Authors:

Guruprasad Madhavan, MS
Julian M. Stewart, MD, PhD
Kenneth J. McLeod, PhD

Affiliations:

From the Clinical Sciences Research Center, Department of Bioengineering, Thomas J. Watson School of Engineering and Applied Science, State University of New York, Binghamton, New York (GM, KJM); and the Departments of Physiology and Pediatrics, Westchester Medical Center and New York Medical College, Valhalla, New York (JMS).

Disclosures:

Supported, in part, by financial grants from the Whitaker Foundation, Arlington, Virginia; Smith and Nephew, Memphis, Tennessee; Juvent Corporation, Somerset, New Jersey; and the New York State Office of Science, Technology, and Academic Research (NYSTAR), Albany, New York.

Presented, in part, at Experimental Biology 2004—The Annual Meeting of Federation of American Societies for Experimental Biology, Washington, DC, April 17–21, 2004.

Correspondence:

All correspondence and requests for reprints should be addressed to Kenneth J. McLeod, PhD, Department of Bioengineering, Thomas J. Watson School of Engineering and Applied Science, State University of New York, Binghamton, NY 13902-6000.

0894-9115/05/8405-0338/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/01.PHM.0000159970.81072.8B

RESEARCH ARTICLE

Effect of Plantar Micromechanical Stimulation on Cardiovascular Responses to Immobility

ABSTRACT

Madhavan G, Stewart JM, McLeod KJ: Effect of plantar micromechanical stimulation on cardiovascular responses to immobility. Am J Phys Med Rehabil 2005;84:338–345.

Objective: We investigated the cardiovascular responses of adult women to the influence of extended quiet sitting and the extent to which these responses may be reversed by micromechanical stimulation of the plantar surface.

Design: The cardiovascular responses of 20 healthy adult women (mean age, 55.9 ± 4.45 yrs) were observed during quiet sitting with and without exposure to a plantar-based micromechanical stimulation. Beat-to-beat heart rate via electrocardiogram was acquired along with preexposure and postexposure blood pressures, from which heart rate variability and mean arterial pressure were determined. Seven stimulus frequencies (0, 15, 22, 44, 60, 90, and 120 Hz, all at 0.2 × *g*, peak to peak) were tested on each subject.

Results: Over one-half of the women tested (11/20) exhibited a significant resting tachycardia (mean, 8.3 ± 0.5 beats/min) with a corresponding decline in their systolic blood pressure (9.45 ± 1.8 mm Hg) after 20 mins of quiet sitting. Plantar stimulation at 44 Hz (25 μm, peak to peak) was able to completely reverse the effect of immobility in this group, resulting in a heart rate decline of 2.5 beats/min ($P < 0.0001$) and a decrease of only 1 mm Hg in systolic pressure ($P = 0.006$).

Conclusion: We interpret these results to suggest that the immobility of quiet sitting has a profound effect on the cardiovascular systems in a large fraction of otherwise healthy women, perhaps due to inadequate muscle tone leading to venous insufficiency. Simple external stimulation of the plantar surface seems to be capable of preventing these cardiovascular stress-based responses.

Key Words: Immobility, Postural Stress, Cardiovascular System, Plantar Stimulation

Immobility exerts profound stresses on numerous physiologic systems. The ability of extended bedrest to instigate significant muscle wasting (sarcopenia) and bone loss (osteopenia), for example, has long been known.[1] In addition, the effect of the orthostatic stresses associated with quiet standing has been well documented.[2,3] Upright posture significantly elevates the hydrostatic pressure in the peripheral vascular supply, resulting in both increased fluid extravasation and caudal venous blood collection. This blood pooling is, in part, compensated for by reflex-mediated vasoconstriction, and, at least in young healthy individuals, venous and lymphatic pooling is reduced by the actions of the skeletal muscle pump, without which systemic cardiac output declines substantially, resulting in tachycardia and compromising orthostatic tolerance.

For the majority of the American population, extended bedrest or long bouts of quiet standing are not common, although in some occupations, extended periods of relatively quiet standing can be required. Instead, modern life involves extended periods of sitting during the typical day, in the office, in cars and airplanes during long-distance travel bouts, and at home due to the ubiquity of passive entertainment options. The immobility of quiet sitting as a physiologic stress has undergone far less investigation as compared with bedrest or the orthostatic stress of standing; nonetheless, studies of quiet sitting suggest similar effects to those of other forms of immobility.[4] In recent tilt-table studies investigating the influence of a 35-degree upright tilt (equivalent to sitting upright) on blood and interstitial fluid flows, we observed that plantar micromechanical stimulation was able to normalize blood flow in immobile individuals.[5] We hypothesized, therefore, that a similar plantar stimulation may serve as an effective means to prevent peripheral fluid accumulation in individuals during quiet sitting, particularly those with inadequate compensatory mechanisms, thereby enhancing cardiovascular function in these afflicted individuals.

To address this hypothesis, we investigated cardiovascular responses to quiet sitting and the extent to which plantar micromechanical stimulation could prevent fluid pooling and, correspondingly, the deleterious cardiovascular responses to this stress. Because orthostatic intolerance is more common in women, we focused our investigation on an adult female population. Furthermore, we utilized a range of plantar-based stimulus frequencies in this study to determine whether the observed cardiovascular responses could be optimized.

MATERIALS AND METHODS

This investigation conformed with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board's Committee on Research Involving Human Subjects at the State University of New York, Stony Brook, and was performed in the University Health Sciences Center in Long Island, NY, from March through early August 2002. During screening, subjects' age, height, and weight were obtained.

Subjects and Study Design

The entrance criteria for this clinical study were healthy adult women with no current fractures, peripheral vascular disease or systemic illness, and the capability of providing informed consent. From an initial upright mobile position, lasting for a minimum of 5 mins, the subjects sat down in a relaxed position with their spine against a chair back. The subjects' feet (shoeless) were positioned on a stimulation platform that was raised approximately 8 cm above floor level, and chair height was positioned so that the subjects' knees were at an approximate 90-degree angle. The stimulation platform permitted exposure of the plantar surface of the subjects' feet to micromechanical stimulation at any one of six frequencies at a time, 15, 22, 44, 60, 90, and 120 Hz, this frequency range being selected so as to be centered around the normal receptive range of somatosensory cutaneous mechanoreceptors of the foot.[6] Stimulus acceleration was kept constant as a function of frequency so as to keep the applied dynamic force constant, though this resulted in different displacements of the stimulus platform at each stimulus frequency. Peak-to-peak accelerations of $\sim 0.2 \times g$ ($g = 9.8$ m/sec^2) were used throughout the study, corresponding to peak displacements of approximately 110 μm at the lowest frequency utilized (15 Hz) and a peak displacement of approximately 1.7 μm at the highest frequency utilized (120 Hz). Correspondingly, peak displacements at 22, 44, 60, and 90 Hz were 50, 13, 7, and 3 μm, respectively. Each subject also completed a 0-Hz (no vibration) control exposure.

The experiment was executed using a randomized, one-factor design to eliminate any potential effect of the training. The study subjects returned once each week for testing, with the seven test frequencies being randomized and conducted with one exposure frequency each week. To ensure that variations in biorhythmic dynamics did not influence the results, the tests were performed on each respective subject at approximately the same time of the day.

Cardiovascular responses were recorded for a

period of 20 mins to provide adequate time for plasma volume to equilibrate after a change in stance.[7] Subjects were asked to minimize their arm and leg movements during the recording period, though conversation was permitted. Heart rate was recorded continuously by an electrocardiograph by using wrist electrodes (Heart Rhythm Scanner, Version 2.0, Biocom Technologies, Poulsbo, WA). Blood pressure values were measured from the arm using a semiautomatic digital blood pressure monitor (HEM 741C, Omron Health Care, Vernon Hills, IL). To minimize the perturbations of the subjects during the therapy, blood pressures were obtained, in duplicate, only at the beginning and end of the 20-min treatment duration. The first set of previbration measurements was acquired within 1 min after the subject sat from the standing position and removed her footwear. A graphical illustration of the recording protocol is presented in Figure 1.

Analysis

Changes in heart rate over the 20 mins of exposure were determined by converting the interbeat R–R interval data stream into beat-to-beat heart rate. These were averaged for the first and the last 3 mins of the session, and the difference was calculated. Heart rate variability (HRV) was characterized using the standard deviation of cardiac cycle length,[8,9] which was calculated from each 2-min interval of the acquired real-time, beat-to-beat interval data using custom software code in Matlab V 6.5 (Math Works, Natick, MA). Time dependent changes in the standard deviation of cardiac cycle length (HRV) were then evaluated by linear regression. These changes in HRV were used in a quadratic regression model to estimate the frequency dependence of the physiologic response to the plantar stimulation. HRV data were also utilized to evaluate changes in respiratory rate through detection of the spectral peak in the 0.18- to 0.4-Hz range of the HR power spectrum.[10] The duplicate systolic and diastolic blood pressure values were averaged, and the respective variations over the treatment duration were plotted as a function of stimulation frequency. Mean arterial pressure (MAP) was calculated as diastolic pressure + 1/3 × pulse pressure, and the change in MAP over the 20-min exposure period was determined. Changes in the mean preexposure and postexposure values of systolic pressure and MAP were also evaluated by polynomial (quadratic) regression against vibration frequency. Regression analyses were carried out utilizing Origin Version 7.0 (Origin Lab, Northampton, MA) and statistical analyses were confirmed with Sigma Stat Version 10.0 for Windows (SPSS, Chicago, IL). Within-group multiple comparisons were performed using analysis of variance. Data are expressed as mean ± standard error of mean. Statistical significance was accepted at $P < 0.05$.

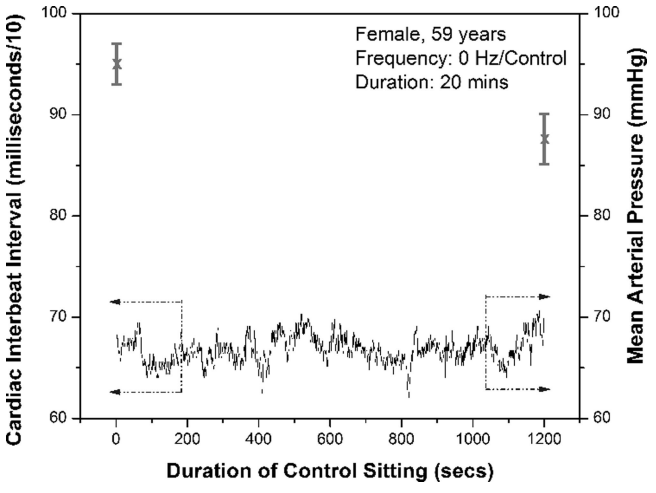

FIGURE 1 *Graphical illustration of the experimental protocol. Systolic and diastolic pressures were measured in duplicate, immediately before and after the 20 mins of quiet sitting, from which the average mean arterial pressure was determined. Electrocardiography was used to monitor interbeat intervals throughout the test period, from which changes in heart rate, heart-rate variability, and respiratory-rate changes were determined. The subject represented is a 59-yr-old woman sampled from the normal cohort.*

RESULTS

A total of 20 healthy adult female volunteers aged 30–75 yrs (mean age, 55.9 ± 4.45 yrs) were recruited for the study and completed the experimental protocol, having undergone a minimum of four of the seven recording sessions. Of the possible 140 trials for these 20 volunteers for the seven stimulus frequencies, a total of 105 trials were accomplished due to missed sessions by some participants. Randomization resulted in the highest participation for the 22-Hz test frequency, and the lowest participation at the test frequency of 120 Hz. The plantar stimulation was readily perceived by the participating subjects, except for the 120-Hz stimulus, which was reported to be barely perceptible. In all of the cases, the subjects reported a "pleasant" stimulus sensation. The subjects had no difficulty remaining seated quietly for the 20 mins, and no experimental complications were observed in any of the trials in this investigation.

Changes in heart rate during quiet sitting were dependent neither on subject body mass index ($P = 0.1$) nor on subject age, but a distinct bipolar distribution in heart rate changes was evident (Fig. 2). Gaussian curve fitting indicated that these results were unlikely to reflect simply normal variation but rather a bimodal distribution ($R^2 = 0.05$, unimodal; $R^2 = 0.66$, bimodal). Approximately one

half ($n = 9$) of the subjects demonstrated a slight decrease in heart rate (mean, 2.8 ± 0.74 beats/min) after their assuming a seated position. The remaining subjects ($n = 11$) demonstrated a significant increase in heart rate (mean increase, 8.3 ± 0.5 beats/min) over the 20 mins of quiet sitting. As both these subgroups had similar heart rates and blood pressures at the start of the sitting regimen (Table 1), we defined the group with a declining heart rate as normal, given the reduction in muscular activity after cessation of locomotion would be expected to result in decreased cardiac output and therefore heart rate, and the group with the significantly increased heart rate as manifesting resting tachycardia. Given these two distinct responses, in subsequent analyses we evaluated the normal and tachycardia subpopulations separately.

Micromechanical plantar surface stimulation had essentially no effect on heart rate in the normal subpopulation (Fig. 3, *left*). However, the plantar stimulation significantly inhibited the elevation in heart rate in the tachycardia group at all frequencies tested (Fig. 3, *right*). Moreover, at 44 Hz, plantar stimulation was able to completely inhibit the tachycardia, resulting in a decrease in the average heart rate by 2.5 beats/min ($P < 0.0001$).

Although no effect of plantar stimulation on heart rate was observed in the normal population, HRV was significantly influenced by this stimulation (Fig. 4, *left*). Indeed, at all frequencies of vibration, HRV was elevated to levels at or above the HRV calculated at the start of the recording period. Similarly, plantar vibration prevented the depression in HRV observed in the tachycardia cohort (Fig. 4, *right*). In this latter subpopulation, efficacy of the plantar stimulation to inhibit the depression in HRV was limited to the 44-Hz frequency ($P = 0.002$).

In the normal subpopulation, a significant decrease in the systolic blood pressure of 7.75 ± 1.6 mm Hg ($P < 0.01$) (Fig. 5, *left*) and a decrease of 2.5 mm Hg in diastolic pressure were observed (data not shown), resulting in an average decrease of 6 mm Hg in MAP (Fig. 6, *left*). Plantar vibration at 44 Hz inhibited these decreases in blood pressure, resulting in normalization of the systolic pressure ($P = 0.03$) and preventing the MAP from decreasing >2 mm Hg ($P = 0.003$).

In the tachycardia subpopulation, average systolic blood pressure declined 9.5 mm Hg (Fig. 5, *right*) and diastolic pressure decreased 2.7 mm Hg (data not shown), resulting in a depression in MAP of 6.2 mm Hg (Fig. 6, *right*). Plantar stimulation at all frequencies mitigated these depressions in blood pressure, with efficacy peaking at the 44-Hz stimulus frequency. Systolic pressure was essentially normalized with the 44-Hz stimulus ($P = 0.002$), with the overall response showing a significant frequency dependence ($P = 0.006$, $R^2 = 0.96$). Correspondingly, the 44-Hz stimulus resulted in a depression in MAP of only 1.5 mm Hg ($P = 0.03$) and again demonstrated a significant frequency dependence of the stimulus ($P = 0.05$, $R^2 = 0.85$).

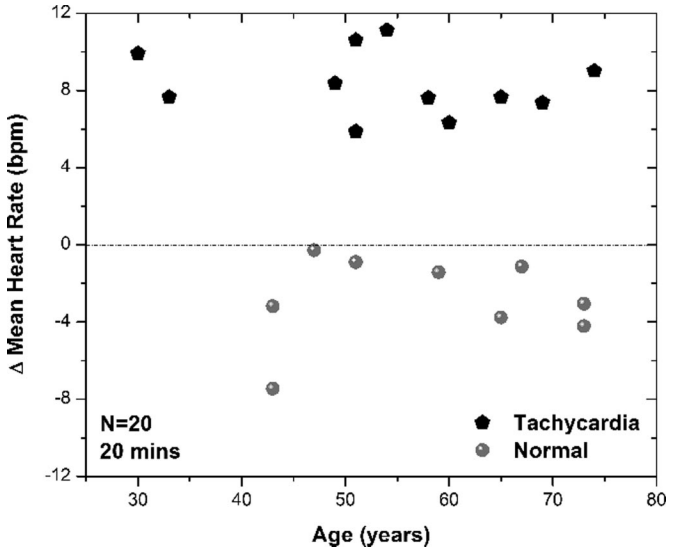

FIGURE 2 *Influence of quiet sitting on heart rate. Twenty minutes of quiet sitting resulted in a slight decrease in heart rate for nine subjects (normal group), consistent with the reduced metabolic demands associated with sitting. For 11 subjects (tachycardia group), quiet sitting resulted in a pronounced elevation in heart rate.*

Analysis of the HRV spectrum to extract respiratory frequency showed that respiration rates were identical for both the normal and tachycardia group during the control exposures (0.25 ± 0.01 Hz). Plantar stimulation, even at 44 Hz, the stimulus at which the largest cardiovascular responses were observed, had no significant effect on respiration rate in either the normal (0.24 ± 0.01 Hz) or the tachycardia group (0.25 ± 0.01 Hz).

DISCUSSION

In previous studies on cardiovascular responses to upright tilt, we observed that a plantar-

TABLE 1 Demographic and baseline characteristics of subjects

		Normal Subjects	Tachycardia Subjects
No. of subjects, n		9	11
Age, yrs (mean ± SE)		52 ± 4	54 ± 4.1
Initial systolic pressure, mm Hg (mean ± SE)	Control	122.9 ± 2.1	122.4 ± 4.4
	44 Hz	122.3 ± 3.4	121 ± 3.6
Initial diastolic pressure, mm Hg (mean ± SE)	Control	77.1 ± 1.7	79.4 ± 2.2
	44 Hz	77.9 ± 2.1	78 ± 2.6
Initial heart rate, beats/min (mean ± SE)	Control	77.7 ± 3.8	77.2 ± 3.1
	44 Hz	77.1 ± 3.8	77.3 ± 3.8

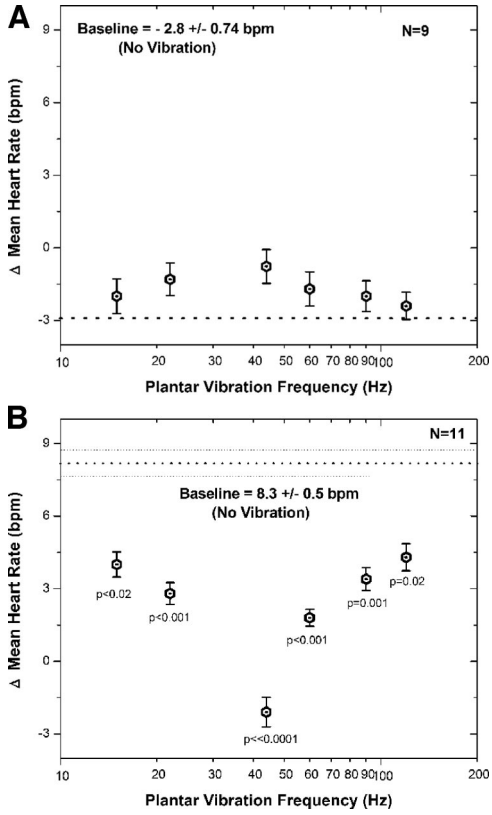

FIGURE 3 *Influence of quiet sitting and plantar stimulation on heart rate during extended sitting.* Top, *plantar stimulation had minimal effects on heart rate in the normal group.* Bottom, *in the tachycardia group, plantar stimulation reduced the tachycardia at all stimulus frequencies and normalized the heart rate response at 44 Hz.*

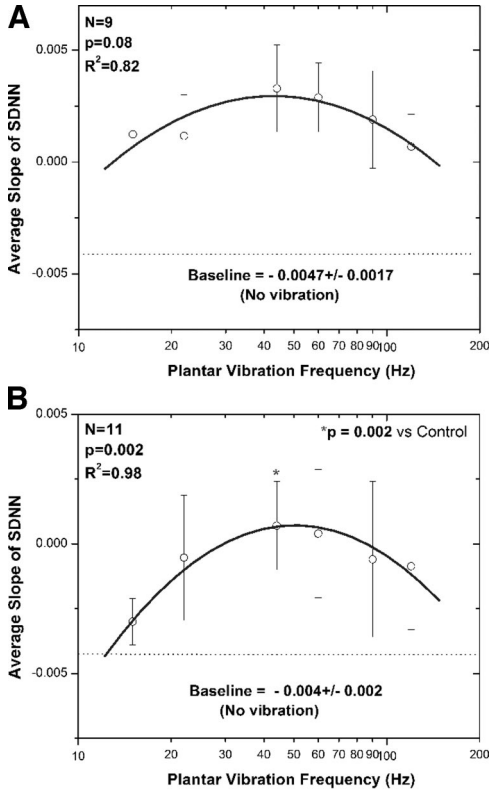

FIGURE 4 *Influence of quiet sitting and plantar stimulation on heart rate variability. Heart rate variability, as calculated by the standard deviation of cardiac cycle length (*SDNN*), shows a distinct depression in both the normal and tachycardia groups during the 20 mins of quiet sitting.* Top, *plantar stimulation returns heart rate variability to levels similar to those when the subjects first sit down, with all stimulus frequencies being equally effective.* Bottom, *in the tachycardia group, the efficacy of the plantar stimulation to inhibit the decrease in heart rate variability was frequency dependent (*$P = 0.002$, $R^2 = 0.98$*), with the 44-Hz stimulus frequency significantly increasing heart rate variability as compared with the controls (*$P = 0.002$*).*

based micromechanical stimulus was capable of inhibiting the reduction in peripheral blood flow commonly associated with this orthostatic stress. This observation may have implications for the prevention of orthostatic intolerance in individuals undergoing long periods of quiet standing; however, the usual remedy for such problems is simply to have the individual sit down. Of greater practical concern are those individuals who find the immobility associated with quiet sitting a significant stress, and so we focused this investigation on characterizing the responses of the cardiovascular system to the influences of both quiet sitting and the extent to which plantar-based micromechanical stimulation was able to inhibit the influence of this stress. Quiet sitting is not normally thought of as a significant orthostatic stress. The transition from ambulatory activity to quiet sitting results in decreased muscle demand for oxygen and therefore cardiac output, which should be evidenced in a decreased heart rate. Consistent with this expectation, we observed that approximately one half of the women tested demonstrated a decreased heart rate during the 20 mins of quiet sitting. However, sitting upright posture still leads to the translocation of thoracic blood volume into the lower limbs, requiring both peripheral venoconstriction and skeletal muscle pump activity to maintain normal systemic blood pressure and heart rate, such that lack of either or both of these adaptive processes can lead to resting tachycardia. Correspondingly, over one half of the adult women we tested developed a pronounced tachycardia (>8 beats/min), concomitant with a substantial (~10 mm Hg) de-

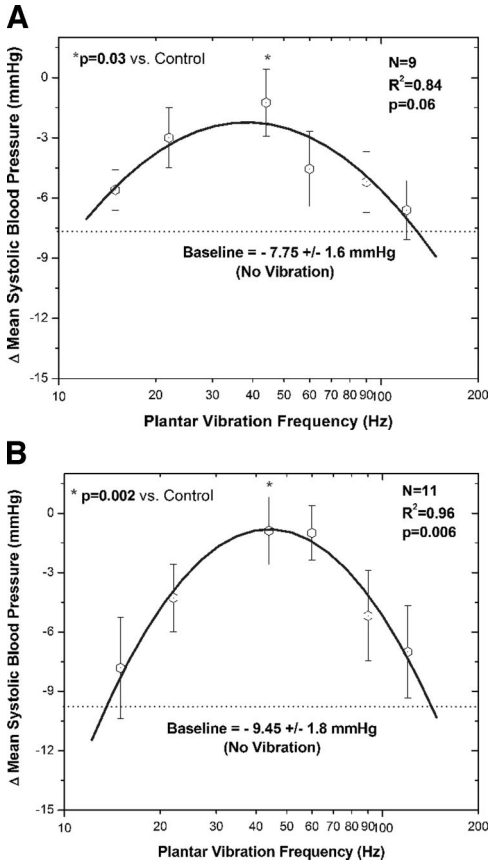

FIGURE 5 *Influence of quiet sitting and plantar stimulation on systolic blood pressure.* Top*, the normal population experienced an average decrease of 7.8 mm Hg in systolic blood pressure during 20 mins of quiet sitting, and plantar stimulation at 44 Hz significantly inhibited this decrease (*P = *0.03), although no clear frequency dependence was observed (*R^2 = *0.84,* P = *0.06).* Bottom*, the tachycardia group experienced an average decrease of 9.5 mm Hg in systolic pressure. Systolic pressure in the tachycardia group responded to plantar stimulation in a highly frequency-dependent manner (*R^2 = *0.96,* P = *0.006), with the 44-Hz stimulus essentially eliminating the decrease in systolic pressure (*P = *0.002).*

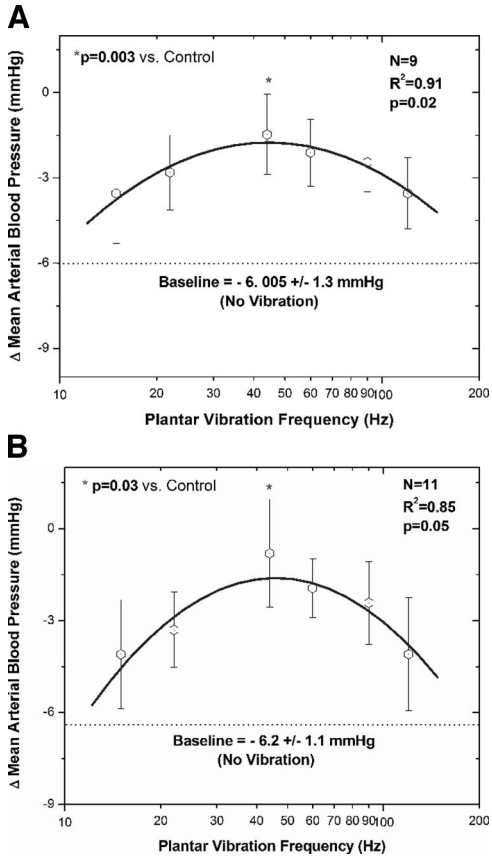

FIGURE 6 *Influence of quiet sitting and plantar stimulation on mean arterial blood pressure. The declines in mean arterial pressure as a result of quiet sitting were remarkably similar (~6 mm Hg) for both the normal (*top*) and tachycardia (*bottom*) groups. Plantar stimulation inhibited this decrease in mean arterial pressure in a frequency-dependent manner (normal group:* R^2 = *0.91,* P = *0.02; tachycardia group:* R^2 = *0.85,* P = *0.05).*

crease in systolic blood pressure. The distribution of heart rate shifts we observed does not seem to represent a normal distribution around a mean change in heart rate but a distinct bimodal distribution. The cardiac response data, therefore, leads us to suggest that, for a significant fraction of adult women, the immobility associated with quiet sitting represents a significant orthostatic challenge with peripheral regulatory mechanisms incapable of providing full compensation.

Numerous physiologic mechanisms could be responsible for these observed cardiovascular responses to immobility, including increased venous capacitance, depressed autonomic function, decreased cardiac function, and reduced skeletal muscle tone. Given the low level of muscle activity during quiet sitting, it is reasonable to consider lack of skeletal muscle pump activity as playing a significant role in the responses of the tachycardia group. It is reasonable to hypothesize, therefore, that the plantar stimulation we found to be capable of preventing this cardiovascular response is serving to enhance the efficiency of the skeletal muscle pump. Because the stimuli we utilized provided a continuous neuromuscular stimulus in the range of 15–120 Hz, it is unlikely that muscle contraction at these frequencies could serve to directly increase muscle pump activity. More likely, these stimuli enhance low-level tonic muscle activity in the postural muscle fibers, thereby enhancing the efficacy

of skeletal muscle pump activity by improving venous sufficiency.

Consistent with the suggestion that the plantar stimulus may be triggering muscle activity is our observation that the 44-Hz stimulus is particularly efficacious in preventing the tachycardia and blood pressure decrease. The stimulus of 44 Hz is very near the central response frequency of the Meissner's corpuscles, an afferent cutaneous mechanoreceptor, well distributed on the plantar surface, that play a critical role in the neuromuscular feedback necessary for maintaining upright posture.[6] Moreover, the muscle fiber groups most commonly associated with stimulation in this frequency range (15–50 Hz) are the fast oxidative-glycolytic fibers (type II-A).[11] Because of the high level of vascularization of type-II-A fibers and because of their chronic contractile activity, this fiber group has been implicated in playing a critical role in skeletal muscle pumping during postural activities.[12] Electromyographic measurements would be required to confirm the possible involvement of this fiber group.

Despite the remarkable similarity between the observed frequency responses in our studies and the frequency response characteristics of Meissner's sensory corpuscles, alternative coupling mechanisms may be responsible for the observed results. Primary muscle spindle receptor endings show a distinct increase in sensitivity near 30 Hz, with thresholds well below the displacements utilized in this study, and thus, muscle spindles may be directly detecting the vibrational stimulus.[13] Because we utilized a constant peak acceleration as a function of frequency, the decreased responsiveness at increasing frequency may be a result of the decreasing amplitude of the stimulus at higher frequency. Alternatively, it is also possible that this stimulus has regional effects on tissue blood flow or vascular resistance. Finally, it is possible that the vibrational stimulus travels sufficiently far up into the body to directly influence vagal activity and thereby the cardiac function. Studies are underway to determine the role of cutaneous reception in this response and the changes in lower limb skeletal muscle activity during plantar stimulation.

Although the cardiovascular response to orthostatic stress is usually measured in subjects moving from supine to upright standing, representing, for example, waking and rising from bed, the transition from walking/standing to sitting is a far more common daily activity. The cardiovascular responses we observed here may have profound effects on health, as reduced venous flow, particularly in the lower limbs, is considered a major cause of pulmonary emboli, the primary cause of death in as many as 200,000 individuals each year in the United States.[14,15] Hypotension has also been implicated in a variety of other common clinical conditions, including syncope,[2] chronic fatigue syndrome,[16,17] and osteoporosis.[5] Hence, these outcomes may have important implications from the perspective of occupational health maintenance and preventative medicine. That the tachycardia and depressed systolic pressure can so readily be inhibited by a simple intervention such as plantar stimulation is encouraging in light of the very high fraction of individuals who seem to manifest a lack of tolerance to quiet sitting.

Although these results are supportive of our initial hypothesis, certain aspects of the experimental design limit the interpretation of these results. First, although neither age nor body mass index of our subjects distinguished the tachycardia group from the normal group, the correlation to body mass index suggested a trend that should be pursued through study of a larger population of women, as the existence of such a relationship may provide an easily obtained indicator of those most at risk of orthostatic tachycardia. Also, we only looked at this response in women, knowing to what extent men exhibit similar responses would be an important extension of this work. In addition, only previbration and postvibration blood pressures were acquired in this investigation. Continuous blood pressure recordings would provide additional insight into the dynamics of the systemic response to the plantar stimulus. Similarly, extending recordings beyond 20 mins would provide knowledge of the ability of plantar vibration to maintain normal heart rate and blood pressure in response to a sustained seated activity, such as encountered during long-distance travel. In addition, it would be useful to know whether the plantar stimulation is effective in reversing the effects of sitting on the cardiovascular system or is only capable of inhibiting the development of these effects. Further studies will be required to address these issues.

CONCLUSION

We suggest that these initial findings are consistent with the hypothesis that the immobility associated with quiet sitting can produce qualitatively similar stresses to those associated with quiet standing, resulting in a significant depression in systolic pressure and tachycardia in a large fraction ($\sim$50%) of adult women. Furthermore, the results support the hypothesis that plantar-based micromechanical stimulation at the appropriate frequency can largely eliminate the effects of this cardiovascular stress. We suggest that these observations may have significant implications given the extended durations over which many Americans remain seated and relatively immobile during the course of their day in the workplace, during passive

entertainment options, and during long-distance travel.

ACKNOWLEDGMENTS

We thank the volunteer subjects and the financial supporters.

REFERENCES

1. Greenleaf JE: Physiological responses to prolonged bed rest and fluid immersion in humans. *J Appl Physiol* 1984;57: 619–33
2. Ten Harkel AD, van Lieshout JJ, Wieling W: Effects of leg muscle pumping and tensing on orthostatic arterial pressure: A study in normal subjects and patients with autonomic failure. *Clin Sci* (*Lond*) 1994;87:553–8
3. Lagi A, Cipriani M, Buccheri AM, et al: Heart rate and blood pressure variability in orthostatic syncope. *Clin Sci* (*Lond*) 1996;91(suppl):62–4
4. Hu G, Eriksson J, Barengo NC, et al: Occupational, commuting, and leisure-time physical activity in relation to total and cardiovascular mortality among Finnish subjects with type 2 diabetes. *Circulation* 2004;110:666–73
5. Stewart JM, Karman C, Montgomery LD, et al: Plantar vibration improves leg fluid flow in perimenopausal women. *Am J Physiol Regul Integr Comp Physiol* 2005;288: R623–9
6. Inglis JT, Kennedy PM, Wells C, et al: The role of cutaneous receptors in the foot, in Gandevia SC, Proske U, Stuart DG (eds): *Sensorimotor Control of Movement and Posture*. New York, Kluwer Academic/Plenum Publishers, 2002, pp 111–7
7. Hagan RD, Diaz FJ, Harvath S: Plasma volume changes with movement to supine and standing positions. *J Appl Physiol* 1978;45:414–7
8. Huikuri HV, Kessler KM, Terracall E, et al: Reproducibility and circadian rhythm of heart rate variability in healthy subjects. *Am J Cardiol* 1990;65:391–3
9. Kautzner J: Reproducibility of heart rate variability measurement, in Malik M, Camm AJ (eds): *Heart Rate Variability*. Armonk, NY, Futura Publishing, 1995, pp 165–71
10. Cerutti S, Bianchi AM, Mainardi LT: Spectral analysis of the heart rate variability signal, in Malik M, Camm AJ (eds): *Heart Rate Variability*. Armonk, NY, Futura Publishing, 1995, pp 63–74
11. Bellemare F, Woods JJ, Johansson R, et al: Motor-unit discharge rates in maximal voluntary contractions of three human muscles. *J Neurophysiol* 1983;50:1380–92
12. Mackie BG, Terjung RL: Blood flow to different skeletal muscle fiber types during contraction. *Am J Physiol* 1983; 245:H265–75
13. Mathews PBC: Muscle spindles: Their messages and their fusimotor supply, in Darian-Smith I (ed): *The Handbook of Sensory Physiology: Sensory Processes*, chapter 6. Bethesda, MD, American Physiological Society, 1984, pp 189–228
14. Hirsh J, Hoak J: Management of deep vein thrombosis and pulmonary embolism: A statement for healthcare professionals. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. *Circulation* 1996;93:2212–45
15. Goldhaber SZ, Tapson VF: A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol* 2004;93:259–62
16. Schondorf R, Benoit J, Wein T, et al: Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst* 1995; 75:192–201
17. Rowe PC: Orthostatic intolerance and chronic fatigue syndrome: New light on an old problem. *J Pediatr* 2002; 140:387–9