are the same for both the IO and IV routes. The findings of this study suggest that higher doses of epinephrine may be needed when administered via the IO route to patients in cardiac arrest, compared with the IV route.

The time to peak concentration was similar in the IV and sternal IO groups, but it was significantly delayed in the tibial IO group. Hoskins and colleagues19 also demonstrated a delay in delivery from the tibial IO compared with other IO sites.

At this time, we do not recommend changing the guidelines of administering 1 mg of epinephrine by the IO route because of the limitations of this pilot study. Specifically, the sample size was small, there was wide variability within the groups, and specimen collection from the
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