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Anatomy and Physiology of Intraosseous Infusion

Andrew Mizerowski
Wayne State University, hh9947@wayne.edu

James Paxton
Wayne State University, jpaxton@med.wayne.edu

Chapter Title:

“Chapter 2 – Anatomy and Physiology of Intraosseous Infusion”

Authors:

- Andrew Mizerowski, MD (hh9947@wayne.edu) – **Corresponding Author**
- James H. Paxton, MD (james.paxton@wayne.edu)

Abstract:

The introduction of fluids and medications via intraosseous (IO) infusion is highly dependent upon many unique aspects of bone anatomy and physiology. Key considerations include differences in the medullary cross-sectional area between insertion sites, age- and location-dependent variation in the distribution of red and yellow bone marrow, volume and pressure capacity within the venous system, and the influence of hormones and other chemical messengers on vasomotor tone. In addition to an exploration of these concepts, this chapter will also discuss the physiologic basis for pharmacokinetic relationships reported in the prevailing literature and propose methods to optimize the use of IO infusion in the care of critically ill patients.

Key Words:

- Intraosseous, catheter, anatomy, physiology, flow, circulation.

Introduction

Unlike the more common method of **direct** infusion of medications and fluids through an intravenous (IV) catheter into the venous drainage system of the human cardiovascular system, intraosseous (IO) infusion utilizes an **indirect** infusion of substances by depositing substances in to the intramedullary space for eventual uptake by the venous drainage system of the bone. Historically, the **long bones** of the human body including the tibia, humerus, and femur have been preferred as catheterization sites for IO infusion. However, the sternum (a flat bone), clavicle, radius, and calcaneus (a short bone), among others have also been studied. Although each site has different physiological properties that uniquely impact the infusion of medications and fluids, the principle of IO infusion remains similar in all cases. This chapter will explore the basic principles behind IO infusion, including common mechanisms relating to bony anatomy and physiology that enable this technique to be effectively used for the treatment of critically ill patients.

Bone Anatomy

Long bones are comprised of three main parts: the **diaphysis** or middle of the bone, the **metaphysis** (proximal and distal to the diaphysis), and the **epiphysis** (proximal and distal to the metaphysis). Most of the **medullary cavity** resides within the boundaries of the diaphysis. The medullary cavity is comprised of a combination of yellow marrow and red marrow. **Yellow marrow** is composed largely of adipocytes within a connective tissue meshwork that additionally supports blood vessels. **Red marrow**, in contrast, consists primarily of hematopoietic cells (i.e., blood stem cells) organized within a loose connective tissue stroma that supports an extensive blood supply.[1] The diaphysis surrounding the medullary cavity is composed of cortical (i.e., compact) bone, while the metaphysis and epiphysis consist primarily of trabecular (i.e., spongy) bone positioned deep to the cortex. The outermost surface of bone consists of the **periosteum**, a highly vascularized, densely innervated connective tissue layer containing both osteoclasts and osteoblasts. The periosteum covers almost the entirety of long bones except at surfaces where bones articulate with one another. Just below the periosteum is the **cortex**, which consists of three layers: the outer circumferential lamellae, the interstitial lamellae, and the inner circumferential lamellae. The interstitial lamellae tend to arrange into **Haversian canals**, bony channels surrounding perforating blood vessels and nerve fibers. This anatomy is illustrated in **Figure 2.1**.

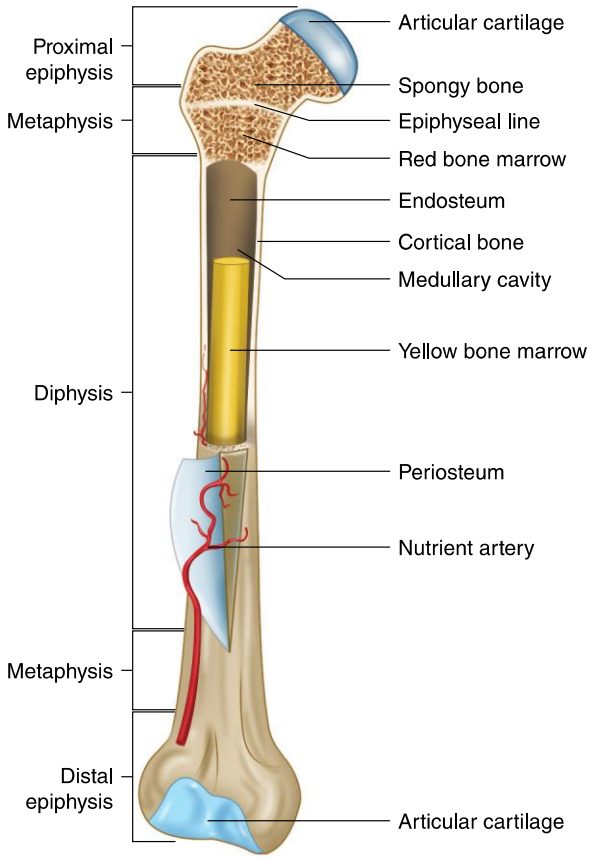

Figure 2.1. Bone anatomy.

The **endosteum** is a highly vascularized connective tissue layer also containing osteoclasts and osteoblasts, and is in contact with both lamellar bone and the medullary cavity.[1] Oxygenated blood supplied to the medullary cavity via **nutrient arteries**, with their number depending upon the size of the bone. These arteries enter the bone through the **nutrient foramen** to supply ascending and descending portions of the marrow cavity before branching into radial arteries. The radial arteries supply the bone marrow and the inner one-third of compact bone before further branching into spiral arteries, which anastomose with the metaphyseal arteries. **Sinusoids** in bone represent the transition point between the human arterial and venous systems. After oxygen in the blood has been extracted by the bone and its contents, deoxygenated blood is removed from the bone via numerous collecting veins. Metaphyseal vessels are separated early in life from epiphyseal vasculature by the epiphyseal growth plate. Upon closure of the growth plate, anastomosis of these vessels occurs. Periosteal supply is accomplished in part by the nutrient artery and by the periosteal arteries, which travel within the **Haversian canals**. Haversian canals communicate with each other via **Volkmann canals**.[2] The relationship between these vascular channels is demonstrated in **Figure 2.2**.

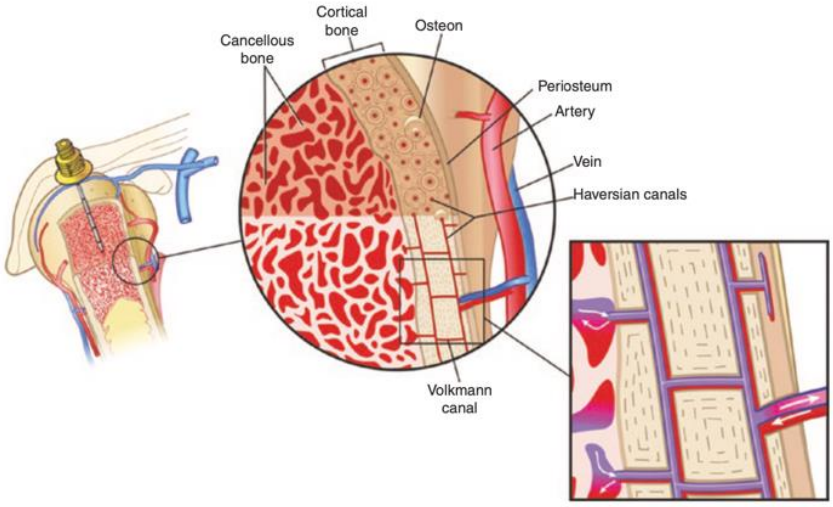

Figure 2.2. Intraosseous vascular anatomy. (Image courtesy of David Baker & Sam Newman. © *2023 University of Texas Health Science Center, San Antonio. All rights reserved.)*

Blood delivery to human bones is quite efficient, with the skeletal system receiving between 5.5% and 11% of cardiac output.[2] Early in life, these blood vessels fuel the rapid growth of long bones from their transition as chondrocytes (i.e., cells that secrete cartilage and become embedded in it) to mature bony tissue. Even after bones cease to grow in size, this rich blood supply is needed to promote continued remodeling of the bone throughout the human life cycle.

Although the anatomy of flat or short bones differs slightly from that of long bones, their structure closely resembles the epiphysis of long bones. Both flat and short bones are composed of a thin layer of cortical bone surrounding trabecular bone. As humans age, their medullary cavities tend to become less haematopoietically active, with red marrow gradually replaced by yellow (i.e., adipose) marrow. This transition occurs more slowly in flat (e.g., sternum) and short (e.g., calcaneous) bones than in long bones (e.g., humerus, femur, tibia) so that **a higher proportion of red marrow is found to reside within the trabecular bone of adults when compared to the long bones**.[1]

Neurohormonal Regulation

Modulation of the blood supply to bone is accomplished by both sympathetic neural and neurohumoral mechanisms. Sympathetic control is modulated through the release of endogenous catecholamines, mainly **norepinephrine** and, to a smaller extent, epinephrine. Catecholamines interact with prejunctional and postjunctional adrenergic receptors on the smooth muscle vasculature to mediate vasoconstriction and vasodilation. The two main categories of adrenergic receptors are alpha (α) and beta (β) adrenergic receptors, and both come in a variety of subtypes. Postjunctional α-1 and α-2 receptors are known to be the two primary mediators of vasoconstriction. The density of these receptors and receptor subtypes vary widely between

different vascular beds. The post-junctional β-2 receptor subtype has been shown to be implicated in mediating vasodilation, although the role of prejunctional β-receptors in bony vasomotor control remains largely unknown. Activation of the prejunctional α-2 adrenergic receptors induces inhibition of norepinephrine release through the process of feedback inhibition. Neurohumoral mechanisms are carried out by stimulation of the adrenal glands to secrete mainly epinephrine (and some norepinephrine), along with the stimulation of the renin-angiotensin aldosterone system (RAAS). The RAAS system ultimately increases blood volume, increases peripheral resistance through vasoconstriction, and can increase sympathetic neural transmission.[59]

The interaction between marrow vasculature and neural stimulation has been extensively studied. Early investigations by Stein et al. documented the vasoactive effects of endogenously synthesized catecholamines, including norepinephrine and epinephrine.[12] This study was one of the first to demonstrate the decrease in bone marrow pressure seen with peripheral intravenous injections of epinephrine and norepinephrine, which is theorized to be due to vasoconstriction of nutrient arteries. Subsequent investigations have reported similar findings.[13,19] The clinical implications of these findings are seen in emergency situations such as cardiac arrest, which is associated with an increased degree of sympathetic activity. Perfusion of bone marrow in such circumstances is limited,[17] ultimately affecting the administration of medications that are given intraosseously. However, studies of vasopressor administration in the treatment of cardiac arrest have shown incongruent results when comparing the pharmacokinetics of IO versus IV routes of infusion. Some authors have shown no significant difference in maximal concentration (Cmax) and time to maximal concentration (Tmax) between IO and IV administration of epinephrine,[19] while others have reported that IV administration of epinephrine is associated with a significantly greater Cmax and Tmax when compared to IO administration.[20] It is unclear whether these discrepancies are due to differences in adrenergic receptor density at the nutrient arteries, or rather the effect of infused epinephrine on adrenergic receptors at the marrow arterioles.

Factors Influencing Vascular Supply to Bone

There have been investigations into other endogenous molecules such as bradykinin, adenosine, vasopressin, and metabolic byproducts that also impact resistance of bone marrow vasculature. The peptide bradykinin has been shown to decrease vascular resistance with subsequent increases in bone marrow blood flow.[14] This should not be surprising considering bradykinin's vasodilatory actions during the inflammatory process. The ubiquitous nucleoside adenosine has also been found to increase bone marrow blood flow,[19] by causing relaxation of the arterial smooth muscle.[38]

Vasopressin demonstrates unique action generating both vasodilatory and vasoconstrictive effects. The determination of vasculature effect is predicted by the receptor that it is acting upon. As vascular beds often contain more than one receptor type, the net effect of a vasoactive substance will depend upon which receptor displays the greater density at that site. Vasoconstrictive responses are carried out by V1 vascular receptors,[45] Katp[44] channels, the NO signaling pathway and the potentiation of vasoconstrictor agents.[43] Vasodilation, on the other hand, is primarily mediated by endothelial oxytocin receptors.[42] The density of these various

receptors at different marrow beds is unknown. One study by Volker et. al measured plasma concentrations of vasopressin following IO and IV infusion, finding that the plasma concentrations achieved were not found to be significantly different.[41] Similarly, Burgert et. al did not observe a significant difference in Tmax or Cmax between IO and IV infusion of vasopressin.[18]

Common metabolic byproducts such as CO_2 and hydrogen ions (H^+) can accumulate in the blood and even in bone through metabolic activity. In conditions such as hypercapnia and acidosis, it has been demonstrated in anesthetized canines that blood flow to the sternum, ribs and femoral marrow were all increased.[34]

The blood supply to bone is intimately tied to the effectiveness of IO infusion. Exogenously administered molecules additionally have the capability to induce an increase in bone blood flow. PTH 1-34, PTH 1-84 and PTHrP were shown to have vasodilator effects on the peripheral nutrient artery of rat femoral bones via NO and endothelial cell mediated mechanisms. [27] The potent vasodilatory capacity of PTH and PTHrP opens the door for investigation into its utilization in IO infusion regimens.

Just as the blood supply to bone can change in the acute setting, it can also change long term. Chronic changes of blood supply to the bone will ultimately impact the effectiveness of IO infusion. A few factors to consider include mechanical loading or exercise, the presence of specific hormones (e.g., estrogen), and aging.

Chronic exercise, both weight bearing and non-weight bearing, has been shown to increase blood flow due to the increased ability of the nitric oxide (NO) dependent vasodilation in rats.[25] This mechanism is depicted in **Figure 2.3**. During exercise, increased blood flow generates a shear stress (SS) on endothelial cells. A downstream cascade following the shear stress further activates the kinases protein kinase c (PKC), Akt, and extracellular signal related kinases 1/2 (ERK 1/2) leading to phosphorylation of endothelial nitric oxide synthase (eNOS) and generation of nitric oxide. Nitric oxide induces smooth muscle relaxation either through large conductance Ca^{+2} activated K^+ (BKCa) channels, and through a series of reactions that upregulate cyclic GMP (cGMP) dependent protein kinase G (PKG). In addition, a host of other molecules depicted in **Figure 2.4** are generated during exercise and increase NO production. Other theories suggest the increased blood flow from consistent exercise is a result of perfusion to a greater percentage of the bone[26]. The demand on bone increases, thus the supply of oxygen and nutrients also must increase.

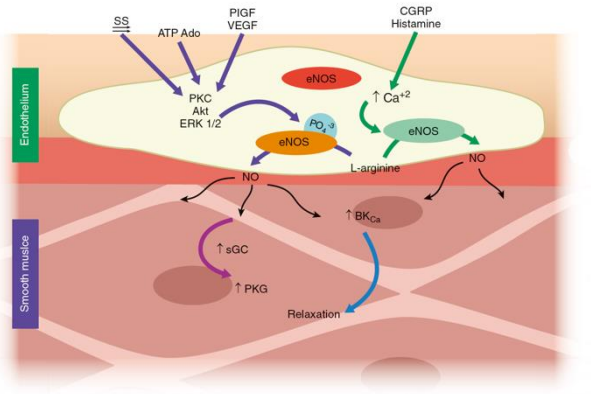

Figure 2.4. Nitric oxide dependent vasodilation.
NOTES: SS (Shear Stress), ATP (Adenosine Triphosphate), Ado (Adenosine), PIGF (Placental Growth Factor), VEGF (Vascular Endothelial Growth Factor), CGRP (Calcitonin Gene Related Peptide), Ca^{+2} (ionized calcium), eNOS (endothelial Nitric Oxide Synthase), PKC (Protein Kinase C), Akt (Akt Serine/Threonine Protein Kinase), ERK 1 / 2 (Extracellular Signal Related Kinases 1 / 2), NO (Nitric Oxide), sGC (Soluble Guanalyl Cyclase), PKG (Protein Kinase G), BKCa (Large Conductance Ca^{+2} -activated K^{+} channel, PO_4^{-3} (Phosphate).

~~Additionally, endothelial dependent vasodilation of the femoral peripheral nutrient artery via NO signaling was found to increase following 15 days of intermittently administered PTH 1-84[28]. Endogenous parathyroid hormone for humans is released because of low blood calcium levels and has been observed to peak between 2:00 – 4:00 a.m.[29]~~

Estrogen is known to have a major impact on bone health in females. Large changes in estrogen levels occur during puberty and menopause. Interestingly, endothelial cells have estrogen receptors on their surface. A study by Griffith and colleagues investigated the effects of reduced estrogen on bone vascularity. They demonstrated that acetylcholine mediated, endothelium dependent vasodilation was impaired, and phenylephrine-induced contraction was enhanced in ovariectomized rats[30]. Vascular endothelial growth factor, VEGF, a signaling protein important for vascular growth, has also been observed to decrease in ovariectomized rats.[31]

~~Endothelial and vascular smooth muscle also respond to vitamin D via vitamin D receptors. Knockouts of the vitamin D receptor on mice reduced the NO bioavailability and a prominent vasodilator modality.[32] Additionally, vitamin D has been shown to be important in blood flow regulation for diabetic individuals, where vitamin D deficiency resulted in a significant brachial artery flow reduction.[33]~~

Throughout an individual's lifetime blood supply to bone does not remain stagnant, but continuously changes. During development, children's bones require a lot of energy which is accomplished by an increase in blood flow to the bone[37]. Further aging effects on medullary perfusion were investigated by Prisby et al. Advanced age was associated with a reduced capacity of endothelial dependent vasodilation in femoral bones mainly attributed to the NO signaling pathway.[35] With a reduced vasodilator capacity associated with aging, so comes an increased reliance upon the periosteal vascular network.[36] Increased reliance on the periosteal vascular network can lead to a reduced medullary flow rate and effectiveness of IO infusion.

Pressure and Flow

The baseline intraosseous pressure (IOP) of long bones is highly variable between sites and is dependent upon several intrinsic physiological parameters. Forward flow of substances into the intramedullary space is only accomplished when infusion pressures exceed the IOP of the target bone. However, different bones have different IOPs, and therefore different tolerances for IO infusion. Baseline IOP values were investigated in a study by De Lorenzo et al. with the

following results: tibia (mean 17.4, SD 8.2 mmHg), femur (18.4, SD 3.8 mmHg), humerus (15.7 +/- 1.8 mmHg), and sternum (5.7 +/- 0.5 mmHg)[3]. These measurements were calculated at baseline and varied based on increases and decreases in blood pressure. This study showed that IO infusion into the diaphysis was drained by a single nutrient foramen, while those infusions introduced at the metaphysis or epiphysis were drained by multiple channels, suggesting that infusion sites near the ends of long bones tend to be more aggressively extracted, possibly due to the presence of an enriched drainage system. Interestingly the only site that showed even a weak correlation with MAP (r = 0.65) in this study was the femur, which also showed the highest IOP among those animals tested.[5] Of course, these results were shown in a swine model, which may relate to the limitations of using animal models in predicting IO flow rates among human subjects as it is possible that human and porcine IOPs differ. What is clear from this study, and likely also true in human subjects, is that different bones have different IOPs. Moreover, those bones with lower IOPs likely enjoy better uptake of infused substances from the medullary cavity, especially when the infusion is introduced near the proximal or distal portions of the long bone. Gravity infusion may not be sufficient to overcome a bone's intrinsic IOP and generate forward flow of infusates; pressurized infusion may be necessary to achieve an acceptable flow rate, especially at sites with a high intrinsic IOP. An extreme example demonstrating the fluctuation in IOP can be seen during hemorrhagic shock, the body works to divert blood flow toward vital organs, with arterial vasoconstriction causing a decrease in bone marrow pressures of 70-80%.[13,12,19] Factors that likely influence the flow rate achievable at a specific infusion site include the size and shape of the medullary cavity, the total sinusoidal cross-sectional area, and the site's proximity to large veins.

The discontinuous capillaries of the medullary cavity are known as **sinusoids**. They allow medications and fluids to enter and make their way into central circulation because they are composed of endothelial cells lacking an organized basement membrane and junctional proteins.[4] **Starling forces** control the exchange of fluids between the capillary intravascular space and the interstitial fluid found between extravascular cells. These forces include the osmotic pressure exerted by proteins and other large molecules in the plasma (i.e., **oncotic pressure**) and **hydrostatic pressure**, which is exerted by a fluid at rest due to the force of gravity. **Starling's equation** describes the net flow resulting from the combined effects of these forces (**Figure 2.3**). In this equation, the flow per unit time is labeled the **fluid flux** (J_v) and is defined as the difference between hydrostatic (P_c-P_t) and oncotic (π_c-π_t) gradients. The symbol P_c represents intravascular hydrostatic pressure, P_t represents interstitial hydrostatic pressure, π_c represents intravascular oncotic pressure, and π_t represents interstitial oncotic pressure. The **filtration coefficient** (K_t) quantifies the conductance or relative ease of fluids to cross the membrane, while the **reflection coefficient** (σ) defines the permeability of the membrane, which is often related to pore size. In order to drive fluid into the sinusoids, a higher hydrostatic pressure (or lower oncotic pressure) must exist within the interstitium than that found within the sinusoids.

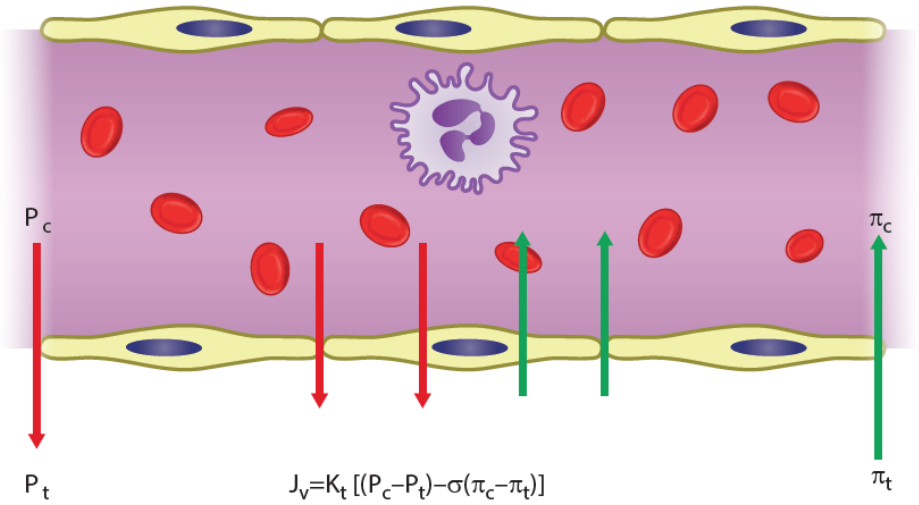

Figure 2.3. Starling's equation, which describes the exchange of fluid between the intravascular and interstitial spaces in human capillaries.
NOTES: J_v (Trans endothelial solvent filtration volume per second), K_t (Filtration coefficient), P_c (Capillary hydrostatic pressure), P_t (Interstitial fluid hydrostatic pressure), σ (Reflection coefficient), π_c (Capillary osmotic pressure), π_t (Interstitial osmotic pressure).

A physiologic limit to the fluid flow rates achievable with IO infusion does exist, but it is not known how this maximal flow rate compares to that achievable with peripheral IV infusion. Warren et al. investigated the IV infusion rate of normal saline compared to the IO infusion rate in a pediatric model at many sites including the humerus, femur, tibia, and medial malleolus under normovolemic and hypovolemic conditions. They also tested the effect of gravity infusion versus pressurized infusion (at 300 mmHg). In this porcine model, the average flow rate for all conditions were as follows: peripheral IV 23.6 +/-7.7 mL/min, humeral IO 22.3 +/- 8.8 mL/min, femoral IO 16.5 +/- 7.8 mL/min, medial malleolus IO 12.1 +/- 7.2 mL/min, and proximal tibial IO 8.8 +/- 6.3 mL/min. This study suggests that humeral IO infusion most closely approximates IV infusion, with proximal tibial infusions performing the worst. Pressurized infusion resulted in an increase of 2-4 times the rates of infusion for both peripheral IV and IO in both the hypovolemic and normovolemic swine models. In addition, this study demonstrated a 32% decreased flow rate on average under hypovolemic conditions when compared to normovolemic subjects for both peripheral IV and IO infusions.[5]

The impact of pressurized infusion on IO flow rates was also studied by Lairet et al. in a porcine model. Investigating high pressures (i.e., above 300 mmHg), the mean infusion flow rate for the tibia was 103 mL/min (+/- 48.1 mL/min), distal femur 138 mL/min (+/- 65.3 mL/min), and proximal humerus 213 mL/min (+/- 53.2 mL/min)[6]. In this study, the proximal humerus flow rate was significantly greater than both the distal femur and proximal tibia. More recent studies demonstrate inconsistent findings between the flow rates at the proximal tibia and distal humerus. Certain studies found significant differences in flow rate between the two sites in both clinical[7] and cadaveric[8] models. On the other hand, further cadaveric[9] and clinical[10] studies did not find significant differences between these two sites.

Schoffstall et al. studied the infusion flow rates of saline and blood comparing larger and smaller pigs. The outcome was an increase in flow rates under pressurized infusion in the larger pigs, but only with the use of a 13-gauge needle and not with an 18-gauge needle.[11] Thus, it appears that the caliber of the IO catheter may also influence flow rates, although the degree to which the IO catheter size restricts flow is unknown.

Factors Influencing Bioavailability

Proximity to the central venous circulation likely affects the degree to which IO infusates exit the marrow via the venous system. Each injection site has a different route to central circulation that ultimately affects the pharmacokinetics and potentially the intended clinical efficacy of the infusion. Intraosseous infusions at the sternum drain into the internal thoracic vein, thence to the subclavian vein, thence the brachiocephalic vein and finally into the superior vena cava before reaching the heart. In terms of distance, more proximal sites of IO infusion (e.g., proximal humerus, sternum) are closer to central circulation compared to more distal insertion sites (e.g., iliac crest, distal femur, proximal tibia, calcaneus; etc). The implications of this principle can be seen in a pharmacokinetic investigation of drug delivery during cardiopulmonary resuscitation in a porcine model by Hoskins et al. In this study, the sternal and tibial IO routes were compared to central venous infusion. Evans blue and indocyanine green dyes were administered along with a 0.014 mg/kg bolus of epinephrine. Comparing the two IO groups (i.e., sternal and proximal tibial), the time to maximal concentration of tracer was significantly lower (53 +/- 11 seconds) for the sternal versus the tibial (107 +/- 27 seconds) route. The authors also found that the time to maximal concentration of tracer was not significantly different between sternal IO and central venous delivery routes (97 +/- 17 seconds, and 70 +/- 12 seconds, respectively). It is important to keep in mind this study was measuring concentrations of dye tracer and not the exogenously administered epinephrine, which may demonstrate different pharmacokinetic effects based on interactions with bone marrow and vasculature.[21]

Interestingly, there is evidence suggesting that red blood cells contain a moderate level of P-450-like activity producing conjugation reactions (e.g., methylation, acetylation, glutathione conjugation).[24] Thus, increased duration of a drug within the bloodstream allows for greater metabolism of this drug before reaching its target site~~. Epinephrine has been shown to have a half-life of only about 5 minutes, with metabolism after IV administration at a rate of 52 +/- 4 ml x min-1 x kg-1.[22-23]~~

~~Shock and Hemorrhage~~

In states of hemorrhagic shock, the body works to divert blood flow toward vital organs, with arterial vasoconstriction causing a decrease in bone marrow pressures of 70-80%.[13,12,19]

~~Adult models investigating epinephrine's ability to induce return of spontaneous circulation (ROSC) have generated mixed results. Burgert et al. found no significant difference in the rate of ROSC in a traumatic cardiac arrest model between tibial IO, humeral IO, sternal IO and~~

~~peripheral IV infusions of epinephrine[39]. Conversely, a more recent study by Beaumont et al. found the humeral IO infusion of epinephrine in a hypovolemic model was not sufficient to facilitate ROSC. The humeral IO normovolemic and peripheral IV hypovolemic groups demonstrated successful ROSC[40]. Coinciding results were demonstrated by Yauger et. al in a pediatric model. Tibial IO infusions of epinephrine were not found to restore ROSC. This was compared to IV hypovolemic and tibial IO normovolemic groups, both successfully facilitating ROSC.~~

~~Along with these findings was a significantly reduced time to maximal concentration in the tibial IO hypovolemic group compared to the IV hypovolemic and tibial IO normovolemic groups[46]. The receptor density of the bone marrow vasculature dictates the mechanism underpinning the observed results. This mechanism may be very similar to what is observed with peripheral IV infusions of epinephrine. In a hypovolemic shock model even greater decreases in marrow blood flow were demonstrated. Vasopressin, on the other hand, did not demonstrate a significant change in bone marrow blood flow. The increased vascular resistance was about 33 times greater for the epinephrine treated group[13].~~

~~Prior discussion focused on the interaction between medication and marrow vasculature. Focus in this section will shift toward medication interactions with the marrow space itself. One example of a critical condition possibly requiring the use of IO catheterization is septic shock. Understanding the physiological interactions medications have with the bone marrow upon IO injection is critical to care as dose or medication adjustments may be required. The standard of care for sepsis indicates the use of antibiotic therapy within one hour of suspected sepsis for increased survival likelihood[47]. Hemodynamic instability is a common occurrence during septic shock especially in the pediatric population. Consequently, requiring the need for IO catheterization for the administration of antibiotics, fluids, and other medications.~~

Depot Effect

The focus of this section will be on medication interactions with the marrow space. One example of a critical condition that may require the use of IO catheterization is septic shock. Investigations into chloramphenicol and vancomycin administration via the IO and peripheral IV routes demonstrated a significant decrease in the maximal concentration of both antibiotics when delivered through the IO route[48]. Important implications for these findings, particularly vancomycin, are due to the largely indicated use of the antibiotic in situations of community acquired pneumonia, meningitis, skin, and soft tissue infection, and when infection is of unknown origin[49]. The mechanism contributing to the decreased maximal concentration from IO administration is not well understood. Vancomycin's lipid solubility, protein binding and calcium binding properties may play a role in the observed results. The results that were observed for chloramphenicol point toward a possible deposition in the bone marrow, also known as the depot effect. Chloramphenicol is highly lipid soluble rendering it susceptible to its persistence in the bone marrow, especially yellow marrow, and markedly reduced uptake in the sinusoids. Further, a more recent study investigated the plasma concentrations following IO and peripheral IV antibiotic administration in a septic shock model. Findings were non-significant for differences in plasma concentrations of cefotaxime and gentamicin[50]. Both gentamicin and cefotaxime are freely soluble in water indicating decreased deposition in the bone marrow[51,52].

The depot effect is most prominently seen in long bones with a higher yellow marrow percentage than red marrow. After age five it is generally believed that red marrow begins to be replaced with yellow marrow. The difference between the two types of marrow is that yellow marrow contains approximately 95% fat cells and 5% non-fat cells. Whereas red marrow contains about 60% hematopoietic cells and 40% fat cells[53]. At the age of 25 years, it is believed that the adult pattern of marrow distribution is reached with yellow marrow the greatest constituent in the appendicular skeleton except for the proximal humerus and femur metaphysis[54]. Red marrow is much more prominent in the axial skeleton, sternum, ribs, and anterior superior iliac crests. However, red marrow distribution decreases with advancing age in the humerus and femur metaphysis and, albeit with a weaker trend, in the axial skeleton, sternum and ribs[55].

In a study by Loughren et al. peripheral IV and tibial IO infusions of rocuronium, a drug with limited lipid solubility were investigated. Investigators measured the time to complete neuromuscular blockade in swine and found no significant difference in the time between IO and IV routes. Noted in the paper, however, was a significantly longer recovery time for the IO group than the IV group[56]. Atropine, an increasingly lipophilic drug, was the subject of an investigation by Prete et al. The researchers compared maximal concentrations and time to maximal concentration following administration at the tibial IO, peripheral IV and endotracheal routes. The time to maximal plasma concentration was significantly shorter and maximal plasma concentration was significantly greater through the IV route compared to the IO and endotracheal routes. Similarly, to the study by Loughren et al., the atropine concentration remained at a greater concentration in the plasma from 5 minutes to 30 minutes after IO administration[57]. This data is suggestive of a slow release from the bone marrow via the depot effect.

To further emphasize this point, Orlowski et al. investigated the pharmacokinetics of hydrophilic solutions, 50% dextrose in water and calcium chloride. They compared the infusion of these solutions through the distal femoral IO, peripheral IV and central venous routes. There was no significant difference between the three routes regarding blood glucose levels following administration of 0.25 g/kg of 50% dextrose in water. Additionally, no significant difference was noted for a change in ionized calcium concentration over time after administration of calcium chloride between the three groups[58]. Interestingly, when investigating lidocaine hydrochloride, a moderately hydrophilic drug[60], a significantly reduced maximal concentration was observed following distal femoral IO infusion compared to both peripheral IV and central venous infusion. There are multiple reasons as to why these results were observed. As lidocaine is only moderately hydrophilic, a percentage of the drug could have been deposited in the bone marrow. However, nuance to this discussion is important. Lidocaine is a weakly basic molecule with a pKa of 7.7, which means that at physiological pH of 7.4 only about 25% of the lidocaine molecules will be un-ionized[61]. Flat bones demonstrate a pH like blood, but long bones have a lower pH ranging from 6.7-6.9[62]. The lower pH of long bones means that there will be a higher fraction of un-ionized lidocaine. Comparing ionized and un-ionized molecules, typically the unionized forms will demonstrate greater lipid solubility. Implications of these findings generate another important physiological parameter to consider for IO infusion. The pH of the marrow space being utilized and the pKa of the medication, for their impact on solubility.

~~Complications~~

~~Complications of IO infusion such as extravasation, osteomyelitis, cellulitis, and fat emboli have been noted in the literature. However, medications effect directly on the trabecular bone and bone marrow of the IO space is largely an unexplored subject. Sodium bicarbonate is one solution that has been tested for its toxicity to bone and hematopoietic cells. There was no effect on the bone or hematopoietic cells detectable in a swine model[63]. IO infusion has become a standard of care for the pediatric patient population when the peripheral IV route is not accessible. The pediatric population, in general, is still progressing through vertical growth of their long bones. The process of growth in long bones is known as endochondral ossification. This process is highlighted by the replacement of hyaline cartilage, made by chondrocytes, with mature bone. There is a diaphyseal center of ossification and an epiphyseal center of ossification. The process of epiphyseal closure and bone growth were not found to be disrupted by infusions of sodium bicarbonate and epinephrine[64]. Following bone damage, the healing process requires osteoblasts and human mesenchymal stem cells to migrate to the site of injury. At the site, the cells proliferate and differentiate. This process has been noted to be inhibited by certain high dose antibiotics, namely gentamicin, vancomycin, cefazolin, rifampicin, ciprofloxacin and aminoglycosides[65]. Vancomycin and cefazolin have been shown to disrupt osteoblast replication and even cause cell death at concentrations of 10,000 micrograms/mL and 200 micrograms/mL respectively[66]. Tobramycin and ciprofloxacin additionally have been shown to inhibit osteoblast replication significantly at 400 micrograms/mL and 20 micrograms/ml respectively[67, 68]. The previous studies were not utilizing IO infusion rather an osteomyelitis model leading to greatly increased local concentrations of antibiotic in the bone. Extrapolation of this data to an IO infusion model is thus limited and necessitates further investigation into these possible complications of antibiotic infusion.~~

Conclusions

The concepts presented in this chapter offer foundational knowledge underlying a method for obtaining indirect vascular access that is extensively utilized during emergent situations. The bone marrow blood supply is principally driven by nutrient arteries. Drainage from the bone marrow is accomplished by the collecting veins. Infusates gain access to the circulation by uptake into the marrow sinusoids which represent the transition point between the arterial and venous systems. At the sinusoids Starling's equation highlights the factors that control fluid uptake. The vascular supply to bone does not remain static, it can change acutely via neurohormonal control, and through endogenous molecules including, but not limited to, vasopressin, adenosine, bradykinin, and metabolic byproducts. Chronic changes to bone vascular supply are influenced by aging and exercise. An additional factor important for IO infusion is the inherent IOP which must be overcome to allow for forward flow of fluid into the marrow space. Bone marrow composition changes over time from mostly hematopoietic cells, red marrow, to mostly fat cells, yellow marrow. Infusates are thus subject to deposition depending on their lipid solubility profiles. Increasingly lipophilic molecules demonstrate greater deposition and reduced uptake into central circulation. The current understanding of IO physiology is not complete and should be the topic of future research. Considerations toward the interactions of infused medications on the IO vasculature may provide insight into optimal sequences of drug delivery, or additional molecules to add into existing infusion regimens. A seemingly simple infusion

technique upon further magnification, opens itself to the complexities that much of medicine shares.

Key Points

- Neurohormonal regulation of the bone vasculature is accomplished by many mechanisms, including the release of endogenous catecholamines.
- Endogenous molecules such as bradykinin, adenosine and vasopressin have been shown to induce vasodilation.
- Vasopressin can induce both vasoconstriction and vasodilation, depending upon the receptor density.
- Forward flow of fluid into the marrow space is greatest during pressurized infusion under normovolemic conditions.
- It remains unclear whether there is a significant difference in flow rate between the humeral and tibial IO sites. Precise calculations of cross-sectional area and volume of medullary cavity may generate greater insights.
- The bioavailability of infused medications is influenced by the site of infusion, with factors including distance to central circulation, extent of deposition in the marrow, and marrow pH.
- Hemorrhagic shock and other hypovolemic states can decrease blood flow to and from the intraosseous space, which may reduce the availability of IO-infused medications and fluids.
- ~~Healing of damaged bone has been shown to be inhibited by certain medications (e.g., high-dose antibiotics), but further study is needed to apply this to an intraosseous infusion model.~~

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