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Pharmacological Regulation of the Circulation of Bone*†

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ABSTRACT: **A study was undertaken to investigate the reactivity of the circulation of bone and to pharmacologically characterize the receptor populations that may be present in this poorly described vascular bed. The nutrient artery of the tibia in skeletally mature mongrel dogs was cannulated, under direct vision, through a posterolateral operative approach. An extracorporeal circuit was established so that the nutrient artery of the tibia could be perfused *in vivo* under conditions of constant blood flow. Diverse vasoactive substances were injected into the perfusion circuit in small volumes as a bolus close to the nutrient artery of the tibia. A range of doses of nitroglycerin, acetylcholine, isoproterenol, methoxamine, U46619 (a thromboxane A_2 mimic), dibutyryl cyclic AMP, 8-bromo-cyclic GMP, and endothelin-1 were injected in a randomized sequence for each experiment. The antagonists that were used were atropine (a non-selective muscarinic receptor antagonist), ICI 118551 (a selective beta$_2$-adrenoceptor antagonist), ONO 3708 (a prostaglandin H_2/thromboxane A_2 receptor antagonist), and prazosin (an alpha$_1$-adrenoceptor antagonist).**

The results of changes in bone-perfusion pressure under conditions of constant blood flow indicated that the vascular bed of bone actively responds to various vasoconstrictor mechanisms, whereas vasodilator mechanisms appear to be considerably less active. Intra-arterial injections of nitroglycerin, acetylcholine, and 8-bromo-cyclic GMP resulted in dose-related decreases in bone-perfusion pressure that were weak relative to concomitant changes in systemic arterial pressure. Intra-arterial administration of methoxamine, U46619, and endothelin-1 resulted in a potent dose-related increase in bone-perfusion pressure. The results of intra-arterial injections of isoproterenol and dibutyryl cyclic AMP were surprising; both substances caused a substantial rise in bone-perfusion pressure. The responses to acetylcholine, methoxamine, and U46619 were blocked in a competitive manner after administration of atropine, prazosin, and ONO 3708, respectively.

CLINICAL RELEVANCE: The results provide the first reported evidence, to our knowledge, that suggests the presence of alpha$_1$-adrenoceptors, muscarinic receptors, and prostaglandin H_2/thromboxane A_2 receptors within the vascular bed of bone. The ability to make predictable alterations in the tone of the medullary arteries and arterioles offers the potential for regulating blood flow to bone and may ultimately lead to major advances in the treatment of fractures, non-unions, osteomyelitis, aseptic necrosis, and bone tumors and to enhancement of the growth of bone into porous-coated implants.

Blood flow to an organ system is regulated by the degree of vasomotor tone of small arteries and arterioles[18]. Vascular constriction and dilation is under sympathetic, autonomic, and humoral control, which allows each organ to have its own unique physiological characteristics. For example, vigorous exercise causes sympathetic discharge, which results in dilation of the vessels that supply contracting muscle and in constriction of virtually all other vessels of the peripheral circulation[18].

Circulation through the vascular bed of bone is essential for maintenance of osseous homeostasis. Normal growth, remodeling, and repair of bone require delivery of nutrients and oxygen through blood flow to bone. Under normal physiological conditions, bone receives 5 to 10 per cent of the cardiac output[12,17,35,36]. The gross and microscopic anatomy of the vascular bed of bone has been studied extensively[2,3,5,6,10,25,46-49]. The long bones receive their blood supply from nutrient, periosteal, epiphyseal, and metaphyseal vessels. The normal mature diaphyseal cortex and medullary canal are supplied primarily by the nutrient artery system[14,44,47]. The nutrient artery enters bone through the nutrient foramen and divides into end-arterioles, which ascend and descend in the medullary canal[5,8,30,32]. Arterial blood flow is centrifugal; blood is delivered to cortical bone through anastomosing medullary arteries, which arise as branches of the nutrient end-arterioles[8]. Blood from the medullary artery system flows into cortical capillaries that traverse the haversian system. Cortical capillaries communicate with both periosteal capillaries and medullary sinusoids, which drain centripetally into the central venous sinus to the emissary veins[6,8].

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