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Bone hemodynamic responses to changes in external pressure

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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

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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

superficial skin and underlying deeper bone tissues [27]. An overview of this measurement technique is presented here.

The PPG system consists of two main components: a light emitting diode (LED) light source, and a photodetector. Our PPG system has two LED light sources, a green light with a wavelength of 526 nm that is located 3 mm away from the photodetector and a near infra-red (IR) light at 805 nm wavelength located 20 mm away from the photodetector, as shown in Fig. 1. Light from a PPG system with this configuration has been shown to have a penetration depth of about 2 mm for the green light and about 13 mm for the near-IR LED, which effectively allows us to probe two different tissue depths [26].

Both of these LEDs operate within the "biological window" of 800 to 1100 nm where skin and bone tissue are transparent to light within this range [72]. However, light at these wavelengths is readily absorbed by blood. Some of the light from the LED will eventually get reflected (after being scattered in the tissue and partially absorbed by blood) and reach the photodetector. Changes in the PPG signal are therefore directly related to the amount of blood in the tissue being probed. Changes to the average peak-to-peak amplitude of the pulsatile (commonly referred to as "AC") component of the PPG signal are representative of changes in the local tissue perfusion, with an increase in the average amplitude corresponding to an increase in perfusion either through increased blood flow, local vasodilation or both. Conversely, a decrease in the peak-to-peak amplitude corresponds to a decrease in the local tissue perfusion [27].

Our PPG probe was placed on the skin on the medial surface of the tibia at a distance (measured from the proximal end of the PPG probe) of about 4–9 cm distal to the tibial tuberosity on each limb. There is only a thin layer of skin at this location, and no muscle tissue in between the tibia and the skin. In previous work we have shown that in this set-up the green and near-IR channels respond selectively and independently to the skin and bone signals, respectively [27].

Equipment set-up

A single-limb pressure chamber was used to expose the lower limb to changes in external pressure. While only one limb was exposed to the pressure difference, PPG probes were placed on both limbs. This allowed for the distinction between myogenic effects and sympathetic reflexes, since a myogenic response should only be present in the limb that is exposed to the pressure difference whereas any large sympathetic reflex, if evoked, should be present in both limbs [33]. A picture of the pressure chamber set-up together with the pressure seal and the sealing ring that attaches the pressure seal to the chamber is shown in Fig. 2. The lower limb starting from the top of the knee is exposed to the pressure difference, while the neoprene pressure seal covers the lower half of the thigh above the knee.

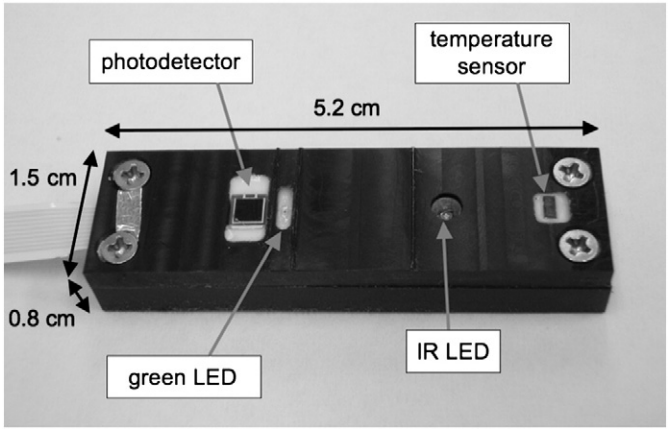

Fig. 1. Head stage of the PPG system showing the green and infrared (IR) LEDs, as well as the photodetector.

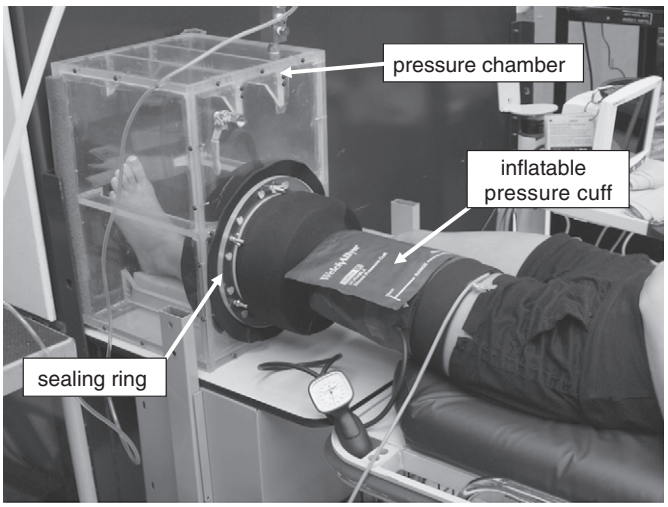

Fig. 2. Pressure chamber with neoprene pressure seal and sealing ring.

Once subjects were lying on a cushioned bed, a custom-made neoprene pressure seal (Surf 'n Sea®, San Diego, CA) was placed around their leg and pulled up towards the upper thigh. The seal remained in contact with the subject's limb from the top of the knee to the top or middle of the thigh for a distance of about 25 cm. A wide pressure cuff (Welch Allyn® Thigh 13 Blood Pressure Cuff, Skaneateles Falls, NY) was placed around the thigh on top of the neoprene seal. The pressure cuff was inflated during the positive pressure segments of the experiment to a pressure equal to the chamber pressure in order to minimize air leakage through the seal. The chamber pressure was monitored using a digital pressure monitor (World Precision Instruments, Sarasota, FL). The PPG cable from the limb inside the chamber was passed underneath the pressure seal, and a sealing ring was used to attach the pressure seal to the chamber and securely tightened to prevent air leakage.

All of the experiments were performed with subjects lying supine. An automated blood pressure cuff (HEM-775, Omron® Healthcare Inc., Bannockburn, IL) was placed around the subject's left arm over the brachial artery, and prior to exposure to any of the stimuli baseline BP and HR were measured. Measurements of the tibia skin thickness were also taken on both limbs by using a skin-fold caliper. Once the set-up was complete, subjects were asked to relax and lay down for 5 min before commencing the experiment. Throughout all phases of the experiment, subjects were instructed to minimize movement and talking.

Pressure protocol

Nine different, relatively mild pressure levels were used in the experiment: −50, −30, −15, −5, 0, +5, +15, +30, and +50 mm Hg (the available pressure pump was limited to a maximum pressure differential of 50 mm Hg). The order of the pressure levels was randomized for each subject, but consecutive pressure levels were always alternated between negative and positive pressure levels to avoid systematic errors due to additive pressure-exposure effects (such as edema with negative pressure). Each pressure level was maintained for 4 min (enough for the signal to reach a steady-state); and after exposure to a non-zero pressure level, the pressure in the chamber was brought back to 0 mm Hg for a period of 4 min prior to going to the next pressure level. A sample of the pressure protocol is shown in Table 1. Half of the subjects were randomly selected to start at a negative pressure level and the others at a positive level. For any given pressure exposure, the PPG data were

Table 1
Sample experimental pressure exposure protocol.

Order	Pressure mm Hg	Duration min
1	0	4
2	−15	4
3	0	4
4	50	4
5	0	4
6	−30	4
7	0	4
8	5	4
9	0	4
10	−50	4
11	0	4
12	30	4
13	0	4
14	−5	4
15	0	4
16	15	4
17	0	4

expressed as a change from the immediately preceding 0 mm Hg baseline level.

Data collection and analysis

PPG data were continuously recorded throughout the entire experiment and analyzed minute-by-minute. Average AC peak-to-peak amplitudes were obtained for both the skin and bone signals for each limb and for each minute in each of the 4-minute segments of the protocol. In processing the PPG data each of these 4 data points were computed as an average over at least 30 s, and care was taken to ensure that no external disturbances were present in this 30 s interval. The last 3 data points of each 4-minute interval were then averaged and used in the statistical analyses. In all cases the PPG data were either expressed as the raw data or as a change from baseline, both in Volts. Blood pressure and HR data were obtained on the third minute of each 4-minute segment. In all cases data in graphs are presented as means and 95% confidence intervals (CI).

Repeated measures analysis of variance (ANOVA) models were used to analyze the bone and skin PPG data separately, and Greenhouse–Geisser corrections were used to correct for violations of the sphericity assumption. The only factor in the model was pressure, with 8 levels corresponding to each of the tested pressure differences. The dependent variable was either the skin or bone average AC peak-to-peak amplitude, which was repeatedly measured on the same subject at each pressure level. We did not expect to see changes in BP and HR at most pressure levels as the pressure differences and fluid shifts were not likely to be large enough to evoke these responses, except maybe at the more extreme pressures of +50 and −50 mm Hg. The BP and HR data at these two pressure levels were tested for normality using the Shapiro–Wilk test, and two-tailed paired t-tests with Bonferroni corrections for multiple comparisons within each dependent variable were used to compare HR and BP changes from baseline at both +50 and −50 mm Hg. In all cases significance is set at $p<0.05$.

Results

PPG data from limb inside the chamber

The skin and bone PPG data for the leg inside the chamber are given in Fig. 3 (A). Both the skin and bone signals decreased at all the negative pressures, with greater decreases noted at the larger pressure differences. An increase in the bone signal was observed at positive pressures ranging from +5 to +30 mm Hg and with larger increases at the higher pressures. This response was reversed at +50 mm Hg, where the bone signal is markedly reduced and falls to levels below baseline. The skin signal followed a similar pattern at the positive pressures; it increased at the +5 and +15 mm Hg levels, but began to decrease at +30 mm Hg and fell below baseline levels at +50 mm Hg. The ANOVA analysis indicated a significant effect of pressure level on both the bone PPG data ($F(2.55, 28.03)=21.73$, $p<0.0001$) and on the skin PPG data ($F(2.97, 32.61)=37.35$, $p<0.0001$).

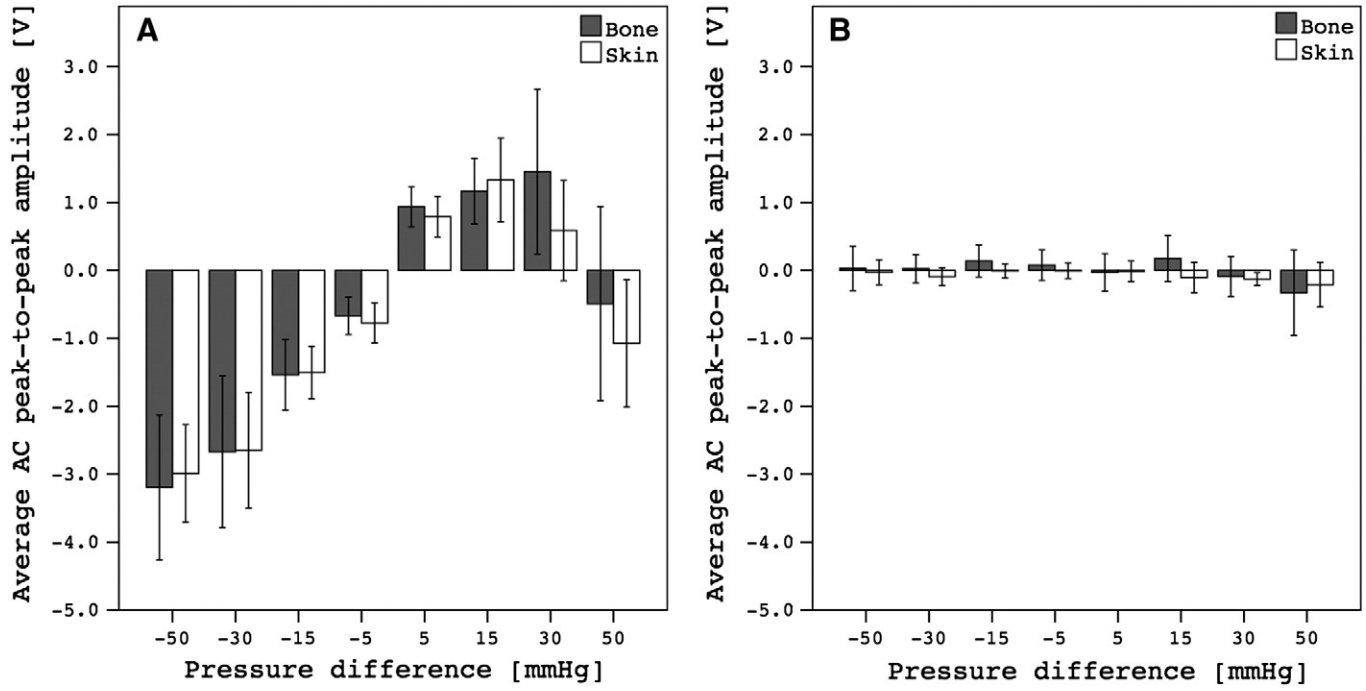

Fig. 3. PPG AC data from the pressure experiment for the leg inside the chamber (A) and outside the chamber (B) for both skin (white bars) and bone (dark bars) signals. Data expressed as means and 95% CI. For the limb inside the chamber pressure significantly affected the AC response in the skin and bone (both at $p<0.0001$), but for the limb outside the chamber pressure did not affect the skin ($p=0.532$) or bone response ($p=0.418$).

PPG data from limb outside the chamber

The skin and bone PPG data for the leg outside the chamber are given in Fig. 3 (B). Both the bone and skin PPG signals in the limb outside the chamber are unaffected by the pressure inside the chamber. The ANOVA analysis did not indicate a significant effect of pressure level on either the bone PPG data ($F(2.77, 30.51) = 0.96$, $p = 0.418$) or the skin PPG data ($F(2.97, 32.65) = 0.74$, $p = 0.532$).

Blood pressure and heart rate data

The BP and HR data for the pressure experiment are shown in Figs. 4 and 5, respectively. Systolic BP at +50 mm Hg was significantly increased from baseline. There were no other significant differences in systolic or diastolic BP from baseline at any other pressure level. The HR data were not significantly different from baseline at any of the pressure levels.

Discussion

Response to negative pressure

At all of the negative pressure levels, we observed significant reduction in both the skin and bone perfusion for the leg inside the chamber. Even for levels as low as −5 mm Hg, reduced perfusion is noted in both the skin and bone. The response at this pressure level is not due to changes in SNS tone or to mechanical compression of the limb. At such low pressure differences the SNS reflexes are not yet activated, as can be seen from the unaltered BP and HR. The myogenic effect is triggered in response to the increase in transmural pressure from the hypobaric exposure [39], and it is the sole mechanism behind the decreased perfusion at this pressure level.

As the pressure difference increases and we progress to more negative pressures, the myogenic effect is enhanced as the transmural pressure is further increased. The absence of changes to systolic BP, HR and vasomotor tone in the limb outside the chamber (even at the higher pressure differences of −30 and −50 mm Hg) indicates that the high-pressure baroreceptors have not yet been activated [53,73].

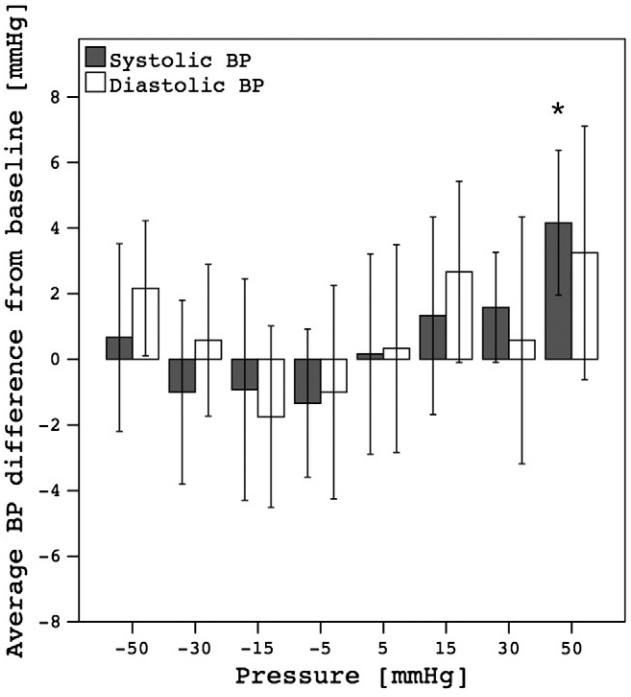

Fig. 4. Systolic (dark bars) and diastolic (white bars) BP data from the pressure experiment. Data expressed as means and 95% CI of differences from baseline; *p<0.01.

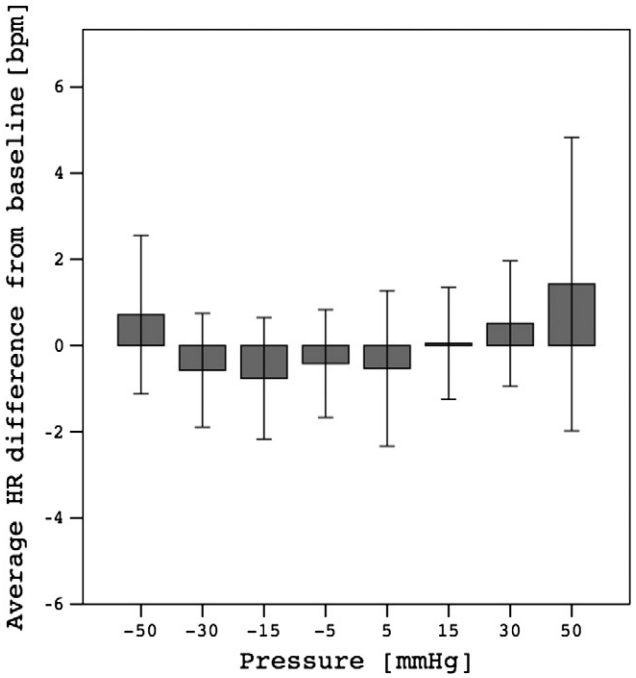

Fig. 5. HR data from the pressure experiment. Data expressed as means and 95% CI of differences from baseline.

Activation of the low-pressure baroreceptors is expected to be associated with vasomotor changes in the limb outside the chamber [57], which is also not observed.

At a pressure of −50 mm Hg, the diastolic BP is noticeably, though not significantly, increased as documented in Fig. 4. The mechanical compression of the limb through the pressure seal produces, on average, 21 mm Hg of pressure (95% CI: 14–28 mm Hg, as measured during testing by Tekscan® pressure sensors) on the limb when exposed to the −50 mm Hg pressure difference. At these pressures, the mechanical compression is likely affecting the venous circulation of the limb by reducing the venous compliance. Reduced venous compliance would tend to sustain the filling pressure of the right heart, mitigating any drop in CO. Since HR remains unchanged, any drop in CO would be reflected in a reduced pulse pressure as is evidenced by the unaltered systolic BP and the increase diastolic BP at −50 mm Hg.

Response to positive pressure

The response to positive pressure can be characterized by an initial increase in perfusion at pressure levels up to +30 mm Hg for bone and up to +15 mm Hg for skin, followed by a reversal of the response that ends with decreased skin and bone perfusion at +50 mm Hg. The increased pressure inside the chamber is transmitted to the leg tissues and decreases the transmural pressure, which triggers myogenic vasodilation. The lack of changes in HR, systolic and diastolic BP as well as in the PPG signal from the limb outside the chamber at pressures up to +30 mm Hg suggests that neither the high or low pressure baroreceptor mechanisms have been activated. Myogenic vasodilation is the predominant mechanism responsible for the increased perfusion seen at pressure levels up to +30 mm Hg.

At all positive pressures we expect the myogenic effect to be active and to promote vasodilation, however, it is clear that above +30 mm Hg another mechanism overrides this effect. Even though the PPG signals are, on average, above the baseline levels, the PPG skin signal is no longer significantly different from baseline. As we move to the highest positive pressure level of +50 mm Hg we observe a significant decrease in the skin signal and a decrease in the bone signal. At +50 mm Hg there is a significant increase in the systolic

BP and a non-significant increase in HR, while the PPG signal from the limb outside the chamber does not show a significant change from baseline. If the baroreceptor reflexes were activated we would expect to see an increase in the PPG signal in both limbs and decreases in the HR and BP data, which is the opposite of the observed changes at +50 mm Hg.

The observed reversal in the PPG trend at +30 mm Hg can be explained by the activation of the intramuscular pressure receptors. Several studies have reported the activation threshold of the intramuscular pressure receptors to be around +30 mm Hg [59,66,71], and it has previously been suggested that they can increase sympathetic tone, BP and HR, and override the inhibition of the SNS induced by the baroreceptor reflexes. At +50 mm Hg, the mechanical compression of the limb through the pressure seal is estimated to be 33 mm Hg (95% CI: 21–46 mm Hg). It is likely that at this pressure level the seal is affecting the limb circulation, in particular it may be affecting the venous return and promoting an increase in the diastolic BP as previously discussed.

Myogenic effect

We have claimed that the myogenic effect is the predominant mechanism effecting the perfusion changes in response to changes in external pressure. While we understand how the myogenic response can affect the vasculature in the soft tissues, it is not clear how the same mechanism can evoke a response in the vasculature that is encased within the rigid bone matrix. One possible mechanism that could explain the bone myogenic response is to consider the bone response as occurring afterwards and as a direct result of the response in the soft tissues. A myogenic response in the soft tissues can also affect the nutrient artery to the tibia as well as other blood supply vessels. In response to positive pressure exposure (decreased transmural pressure) the vessels in the soft tissue would vasodilate, thereby decreasing the blood pressure in the arterial supply to the bone. This internal drop in pressure inside the supply vessels could be propagated downstream, resulting in a decreased transmural pressure of the blood vessels inside the bone, thereby triggering a secondary myogenic response. This is one untested hypothesis of how the myogenic effect could affect the blood vessels inside the bone that warrants further study. This hypothesis could be tested by measuring if there is a time delay between the PPG responses from the skin and bone in response to a change in external pressure.

Limitations

The activation threshold for the various mechanisms we have discussed may vary across different experimental set-ups, even if the same pressure differences are used in both experiments. An experiment with the pressure seal located around the calf of one limb may produce different responses compared to an experiment where traditional LBNP (with the seal at the iliac crest and both limbs exposed to the pressure difference) is used [73]. In the latter, the same pressure difference will result in a larger fluid shift volume which will activate the baroreceptor reflexes at a much lower pressure than if only a small part of one limb was exposed to the pressure difference. It appears that some mechanisms, such as the intramuscular pressure receptors, may be activated at the same pressure regardless of the surface area of the body that is exposed to the pressure difference. However, it may still produce effects of different magnitude that are a function of how much body tissue is exposed to the pressure difference. The pressure differences that can be studied are partially limited by the fact that at very high pressure differences the pressure sealing mechanism will likely affect the circulation. As we have previously noted this may be a contributing factor affecting the response at the 50 mm Hg pressure differences.

The measurements from the PPG device are always expressed as relative changes from a baseline condition, and the lack of a direct relationship to an absolute scale of measurement is one of its major limitations. PPG measurements of bone are also not possible at all anatomical locations, the thickness of the tissue above the bone and the penetration depth of the PPG signal are the two limiting factors in determining where this technique can be applied.

Conclusions

While the response of muscle, skin and other tissues to altered external pressure was previously studied, we have provided the first description of the changes that occur in bone perfusion in response to changes in external pressure. These new results provide a basic understanding of the predominant hemodynamic control mechanisms affecting bone and skin circulation and support our two initial hypotheses. While previous work on non-osseous tissues suggests that the myogenic effect is the predominant mechanism regulating arterial inflow to the limbs in response to negative pressure exposures up to −75 mm Hg [33], we have shown that the myogenic effect is also the predominant mechanism responsible for reduced bone perfusion at negative pressures and for increased bone perfusion at moderate positive pressures. This study represents the first report of a myogenic response in bone, and significantly expands our understanding of the importance of the myogenic effect [35,41].

For our experimental set-up and at the pressure levels tested, sympathetic reflexes are not significantly activated. Different set-ups in which larger parts of the body are exposed to the pressure differences will probably evoke the SNS reflexes at lower pressure differences. Our data support the hypothesis that intramuscular pressure receptors are activated at +30 mm Hg and result in decreased perfusion, as has previously been suggested in other studies that have looked at muscle responses to positive pressure exposure [59,66,71]. At high positive pressures the intramuscular receptors are powerful enough to override the myogenic-induced vasodilation.

Understanding the mechanisms that regulate bone circulation and the relationship between bone hemodynamics and bone health are two important missing pieces in our knowledge of integrated physiology. Knowledge of the predominant mechanisms regulating perfusion of bone and other tissues may contribute to more effective treatments and pharmaceutical approaches to treating specific bone disorders. Additionally, the increased perfusion observed at moderate positive pressures may be clinically exploited to aid in fracture repair and other pathologies. PPG bone measurements during spaceflight would be a useful way to further our understanding of microgravity induced fluid changes and the effect of these changes on BMD loss. A better understanding of the relationship between bone perfusion and bone health is an important step in improving and developing Earth-based clinical applications for osteoporosis and other pathologies as well as developing new and effective countermeasures for spaceflight-induced bone loss in long duration space missions.

Acknowledgments

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