REVIEW

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Intraosseous circulation from physiology to disease

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Summary – Blood flow within bones is unique in two ways: (1) the blood circulates within a closed cavity in which pressure must remain constant, a feat achieved in part thanks to the considerable distensibility of the intraosseous vessels and, above all, veins; (2) the intraosseous circulation allows traffic of minerals between the blood and bone tissue and sends the blood cells produced within the bone marrow into the systemic circulation. In contrast, the arterioles and capillaries within bones have the same anatomic structure as those located elsewhere in the body and are susceptible to arteriosclerosis, arteritis, or thrombosis. The mechanisms that regulate blood flow within bone are incompletely understood, probably because they are difficult to study in vivo. The cytokines and growth factors that regulate intraosseous angiogenesis also regulate bone remodeling, and close links exist between the blood supply to bone and bone formation and resorption: most diseases characterized by increased bone resorption are associated with increased bone vascularization. The vascular bud located at the center of bone multicellular units (BMUs) may determine the timing of bone resorption and bone formation. Avascular bone necrosis and bone infarction may result from acute blood vessel occlusion (thrombosis, lipid emboli, fat cell hypertrophy with compression of intraosseous capillaries), whereas arteriosclerosis may contribute to the development of osteoporosis. Joint Bone Spine 2002 ; 69 : 262-9. © 2002 Éditions scientifiques et médicales Elsevier SAS

anatomy / intraosseous blood flow / osteonecrosis / osteoporosis / physiology

In the 1970s, Professor Jacques Arlet taught that "intraosseous blood flow gives life to bone, just as intracerebral bone flow gives life to the brain and coronary blood flow life to the heart". In an anatomy textbook published in 1965, Burkhardt described the intraosseous blood vessels in admirable detail and underlined their importance under normal conditions and in bone and blood diseases [1]. The hematopoietic bone marrow is so intimately intermingled with the bone trabeculae that one cannot be studied without the other: thus, specimens described by some authors as bone biospies are in fact bone and marrow biopsies. A simple glance at a bone and marrow biopsy specimen under the microscope suggests a major role for intraosseous blood flow in the physiology of hematopoiesis and bone remodeling: the vessels run along the bone trabeculae that are undergoing remodeling, mark the center of each resorption bay *(figure 1)*, come in contact with lymphoplasmacytic nodules, and proliferate in patients with hyperparathyroidism or regenerative anemia. Very recently, Parffit, whose studies and reviews on bone remodeling are recognized throughout

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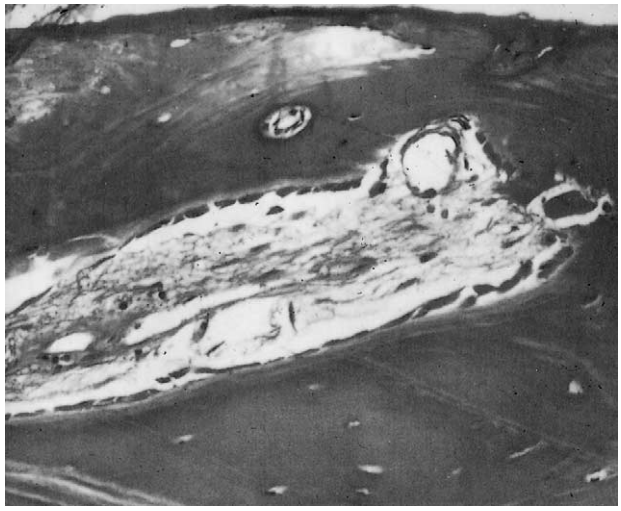

Figure 1. resorption bay (x40) with large osteoclasts and numerous osteoblasts in the midst of which capillary structures are undergoing individualization.

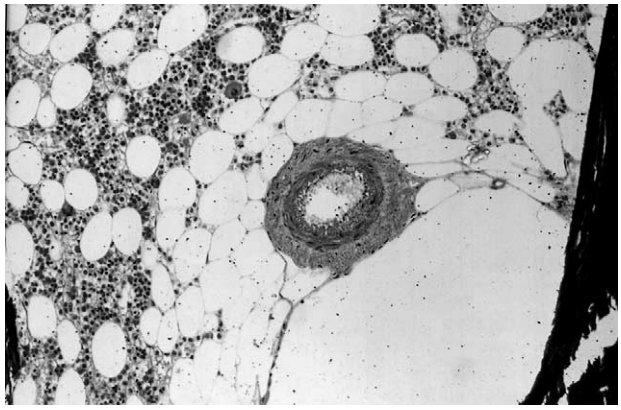

Figure 2. Intraosseous arteriole (x25), Goldner monochrome: the various layers of the vessel wall are visible, with a scalloped intima, a media composed of three to four layers of muscle cells, and an adventitia heterogeneously stained in green (suggesting possible calcification of this layer).

the world, posited that the vascular bud may be involved in regulating the BMU by determining the order in which cellular events occur, namely, osteoclastic resorption, osteoblastic formation and, finally, quiescence [2]. His excellent article prompted us to write this review.

ANATOMY OF THE INTRAOSSEOUS BLOOD VESSELS [3]

Blood vessels within long bones

Middle-sized arteries penetrate the bone cortices then branch into arterioles and, finally, capillaries. The walls of intraosseous arterioles are similar to those of arterioles located elsewhere in the body: they comprise an intima, a muscle layer composed of pericytes, and an adventitia composed of fairly loose connective tissue *(figure 2)*. The adventitia is often colored green by Goldner's monochrome, which probably reflects some degree of calcification, a specific feature of intraosseous arterioles. In the arterial capillaries, an intima and a muscular layer composed of one or two pericytes delineate the lumen.

Oxygen-rich blood enters the long bone through six groups of arteries that are interconnected by a rich network of anastomoses named according to their location, as follows *(figure 3)* [4-6]: one or two diaphyseal or feeding arteries, superior and inferior metaphyseal arteries, superior and inferior epiphyseal arteries, and periosteal vessels forming a network of rings circling the diaphysis and metaphysis and connected by longitudinal anastomoses. The lateral aspect of this network is in continuity with the arteries supplying the neighboring

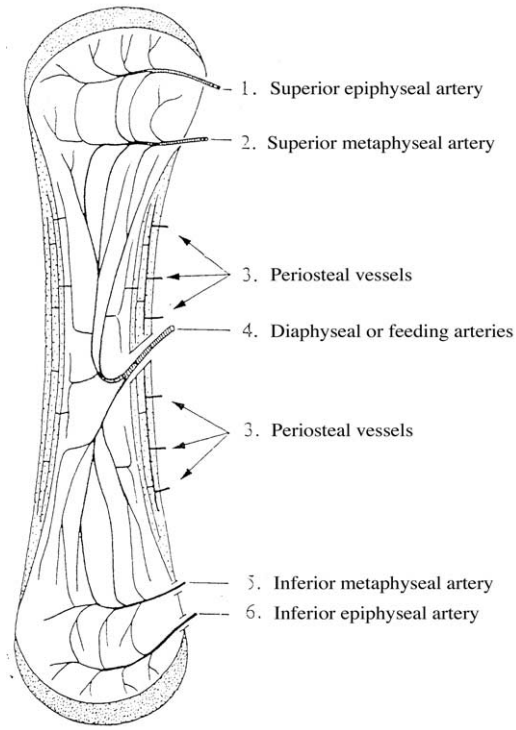

Figure 3. Diagram of the arterial vascularization of a long bone.

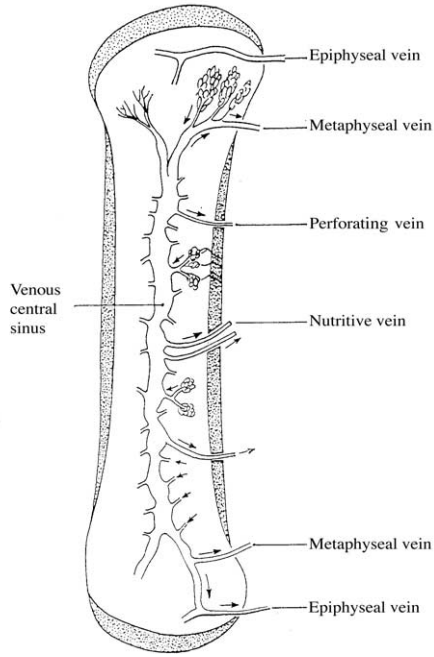

Figure 4. Diagram of the venous vascularization of a long bone.

muscles. A vast central sinus *(figure 4)* runs along the middle of the diaphysis [7]. The sinus wall is composed of a single layer of extremely distensible endothelium. Thus, the sinus can show up to fivefold changes in volume in response to normal or abnormal conditions. The sinus drains into veins that run parallel to the arteries: metaphyseal veins, epiphyseal veins, and centromedullary veins [8]. The emissary veins run with the arteries, often two to an artery. The venous blood can also drain into perforating veins that rapidly exit the bone through the cortex and empty into the large venous trunks of the limb.

Intracortical vascularization

The intracortical vessels travel in canals located within the cortex, mainly Havers's canals and secondarily Volkmann's canals. Although the widest canals contain both an artery and a vein, most canals contain a single vessel of capillary structure. This network undergoes continuous remodeling, as does the surrounding cortical bone [3].

Vascularization of flat bones

The arterial network is similar to that in long bones. However, there are multiple, ramified, interconnected

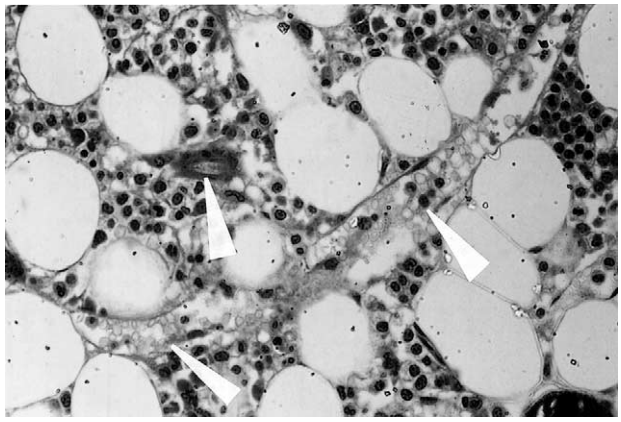

Figure 5. Venous sinus and arterial capillary (X 40) within the hematopoietic marrow.

venous sinusoids whose wall is a simple endothelial layer *(figure 5)*. The surface area occupied by these sinusoids varies widely. The sinusoids empty directly into the cortical veins.

Normal intraosseous circulation [9]

The physiology of the intraosseous circulation has received far less attention than blood flow in other organs such as the kidney, heart, and brain, where the regulatory mechanisms have been fully elucidated. Intraosseous blood flow can adjust either through changes in the intraosseous blood flow rate (IOBFR) or through stimulation or inhibition of intraosseous angiogenesis, which is growth of new capillaries from preexisting capillaries.

The intraosseous circulation operates under two unique constraints. One is that the bone is a closed cavity within which pressure must remain constant. Variations in intraosseous pressure (IOP) can cause pain. For instance, the pain related to avascular necrosis of the femoral head is related in part to increased pressure within the bone. When pressure is measured via the trochanteric route, the slightest movement of the guide within the trocant or injection of saline replicates the patient's pain, whereas vasodilators and core biopsy provide rapid pain relief [9]. Whether the increase in IOP is a cause or a consequence of the necrosis remains unclear. The considerable distensibility of the intraosseous veins helps to maintain the IOP constant. IOP often changes in the same direction as the IOBFR, and most disease processes that increase IOBFR also increase IOP. The second constraint is that the intraosseous circulation must allow trafficking of

calcium, phosphate and other minerals between the bone tissue and the serum and must carry newly formed blood cells from the marrow to the peripheral blood: these two functions are apparently very different, since one supplies nutrients to a tissue that supports and protects the body, whereas the other contributes to effective production of hematopoietic cells.

Techniques for investigating intraosseous blood flow rate [10-13]

Experimental techniques for measuring IOBFR were developed mainly in animals and are not readily applicable to routine practice. They use a variety of means including thermocouples; labeled microbeads (with dissection of the bone); hydrogen or Freon washout; and radioactive substances such as erythrocytes labeled with chrome-31, phosphate-32, calcium-45 or, above all, strontium-85. Labeled erythrocytes have been used in vivo in humans. The dilution, clearance from blood, or uptake of the radioactive marker is measured. In clinical practice, angioscintigraphy with measurement of the emission of 99m-technetium pyrophosphate within the first few seconds after the injection, i.e., at the vascular phase before the marker binds to bone, provides a rough idea of IOBFR [14]. Laser Doppler probes cannot be used because they would have to be inserted inside the bone, which would modify the IOBFR. Positron emission tomography holds considerable promise and has been used to show an increase in IOBFR in some forms of blood disease.

Intraosseous blood flow rate: normal values

With all available methods, in all bones studied to date, IOBFR values have ranged from 5 to 20 ml/min/100 g of bone, in humans and animals.

Regulation of intraosseous blood flow rate

IOBFR is regulated by vasodilation and vasoconstriction of arterioles and capillaries and by closure or opening of the precapillary sphincters. Sympathetic and parasympathetic nerve fibers travel in the hematopoietic marrow and bone, running parallel to the blood vessels: stimulation of sympathetic efferent fibers causes vasoconstriction. Numerous substances act on the vessel wall, although their exact role under normal conditions remains unclear. Parathyroid hormone (PTH) and PTH-related peptide cause vasodilation. Other vasodilators include nitrous oxide (NO), some prostacyclins (PGI 2), and IGF1. Conversely, endothelin, vasopressin, and catecholamines cause vasoconstriction and reduce the IOBFR [15-18].

Regulation of angiogenesis

Angiogenesis is growth of new capillaries from preexisting capillaries or from postcapillary venules. The endothelial cells detach and migrate through the basement membrane, break down the extracellular matrix, proliferate, and arrange themselves in a line to form a new blood vessel. The many factors that regulate this process include VEGF, PDGF, FGF, TGF, and angioproteins [15]. VEGF or vascular endothelial growth factor is a 45 kD-glycoprotein. Chronological and spatial correlations have been found between VEGF RNA expression and new vessel growth. VEGF targets only endothelial cells, stimulating their growth and regulating capillary permeability. Hypoxia induces expression of the VEGF gene. PDGF or platelet-derived growth factor is a polypeptide found in granules in platelets and macrophages. PDGF may ensure organization of endothelial cells into tubes. Furthermore, PDGF induces VEGF expression. FGFs (fibroblast growth factors) may be released in response to heat shock, cell death, and shear forces. FGFs are needed to digest basement membranes, an indispensable prerequisite to endothelial cell migration and proliferation.

The data above reflect both the complexity and the complementariness of these systems. They also suggest links among mechanical stresses (stimulation of FGF release by shear forces), hypoxia (which induces VEGF expression), and intraosseous angiogenesis in some normal situations and disease processes.

Relations linking intraosseous circulation, bone remodeling, and hematopoiesis

Several observations from anatomy, physiology, and disease illustrate the functional relationships linking intraosseous circulation, bone remodeling, and hematopoiesis. Thirty years ago, Burkhardt reported fatty involution of the hematopoietic marrow and loss of arterial capillaries in osteoporotic bone. Primary hyperparathyroidism, in contrast, was associated with increased vascularization accompanied with increased bone resorption and excessive marrow cellularity [19, 20]. Reeve et al. found positive correlations between bone apposition and IOBFR as measured by the strontium clearance method [21]. We have shown that oophorectomy in rats was followed not only by increased osteo-

clastic resorption but also by increased intraosseous vascularization. The bisphosphonate tiludronate inhibited excessive resorption but had no effect on the increase in vascularization [22]. Hypervascularization is also seen in regenerative anemia and in the bone marrow response to inflammation [20]. The cytokines and growth factors that regulate angiogenesis or vasomotility (IGF, PTH or PTHrp, NO, VEGF, and others) are also involved in bone remodeling.

Regulation of bone remodeling by the vascular bud: Parffit's hypothesis applied to Frost's theory [2]

Cortical and cancellous bone undergo ceaseless remodeling that involves a fixed and cyclic sequence of events: osteoclastic resorption, bone formation to fill the resorption bay, and finally a phase of quiescence. The mechanisms that regulate these events and ensure their orderly unfolding in time and space have generated considerable interest. One of the earliest hypotheses was that osteoblasts and osteoclasts originated from the same stem cell and were capable of subsequent dedifferentiation with transformation of osteoclasts into osteoblasts. This hypothesis has been refuted. The possibility that osteoblasts may be subjected to biomechanical attraction by bone trabeculae previously fragilized by bone resorption cannot apply to the cortical bone. Substances released into the bone matrix by osteoclasts and capable of attracting osteoblasts have not been found despite 15 years of research.

The vascular bud *(figure 1)* present at the center of every BMU is ideally located for coordinating the coupling of formation and resorption. The endothelial cells that delineate the end of this capillary may undergo rapid sequential genome modifications, which may induce signals that allow osteoclast precursors, then pericytes and/or osteoblast precursors, to exit the capillary through its wall. Endothelial cells may respond to a number of stimuli including tensile forces and growth factors. This possibility does not necessarily come into conflict with the recent discovery of the RANK-RANK ligand osteoprotegerin system, which explains in part the recruitment of osteoclasts by stimulated osteoblasts [23].

Adverse consequences of alterations in intraosseous bone circulation

As illustrated clearly by Burkhardt [1], the intraosseous arterioles share with arterioles in the brain or muscles a susceptibility to arteriosclerosis, thrombosis, or vasculitis. In any organ, alterations in circulation, blood vessel occlusion, or flow reduction lead to severe abnormalities. For instance, sudden occlusion of a coronary artery causes a myocardial infarction. Similarly, multiple arteriosclerotic lesions of the coronary arteries set the scene for ischemic cardiomyopathy, and lesions of the cerebral vessels can result in age-related dementia.

Aseptic osteonecrosis, bone infarction, and osteoporosis: are these vascular diseases?

Avascular osteonecrosis is common at the hip. The word 'necrosis' strongly suggests a vascular process. In the 1960s, Arlet and Ficat found convincing evidence that intraosseous circulation was abnormal in hip osteonecrosis [24]: IOP was increased throughout the proximal femur in the overwhelming majority of cases, and phlebographies showed major changes with marked stasis of venous blood. In normal individuals, an iodinated contrast agent injected through the trochanter took only a few minutes to drain into the return venous circulation, whereas in patients with osteonecrosis it remained for several hours in the trochanteric mass and abnormal femoral head. Histopathological studies have confirmed these findings: bone marrow ischemia precedes necrosis of the bone. A reasonable hypothesis is that this ischemia sequentially affecting the bone marrow and bone results from arterial occlusions *(figure 6)*, although these is no compelling evidence from experimental studies or clinicopathologic studies to substantiate this. Ligation in animals or traumatic rupture in humans of the artery supplying the ligamentum teres induce osteonecrosis. Vascular thromboses have been found in some, but not all, patients with osteonecrosis and lupus or antiphospholipid syndrome [25]. Smoking, hypercholesterolemia, and diabetes mellitus, which are major risk factors for vascular disease, are not associated with osteonecrosis of the hip. Peripheral arterial occlusive disease of the lower limbs rarely causes osteonecrosis. Conversely, taken together, alcohol abuse and short-term but very high dose glucocorticoid therapy account for 70 to 90% of all cases of hip osteonecrosis but do not cause vascular disease at other sites. The explanation for this apparent contradiction probably lies in the fact that intraosseous vessels are located in a closed cavity and that, consequently, intraosseous blood flow remains normal only if IOP is constant. It has been shown that fat emboli or sudden fat cell swelling related to the ingestion of alcohol or

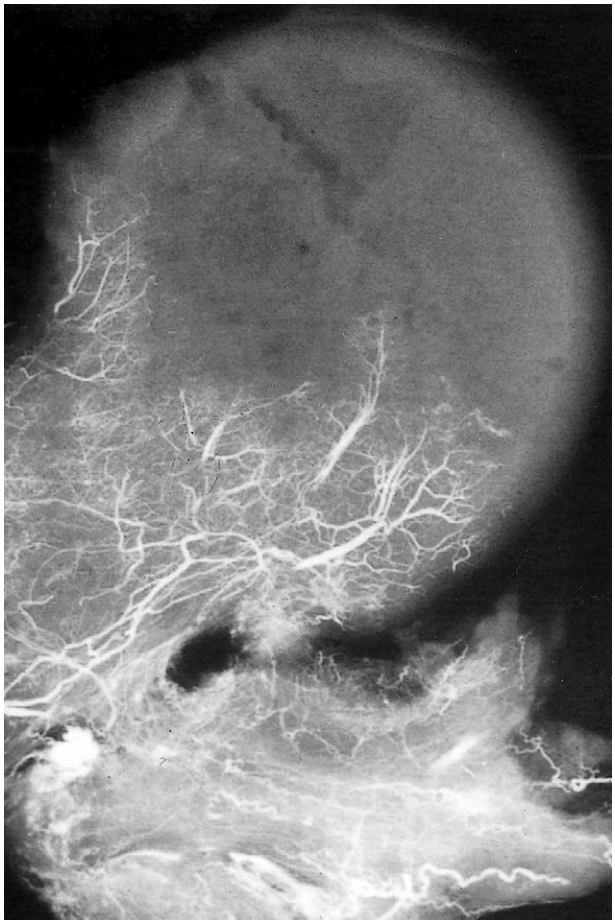

Figure 6. Arteriography of the proximal femur in a patient with stage III osteonecrosis: arrest in arterial blood flow extending beyond the sequestrum.

glucocorticoids can impair the arterial blood supply [24, 26]. At the hip, the osteonecrosis becomes symptomatic because of changes induced by the unique mechanical constraints placed on this joint, with individualization and finally rupture of a sequestrum. Nonvascular mechanisms may cause some cases of osteonecrosis but will not be discussed here.

Intraosseous infarctions

Intraosseous infarctions are asymptomatic lesions found fortuitously when a radiograph is taken. However, pain can occur at the acute phase. The few available histological studies showed bone sclerosis in response to necrosis.

Osteoporosis and vascular disease

Whether chronic changes in intraosseous vascularization secondary to arteriosclerosis can induce bone remodeling abnormalities and demineralization deserves discussion. Epidemiological studies have found a link between osteoporosis and arteriosclerosis. For instance, men with peripheral occlusive arterial disease had lower bone mineral density values and more fractures than matched controls [27]; lower limb occlusive arterial disease was more common in women admitted for nontrauma-related fractures of the femoral neck than in women without such fractures [28]; femoral head arterioles collected after total hip arthroplasty were more likely to show arteriosclerosis when the reason for surgery was femoral neck fracture than when it was osteoarthritis [29], bone mineral density was a better predictor for death by stroke or myocardial infarction than was blood pressure measurement [30, 31]; and associations have been found between bone mineral density and vascular calcifications [32-34].

These associations may stem from shared risk factors, such as the menopause, an inactive lifestyle, and smoking. However, in a study of patients with unilateral occlusive arterial disease of a lower limb, we found demineralization in the affected limb as compared to the healthy limb [35]. This confirmed older autopsy studies that showed demineralization in patients with peripheral occlusive arterial disease [36]. More recently, Naito et al. [37] reported that stroke-prone spontaneously hypertensive rats showed not only epiphyseal necrosis but also decreased femoral strength and bone mineral density.

Other possible effects of abnormalities in intraosseous circulation

We elected to focus this review on osteonecrosis and osteoporosis. However, other bone diseases are clearly related to changes in intraosseous circulation. Reflex sympathetic dystrophy syndrome is associated with major vascular changes detectable by histology or angioscintigraphy. Vascularization is increased in pagetic bone; a murmur is sometimes heard over the pagetic focus, and high output heart failure develops in some patients. Bone angiogenesis is indispensable to growth and to fracture repair. It also plays a key role in the development of bone metastases. The bone lesions seen in blood diseases such as sickle cell anemia are caused by blood vessel occlusion. Antibiotics are effec-

tive in osteomyelitis only because blood vessels are present in the infected foci.

CONCLUSION

The profusion of studies on bone cells, cytokines, and bone remodeling contrasts with the paucity of investigations into intraosseous circulation. The close anatomic and physiological ties between intraosseous circulation and bone remodeling [38, 39] suggest that alterations in intraosseous vascularization may have adverse effects on bone trophicity. Better knowledge of the regulation of angiogenesis and intraosseous blood flow rate may provide insight into the mechanisms underlying avascular osteonecrosis and perhaps osteoporosis In avascular osteonecrosis, a potentially promising treatment may be local administration of angiogenic factors, particularly after core biopsy.

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