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Original article

Comparison of vasopressin delivery via the proximal humerus and proximal tibia in healthy dogs under general anesthesia: implications for emergency intraosseous administration

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Abstract

During cardiopulmonary resuscitation, securing intravenous access for medication delivery can be problematic due to the size of the patient and vasoconstriction due to hypotension. The osseous route is a promising alternative to the intravenous route. The proximal humerus and proximal tibia are two commonly utilized sites in dogs. While some studies have reported the superiority of the proximal humerus route over the proximal tibia route for drug delivery in humans, there is a lack of knowledge on this topic in dogs. This study evaluated the difference in intraosseous vasopressin effect between the proximal humerus and proximal tibia in dogs. Seven healthy dogs were under general isoflurane aesthesia and intraosseous access was achieved in a crossover design. 0.05 U/kg vasopressin was administered and perfusion index (PI), heart rate (HR), and mean arterial blood pressure (MAP) were recorded. PI and HR decreased more dramatically when vasopressin was injected into the proximal humerus than into the proximal tibia, and MAP increased more distinctly when vasopressin was injected into the proximal humerus than into the proximal tibia. These results suggest that vasopressin is more effectively delivered when injected into the proximal humerus than into the proximal tibia. We performed histopathologic exploration of the humerus and tibia and found the difference in the distribution of vessels with cell composition of the bone marrow, and this would be a factor to affect the drug absorption of the each site. These results support the opinion that humerus is a superior intraosseous route for the administration of vasopressin.

Keywords: humerus, intraosseous injection, tibia, vasopressin

Introduction

During cardiopulmonary resuscitation (CPR), gaining access to the central circulation is vital to providing advanced life support. Peripheral intravenous catheter placement is often the first-line approach. However, the blood circulation of emergency patients might have low perfusion because of hypotension, which makes it difficult to access the shrunken peripheral vessels. In these situations, we try another promising vessel, such as the Juglar vein; however, achieving vein access takes longer. Also, the procedure of the central indwelling vein is sometimes obstructed by other CPR procedures, such as chest compression. The osseous route is an alternative to the vascular route, and the drugs administered are almost as potent as those injected via the vascular route (Sá et al. 2012). Furthermore, the osseous route access is more convenient when the vessels are unavailable, especially in pediatric patients who have small vessels (Otto et al. 1989); therefore, in pediatric animals, small dogs, and cats, the osseous route could be a reasonable alternative in emergencies.

In humans, the proximal humerus and proximal tibia are commonly used as injection sites. The humerus is generally preferred over the tibia due to its more effective drug delivery (Philbeck et al. 2022). The reasons for the differences are still debated; however, variations in the perfusion rate at each injection site or anatomical differences are promising factors (Lairet et al. 2013, Brebner et al. 2023). Lange et al. (2019) assessed intra osseous catheter placement at four anatomical sites – proximal medial tibia, proximal lateral humerus, distal lateral femur, and iliac wing – in canine cadavers. Their study demonstrated that the femur and humerus provided the highest success rates, shortest placement times, and lowest placement difficulty. Furthermore, these sites also showed the greatest pressurized fluid flow rates. These findings suggest that the humerus and femur may be preferable IO access points in clinical settings, especially during emergencies.

Therefore, in the present study, we aimed to determine the most effective IO route for drug delivery in live dogs. We administered vasopressin (0.05 U/kg) via either the proximal humerus (Hum group) or the proximal tibia (Tib group), and assessed the resulting vasoconstrictive effects in seven clinically healthy beagle dogs.

Materials and Methods

Experimental animals

All the experimental procedures were reviewed and accepted by the Kitasato Experimental Animal Committee (license no. 23-080, 21.02.2024).

Seven clinically healthy 3-year-old beagle dogs (three neutered females and four neutered males; body weight 9.2–13.6 kg) held as experimental animals were registered for this study. The animals were housed individually in cages under controlled sunlight, temperature, and food conditions. They were also fasted for 12 hours before the experiment.

Experimental procedures

Two groups were established for the experiment. The Hum group received an intramedullary injection of Vaso at 0.05 U/kg into the humerus. The second group, the Tib group, received the same dosage of Vaso but into the tibia. The order of the experiments was randomized among the experimental dogs, and there was a minimum interval of one week between each experiment.

All dogs were administered a 22G catheter (Surflow Flush® 22G x 1: Terumo) into the radial cutaneous vein. They received 0.025 mg/kg of atropine sulfate (ATROPINE SULFATE injection 0.5 mg; Mitsubishi Tanabe Pharma Corporation) subcutaneously as premedication, followed by an intravenous dose of 0.2 mg/kg of butorphanol (Vetorphale®: Meiji Seika Pharma). To induce anesthesia, 6 mg/kg of alfaxalone (Alfaxalone®: Meiji Seika Pharma) was administered intravenously, followed by tracheal intubation. After anesthesia induction, all dogs were maintained in a dorsal recumbency. A continuous intravenous infusion of butorphanol at 0.3 mg/kg/h was provided for analgesic treatment. Mechanical ventilation was conducted using a ventilator (Minivent 3-animal: Kimura Medical Co., Ltd.) with the following initial settings: oxygen flow at 2.0 L/min, isoflurane concentration at 2.5%, a respiratory rate of 12 breaths per minute, an airway pressure of 12 mmHg, and an inspiratory/expiratory (I: E) time ratio of 1:2. The end-expiratory carbon dioxide concentration ($ETCO_2$) was maintained at 32–35 mmHg. Additionally, a 22G catheter was placed in the femoral artery for serial mean arterial blood pressure (MAP) measurements and connected to a transducer (Standard kit with disposable transducer (single): Edwards Lifesciences Inc.) that was then linked to a biometric monitor (Biometric Monitor BP-608EV: OMRON).

We measured the MAP, heart rate (HR), and perfusion index (PI) over time, PI values were obtained by attaching the tongue tip to a pulse oximeter probe (Radical-7®: Masimo Japan Co.) and calculating the ratio of pulsatile to non-pulsatile blood flow.

The site for the bone marrow puncture was prepared for the surgical procedure. A manual bone marrow puncture was performed using an 18G bone marrow

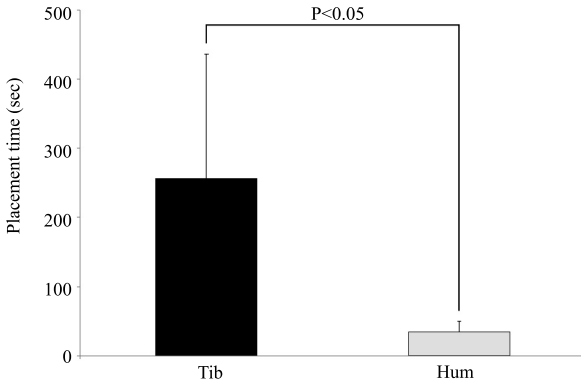

Fig. 1. Time required to achieve intraosseous access in the tibial (Tib) and humeral (Hum) dog groups. Bars represent mean ± standard deviation (SD). A significant difference was observed between the groups ($p<0.05$; Student's t-test).

needle (Illinois bone marrow puncture needle: Fuji Systems, Inc.) at either the proximal tibia (Tib group) or the proximal humerus (Hum group). All procedures for securing the IO route were performed by a single veterinarian with over 10 years of experience in veterinary emergency and critical care, and who has substantial expertise in performing bone marrow punctures.

Each injection site was shaved and disinfected before the bone marrow puncture. For the proximal humerus injection, the site was located at the base of the greater tubercle. The site was identified as medial to the tibial tuberosity for the proximal tibia injection.

The time taken from the start of the puncture to the confirmation of blood aspiration was recorded as the placement time. After placing the bone marrow needle at each site, 3 ml/kg/hr of Lactated Ringer's solution (Lactec Injection: Otsuka Pharmaceutical Co., Tokyo, Japan) was initiated. During the first 5 minutes of infusion, baseline values for HR, arterial MAP, and PI were recorded as 0-minute values. Following this, 0.05 U/kg of Vaso was administered intramedullary at each site. All values were subsequently recorded every 0.5 minutes (30 seconds) for 30 minutes. After data collection was completed, all dogs recovered from anesthesia. Prior to anesthesia recovery, the intraosseous needle was removed, and the insertion site was closed with a suture, covered with a sterile film dressing, and a compression bandage was applied for two days. To prevent infection, 25 mg/kg of cefazolin sodium (Cefamezin α for Injection: LTL Pharma Co., Tokyo, Japan) was administered during for 5 days.

Two of the dogs were humanely euthanized for reasons unrelated to this study. Samples from both injection sites were submitted for histopathology.

Statistical analysis

We compared the time required to establish intraosseous access using the tibial and humeral routes with a Student's t-test after confirming normality and homogeneity of variance. All changes in MAP, HR, and PI values from 0 min are expressed as mean ± SD. A one-way ANOVA was performed to identify statistically significant differences among the group means, followed by Dunnett's post hoc test for comparisons against the 0 min value. The Wilcoxon signed-rank sum test was used to determine the specific differences between the groups. Significant between-group differences were defined as p-values <0.05.

Results

In this study, the placement of catheter was successfully established at first attempt in all procedures. Bone marrow access took 34.6 ± 14.6 seconds in the Hum group and 256.9 ± 179.9 seconds in the Tib group. The placement time was significantly shorter in the Hum group. (Fig. 1)

MAP increased in both groups following the Vaso challenge, but the rise in MAP was significantly sharper in the Hum group. A noteworthy difference was observed between the pre- and 1.5 to 14 minutes after the Vaso challenge. The maximum increase in MAP was 49.5 ± 20.8 mm Hg, which occurred at 3 minutes. In contrast, the increase in the Tib group was slower, and no apparent peak was reached; moreover, no significant difference from the baseline was observed during the experimental period. Overall, the increase in MAP in the Hum group surpassed that of the Tib group, with significant differences noted between 0.5 and 11 minutes after the challenge. (Fig. 2)

Both groups experienced decreased HR following the Vaso challenge. HR significantly dropped after the challenge in the Hum group, with a maximum reduction of 18.3 ± 11.6 bpm observed at 6 minutes. A significant difference between 0.5 and 9.5 minutes was noted in the pre-challenge levels and 11 – 30 minutes after the Vaso challenge during the experimental period. In contrast, the Tib group showed a comparatively smaller decrease

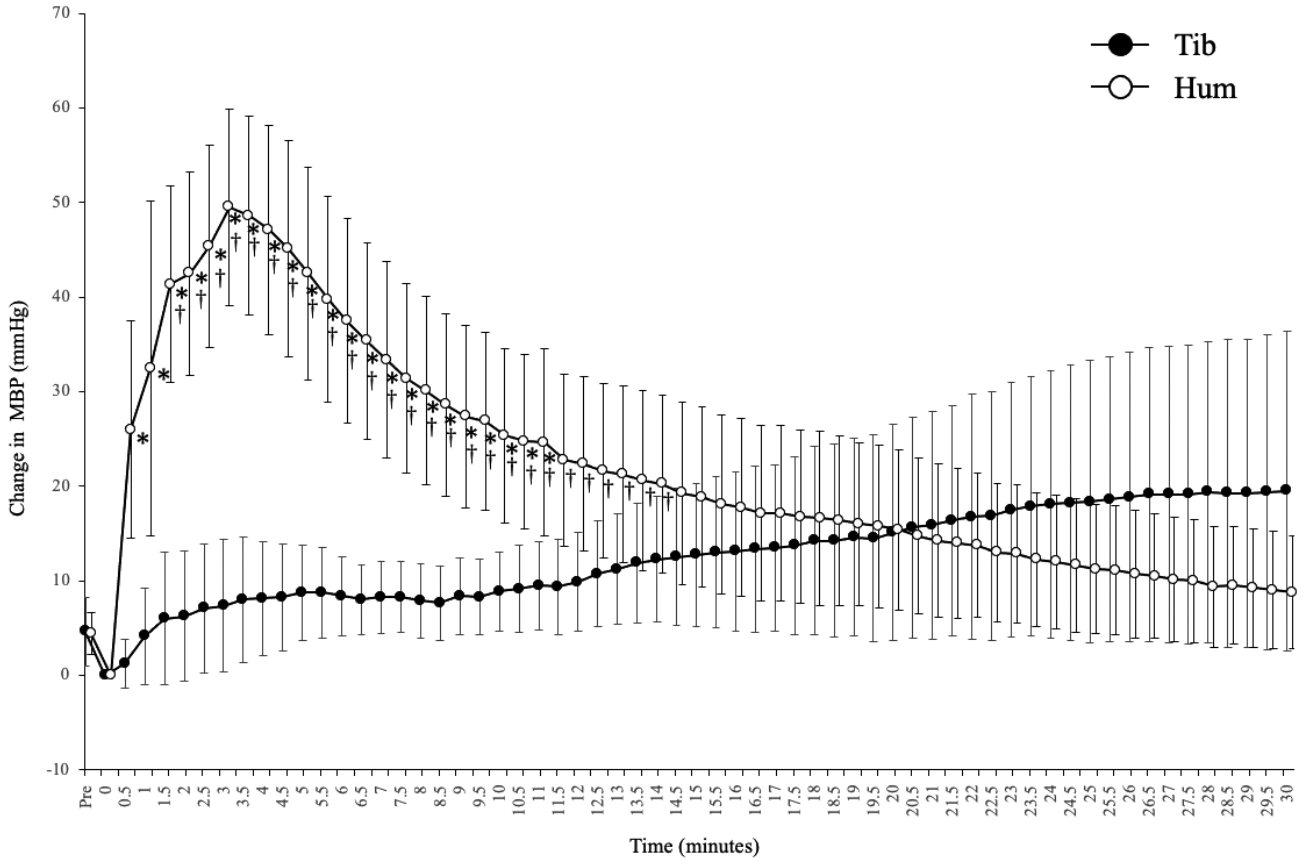

Fig. 2. Changes of mean blood pressure after vasopressin challenge in Tib dog group and Hum dog group.
* indicates significant difference ($p<0.05$; Dunnett's test) relative to the 0 min.
†indicates significant difference ($p<0.05$; Wilcoxon signed-rank sum test) between the groups.

in HR, with a maximum reduction of 12.4 ± 14.0 bpm observed at 7 minutes. Significant differences from prechallenge levels were recorded at 4, 4.5, and 5.5 minutes. An significant difference between the groups was observed at 0.5 to 3 min. (Fig. 3)

PI decreased following the Vaso challenge in the Hum group. There was a significant drop in PI immediately after the challenge, with notable differences from the baseline measured between 3.5 and 12.5 minutes. The maximum reduction in PI was recorded at 16.7 ± 0.8, occurring at 4.5 minutes post challenge.

In contrast, the Tib group experienced only a slight decrease in PI throughout the experimental period. The maximum decrease noted was 0.5, recorded at 7.5 minutes, and no significant difference from the baseline was observed in this group. A significant difference between the two groups was evident from 0.5 to 18.5 minutes. (Fig. 4).

Macroscopic morphological examination

Histological evaluation showed that the bone marrow samples from the humerus had a higher proportion of hematopoietic (cellular) components relative to the adipose tissue, occupying approximately 50–70% of the marrow space, compared to about 10% in the tibia.

These cells include three different lineages, although the proportions vary by location. The ratio of erythroblasts to myelocytes is approximately 1:1 to 1:2. Megakaryocytes are also present, with 1–2 found per visual field. The tissue samples show a high density of cells, particularly in the humerus bone marrow. Reflecting these differences in cellular composition, the macroscopic appearances of the bone marrow at each site also differed (Fig. 5).

Discussion

The current study aimed to evaluate whether the proximal humerus or proximal tibia provide superior intraosseous absorption of vasopressin in dogs. This information may help clinicians select the optimal intraosseous access site in veterinary emergency medicine. In human medicine, the sternum is the primary choice, followed by the clavicle, distal radius, ulna, ilium, and medial malleolus for intraosseous injection (Iserson 1989, Schaefer et al. 1992, Iwama et al. 1994, Kruse et al. 1994). During CPR, chest compressions can be performed, and only certain extremities, like the

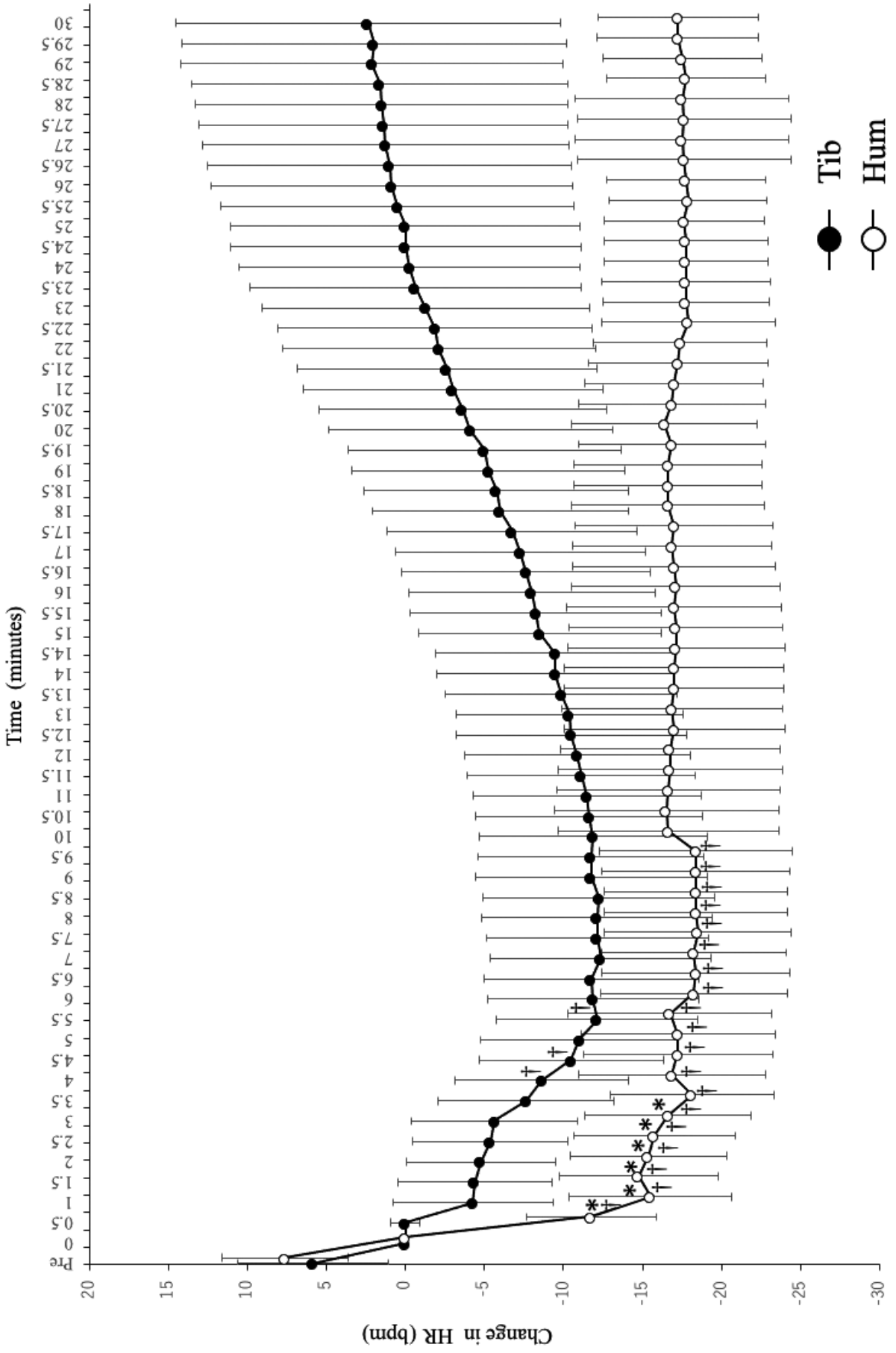

Fig. 3. Changes of heart rate after vasopressin challenge in Tib dog group and Hum dog group.
* indicates significant difference ($p<0.05$; Dunnett's test) relative to the 0 min.
† indicates significant difference ($p<0.05$; Wilcoxon signed-rank sum test) between the groups.

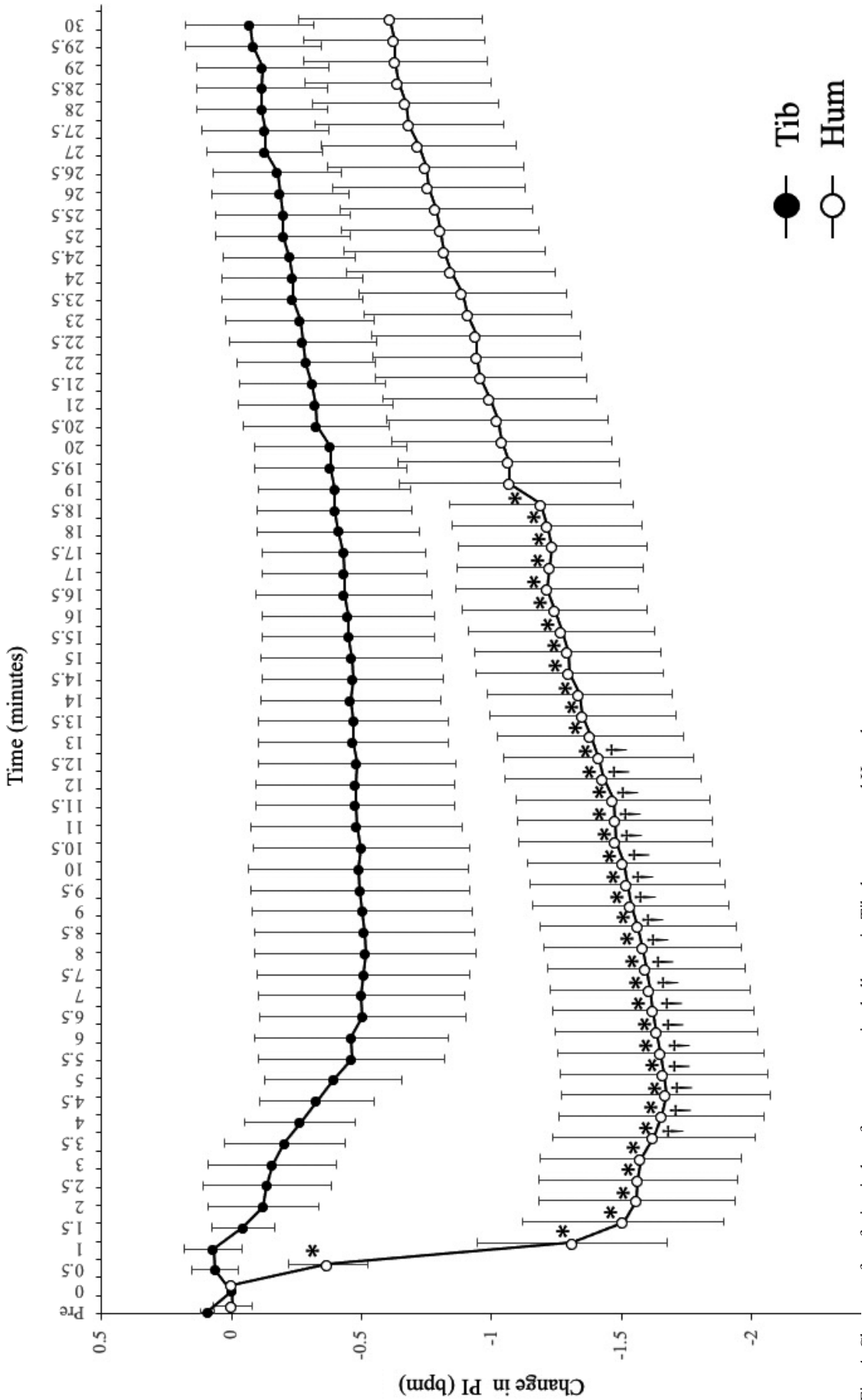

Fig. 4. Changes of perfusion index after vasopressin challenge in Tib dog group and Hum dog group.
* indicates significant difference ($p<0.05$; Dunnett's test) relative to the 0 min.
† indicates significant difference ($p<0.05$; Wilcoxon signed-rank sum test) between the groups.

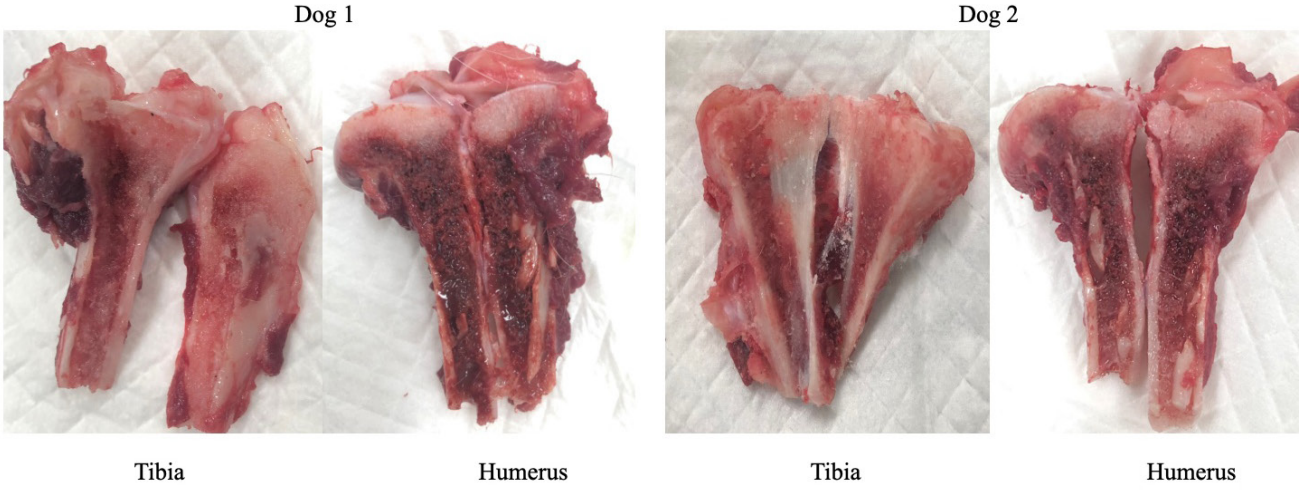

Fig. 5. Macroscopic difference between injection site of Tibia and Humerus in two dogs.
The density of bone marrow cells were very different between each site, twice of the density was observed in the humerus than that of in the tibia.

tibia or humerus, may be easily accessible. Due to anatomical size considerations, the proximal tibia or proximal humerus is preferred for achieving intraosseous access in pediatric or juvenile patients during CPR (Olivieri and Brenner 2023). We chose the proximal humerus and proximal tibia as accessible injection sites during CPR for small animals, such as dogs. In an emergency, quick drug infusion is crucial for maintaining adequate blood levels of the injected medication. Our study examined the time required to achieve intraosseous access at each site, including the proximal humerus and proximal tibia. Each procedure was performed by a single veterinarian, measuring the time from the initial puncture to when blood was successfully flushed back through the needle.

The results showed a significant difference in the time required between the two sites; accessing the proximal humerus took less time than the proximal tibia. This discrepancy can be attributed to the thickness of the bone cortex. The veterinarian experienced greater difficulty with the stiffer, thicker cortex of the tibia, while access to the intraosseous region of the humerus was achieved more easily.

Huo et al. (2024) indicated that the choice of puncture site significantly influences manual intraosseous infusion's effectiveness because of bone cortical thickness variations. The proximal humerus may provide better puncture efficacy than the proximal tibia in humans. Similarly, Lange et al. reported that the humerus site allowed for faster and more successful intraosseous catheter placement in canine cadavers compared to the tibia. Although their study used a mechanical injection system (EZIO) in cadaver models, and ours involved manual needle placement in live animals, the consistent findings across both studies reinforce the humerus as a superior IO access site. These methodological differences likely explain the discrepancy in absolute times, but not the overall trend favoring the humerus.

However, there are some complications after establishing the IO route, such as fat embolisms (Castiglioni et al. 2023), osteomyelitis (Chalopin et al. 2018), and tissue damage caused by the extravasation of agents. Extravasation is highly correlated with the failure of multiple bone marrow punctures. (Christensen et al. 1991). In this study, we successfully accessed the bone marrow at each injection site on the first attempt; therefore, we did not experience any complications associated with IO establishment, including fat embolisms or osteomyelitis.

In this study, we assessed the vasopressor effect of Vaso by measuring the change in MAP from the baseline. When injected into the humerus, the mean blood pressure increased dramatically and was maintained higher than injections made through the tibia. Additionally, the onset of Vaso – defined as the time needed to observe a significant difference from baseline – was shorter with humeral injections than with tibial injections.

The baroreflex reduces cardiac afterload when blood pressure increases (Johansson et al. 2007). Vaso can increase afterload by constricting peripheral vessels, which results in a reduction of HR. In our findings, HR decreased following the Vaso challenge via both administration routes; however, no significant difference from baseline (t0) was observed with the tibial route. In contrast, a notable effect was seen with the humeral route. It was indicated that Vaso does not significantly impact cardiac function; the variations noted were likely due to the baroreflex. Therefore, the vasopressor effect was more pronounced in the humerus route compared to the tibia route.

This finding is supported by changes in the PI, which reflects peripheral vascular tone. PI indicates peripheral perfusion status derived from the arterial blood oxygen saturation waveform measured by a pulse oximeter (Coutrot et al. 2021). It serves as a measure of peripheral blood flow; specifically, vasoconstriction leads to a decrease in PI (Kim et al. 2020). In the results, the Vaso challenge reduced PI values for both injection routes, indicating that vasoconstriction occurred. However, the decrease in PI was more pronounced in the humerus route compared to the tibia route, where a stronger vasoconstriction effect was observed. Consequently, the reduction in HR resulted from vasoconstriction, and the difference in responses between the injection routes can be attributed to the enhanced vasoconstriction effect influenced by the injection site.

The results indicate that Vaso injected into the humerus enters the systemic circulation more quickly than when injected into the tibia. This difference is not yet understood, but it may be due to the density of blood vessels at each injection site.

Our histopathological analysis revealed differences in the density of bone marrow cells at each injection site. When we histologically examined the tibia and humerus bone marrow, we found that the proportion of the three types of red bone marrow cells was more than twice as high at the proximal end of the humerus compared to the proximal end of the tibia.

At the tibial injection site, there was a limited delivery of blood vessels, with most of the bone marrow being replaced by the adipose tissue. In contrast, the bone marrow in the humerus injection site maintained its vascular structure. Previous reports in humans support these findings; Blebea et al. (2007) explored the histological differences in the humerus using F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging.

The primary function of the bone marrow is to produce blood cells, which can be classified into two types: red bone marrow, rich in blood vessels and capable of producing blood cells, and yellow bone marrow, which lacks blood-producing ability and has few blood vessels. In humans, most bone marrows are red during early childhood, but it is gradually replaced by yellow bone marrow as we age. It has been reported that only the proximal end of the humerus and the epiphysis of the femur retain the red bone marrow after adulthood. In contrast, the yellow bone marrow in the tibia replaces all the bone marrow (Blebea et al. 2007). All of the dogs in our study were adult, and most of their tibial bone marrow would have been replaced by the fatty tissue. For the sake of animal welfare and protection, we only examined two dog cadavers. While this result would only provide supplemental information, we believe the consistency across both specimens supports our findings.

In general, when a drug is injected into the tissue, the absorption of the drug can affect muscle blood flow. For example, Evans et al. (1975) reported that drug absorption varies with differences in blood flow between the gluteus maximus, vastus lateralis, and deltoid muscles. Therefore, Vaso would have been absorbed immediately in the humerus rather than the tibia, as in muscle injection. In addition, the liposolubility of the drug also affects its absorption when injected into tissue. In addition, the absorption of drugs injected into the tissue would be affected by liposolubility. Highly liposoluble drugs tend to accumulate in the fatty tissue around the injection site; in the tibia, the rich fatty tissue would trap the injected agent, and the vessel absorption would be delayed. Vaso is a peptide hormone; its effector receptor is located on the cell surface and is known to be water-soluble.

In fact, a drug administered via the intraosseous (IO) route can distribute to the bone marrow and be retained by the adipose tissue, a phenomenon known as the "depot effect." Theoretically, drugs with high lipophilicity are more easily affected by the depot effect and are released into the bloodstream more slowly than water-soluble drugs. However, in swine, the recovery time from the muscle relaxant rocuronium was prolonged when it was injected intraosseously via the tibia compared to intravenous injection, and some of the rocuronium was trapped in the adipose tissue in the medulla (Loughren et al., 2014). In this study, Vaso injected via the tibia should have been more trapped than when injected via the humerus because the tibia has more yellow bone marrow than red bone marrow.

In swine, the flow rate through the proximal humerus was statistically greater than through the proximal tibia (Lairet et al. 2013). Previous research by Lange et al. (2022) demonstrated that pressurized fluid flow rates were higher at the humerus and femur sites than at the tibia site in canine cadavers. This anatomical difference in flow characteristics may explain the more pronounced systemic effects observed following humeral administration in the present study.

In this study, the blood levels of Vaso were not measured. Based upon MAP, PI and HR, we infer that blood levels in the Hum group were higher than in the Tib group, though pharmacodynamics information was not calculated. However, with the results of MAP, PI and HR the serial blood levels of Vaso in the Hum group should have remained higher than those in the Tib group. One limitation of this study is that the intraosseous puncture was performed manually. This may have affected the consistency and reliability of securing the tibial route. Several commercially available intraosse-

ous injection devices exist, which could potentially improve this aspect in future studies. The 0.05 IU/kg dose used in this study was lower than the clinically recommended dose because the 0.8 IU/kg dose caused excessive vasoconstriction in healthy dogs, making it impossible to obtain meaningful hemodynamic data. Nevertheless, the aim of this study was to compare vasoconstrictive effects between different intraosseous administration sites at the same dose. Even at this lower dose, vasopressin administered via the humerus resulted in a stronger vasoconstrictive effect compared to the tibia. Therefore, we believe our findings are still clinically relevant. Our study demonstrated differences in parameters such as access time and pharmacokinetics between the humeral and tibial intraosseous routes. However, it remains unclear whether these differences lead to better clinical outcomes, such as return of spontaneous circulation (ROSC), during CPR. Previous studies, including those by Johnson et al. (2016) have reported differences in pharmacokinetics between intraosseous and intravenous administration routes without corresponding improvements in ROSC rates. The primary aim of this study, however, was to compare the relative efficacy of the humeral versus tibial intraosseous routes in situations where intravenous access is not feasible. Further clinical studies are necessary to clarify how these differences impact meaningful clinical endpoints. There is a possibility that atropine administration affected the data, particularly heart rate. However, the injection was performed prior to anesthesia induction, and its pharmacological effects were considered minimal by the time data collection began in each group.

Conclusion

These results support the humerus as a superior intraosseous route for the administration of vasopressin when compared to the proximal tibia. Histopathologic results suggest additional potential benefits of this site when administering lipophilic medications. Intraosseous access via the humerus should be considered in emergency situations where intravenous access cannot be promptly achieved.

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