Bone 52 (2013) 604–610

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Bone hemodynamic responses to changes in external pressure

Jaime Mateus [a,*], Alan R. Hargens [b]

[a] Massachusetts Institute of Technology, Man-Vehicle Laboratory, Department of Aeronautics and Astronautics, 77 Massachusetts Avenue, Room 37-219, Cambridge, MA 02139, USA
[b] University of California, San Diego, Department of Orthopaedic Surgery, UCSD Medical Center, 350 Dickinson Street #121, MC 8894, San Diego, CA 92103, USA

ARTICLE INFO

Article history:
Received 14 April 2012
Revised 15 October 2012
Accepted 13 November 2012
Available online 17 November 2012

Edited by: R. Baron

Keywords:
Perfusion
Hemodynamics
Myogenic
Bone
Photoplethysmography
PPG

ABSTRACT

Adequate blood supply and circulation to the bones is required to maintain a healthy skeleton. Inadequate blood perfusion is associated with numerous bone pathologies and a decrease in bone mineral density, yet bone hemodynamics remains poorly understood. This study aims to 1) quantify bone hemodynamic responses to changes in external pressure, and 2) identify the predominant mechanisms regulating bone hemodynamic responses to pressure changes. Photoplethysmography was used to measure bone and skin perfusion in response to changes in external pressure. Single-limb pressure chamber experiments were performed over a pressure range of −50 to +50 mm Hg. Bone perfusion is decreased at all negative pressures, and larger decrements in perfusion are observed at the more extreme pressure differences. At positive pressures we observed an initial increase in perfusion followed by activation of intramuscular pressure receptors at +30 mm Hg, which overrides the initial response and results in decreased perfusion at the highest positive pressure levels. The myogenic effect is observed and is shown to be the predominant control mechanism in bone over a wide range of pressure exposures. Greater understanding of these hemodynamic mechanisms may be important in developing new drugs and therapies to treat various bone disorders.

Introduction

Much progress has been made in understanding the anatomy, function, and mechanisms regulating the circulatory physiology of the cardiovascular system as well as the microcirculation of skin, muscle and many other organs [1]. In contrast, however, much less progress has been made in understanding the physiology of bone blood flow [2,3]. There is still some debate on the anatomical structure and function of the blood vessels in bones, and there is even more uncertainty about the mechanisms that regulate bone blood flow [4,5]. While we traditionally think of the circulatory system as being independent from the skeletal system, the two are intricately connected and a full understanding of one system cannot be had without consideration for the other.

Bone blood and interstitial fluid flow play a crucial role in fracture repair, bone remodeling, and bone pathology [3,6,7]. For instance, chronic insufficient blood supply to the bone is a known precursor to osteoporosis, and an increase in bone blood flow is observed during fracture repair [4,7,8]. Reduced blood flow due to peripheral arterial disease is also associated with an increased fracture risk due to lower bone mineral density (BMD) [9,10]. Several studies have found a strong association between atherosclerosis and other cardiovascular diseases with osteoporosis [11], including several studies on postmenopausal women [10,12,13].

One of the main limiting factors of long duration human spaceflight is the large BMD loss that is accrued by astronauts. Despite the rigorous exercise countermeasures designed to mitigate bone loss, crewmembers still experience between 0.5% to 2.0% BMD loss per month in the weight bearing parts of the skeleton such as the lumbar spine, the hip and the lower extremities [14,15]. This rate of BMD loss is about an order of magnitude larger than what is observed in postmenopausal women [16]. Interestingly, small increases in BMD have been noted in other parts of the skeleton such as the skull and upper arms [14,17,18]. One hypothesis postulates that the cephalad fluid shift that occurs in weightlessness is, at least in part, responsible for the observed association between BMD loss and the weight-bearing parts of the skeleton [19–22]. However, the exact mechanism of how the fluid shift affects bone health is not clear. At least a couple of studies have provided additional data supporting the idea that bone circulation and BMD are tightly interconnected [9,23].

Photoplethysmography is a non-invasive method of evaluating tissue perfusion [24]. While it has traditionally been used for assessing skin microcirculation, recent developments have enabled the use of PPG for measurement of hemodynamic responses in deeper muscle tissues as well as bone [25,26]. We recently reported a detailed validation effort on the use of PPG for measurement of bone hemodynamics [27]. Building upon this technique, this paper aims to better understand the relative importance of different mechanisms in regulating bone circulation by

* Corresponding author. Fax: +1 617 258 8111.
E-mail addresses: jmateus@alum.mit.edu (J. Mateus), ahargens@ucsd.edu (A.R. Hargens).

8756-3282/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bone.2012.11.010

measuring the bone hemodynamic responses in a limb in response to changes in external pressure.

The specific aims of this study are to 1) characterize bone hemodynamic responses to single-limb exposure to hypobaric (negative) and hyperbaric (positive) external pressures and 2) investigate the relative contribution of systemic sympathetic and local myogenic mechanisms in the regulation of bone circulation. A better understanding of the relationship between bone circulation and bone health is an important step in our understanding of integrated human physiology.

Mechanisms regulating bone blood flow

Moving from lying supine to standing results in a gravitationally induced orthostatic stress, yet we are capable of maintaining normal blood pressure (BP). Activation of sympathetic reflexes and the myogenic responses are two important mechanisms that contribute to orthostatic tolerance by increasing peripheral resistance. Bone is highly innervated with sympathetic fibers and several studies have examined effects of sympathetic activity on bone blood flow [4,28–32]. While the sympathetic reflexes have been extensively documented, the myogenic effect has received less attention and only recently have researchers begun to quantify the relative contribution of each mechanism to vasomotor responses [33–35].

The myogenic response is an important mechanism regulating blood flow in skin, muscle and many other organs [35–37]. However, the exact mechanism is not yet fully understood [38–40], and to date the myogenic effect has not been documented in bone. The myogenic effect was first reported by Bayliss in 1902, where he described the natural tendency of blood vessels to vasodilate in response to a decrease in transmural pressure, and to vasoconstrict in response to an increase in transmural pressure [41]. While the myogenic effect may be enhanced during sympathetic stimulation, it is a separate mechanism that can be seen even when all innervation has been cut [39,42–44]. Changing the external pressure through either lower-body negative pressure (LBNP) or lower-body positive pressure (LBPP) are two ways to alter the transmural pressure and hence elicit the myogenic effect [33,45,46].

Physiological responses to negative (hypobaric) pressure exposure

In 1834 Junod performed the first studies of the application of reduced pressure to parts of the human body [47–49]. The general response is characterized by vasoconstriction at low to moderate pressures, followed by vasodilation at large pressure differences of −130 mm Hg or greater. At high enough pressure differences the smooth muscle along the vessel walls is no longer able to compensate the large increase in transmural pressure and eventually gives way, resulting in vasodilation. LBNP results in fluid shift from the upper to the lower body, first to the venous system and over a longer time (if the pressure is sustained) to the extravascular fluid space [34,50–52].

LBNP results in a drop in central venous pressure (CVP) and is accompanied by a reduction in stroke volume and cardiac output (CO) of 50% and 30%, respectively, at −50 mm Hg. Systolic BP consistently drops but no consistent trends are seen in diastolic BP [51]. The drop in BP is compensated by a marked increase in HR of about 20% at −40 mm Hg [53], and increase in total peripheral vascular resistance [54,55]. The loss of systolic BP sensed by the high-pressure arterial baroreceptors [56] triggers an increase in sympathetic nervous system (SNS) tone, which results in an increase in HR and a large increase in peripheral vascular resistance. Pressure differences as low as −5 mm Hg have been shown to activate the cardiopulmonary low-pressure baroreceptors and increase forearm vascular resistance [57].

The myogenic effect also contributes to the vasoconstrictive response at all levels of LBNP, and one study has quantified the relative contributions of the myogenic and SNS reflex mechanisms, noting that the myogenic effect is dominant at pressure levels up to −75 mm Hg and SNS reflexes dominate at higher pressure differences of −100 mm Hg [33]. All of these pressure exposure experiments have assumed that the pressure applied to the surface of the skin is equally transmitted to all parts of the underlying soft tissues, an assumption that Lundvall et al. have studied and validated [45,58]. Although many aspects of LBNP have been examined, no study has looked at the effect of negative pressure on bone hemodynamics.

Physiological responses to positive (hyperbaric) pressure exposure

Although many cardiovascular and hemodynamic effects of lower-body positive pressure (LBPP) have also been studied [59–67], little is known about its effect on bone circulation [23]. In one of the first LBPP studies, exposure to +40 mm Hg of LBPP resulted in significant increases to mean arterial pressure and CVP, but no changes were noted in HR or peripheral vascular resistance, although forearm vascular resistance was decreased [68]. Many researchers have expanded this work and shown similar general trends in their results [65,66,69,70].

In another LBPP experiment Shi et al. increased the pressure gradually from 0 to +40 mm Hg in order to observe the baroreceptor activation thresholds, and concluded that the intramuscular pressure receptors (located in the skeletal muscle) are activated at pressures between +20 and +40 mm Hg [66,69,71]. Interactions between the SNS and the intramuscular pressure receptors have been further studied and it has been suggested that the decrease in SNS tone observed at low LBPP pressures is countered at higher pressures due, at least in part, to the activation of the intramuscular pressure receptors [59]. No study has yet looked at the effect of LBPP on bone circulation, or at the relative contribution of the SNS and myogenic effects in bone vasomotor responses to LBPP.

Hypotheses

Based on the existing literature and considering only pressure exposures within the range of −50 to +50 mm Hg, we hypothesize that bone hemodynamic responses to altered external pressure will be characterized by: 1) reduced perfusion at negative pressures due to a myogenic response, with even greater reductions in perfusion at the higher pressure differences as the low and high pressure baroreceptors are activated; and 2) increased perfusion due to the myogenic effect at mild positive pressures followed by activation of the intramuscular pressure receptors at around +20 to +40 mm Hg, leading to a reversal in the response and to decreased perfusion as the pressure difference increases.

Materials and methods

Subjects

Based on a power analysis from preliminary data, we recruited 12 subjects, 6 male and 6 female, to participate in the experiment. For each gender, the left leg was placed inside the chamber for 3 subjects, and the right leg was used for the other 3 subjects. Subjects were randomly selected for the left/right limb groups. Healthy male and female subjects were recruited for all experiments. The institutional review boards at MIT and University of California — San Diego approved this study, and all subjects gave informed written consent prior to participating. Subjects had an average (±standard deviation) age of 24 ± 5 years, weight of 71 ± 15 kg, height of 1.73 ± 0.08 m, and tibial skin thickness of 4.0 ± 1.9 mm.

PPG measurement of bone hemodynamic responses

Hemodynamic responses in the skin and bone tissue were measured using photoplethysmography (PPG). In previous work we described in detail the design of our PPG system, and provided data validating the use of PPG as a tool to measure hemodynamic responses in both