ORIGINAL ARTICLE

Prevalence and Etiology of Delayed Orthostatic Hypotension in Adult Women

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ABSTRACT. Madhavan G, Goddard AA, McLeod KJ. Prevalence and etiology of delayed orthostatic hypotension in adult women. Arch Phys Med Rehabil 2008;89:1788-94.

Objective: To evaluate the contributing roles of venous status, microvascular filtration, and calf muscle pump activity in the etiology of delayed orthostatic hypotension (OH).

Design: Unblinded within-subjects trial.

Setting: Academic clinical research center.

Participants: Convenience sample of healthy adult women (N=30) with an age range of 30 to 65 years.

Intervention: Plantar micromechanical stimulation applied at a 45-Hz frequency and a 50-μm amplitude for a duration of 30 minutes during upright sitting.

Main Outcome Measure: Diastolic blood pressure (DBP).

Results: White women (mean age, 51.8±1.3y) were recruited and screened for delayed OH. About one quarter (9/33) of the screened subjects showed delayed OH as determined by a significant decrease in blood pressure after at least 15 minutes of quiet sitting. Air plethysmographic assessment provided no evidence of venous insufficiency (venous filling index, >2.5mL/s; venous volume, >80mL) or excessive microvascular filtration in the affected subjects, whereas activation of the calf muscle pump (CMP) through plantar-based micromechanical stimulation consistently resulted in a significant increase in systolic blood pressure (SBP) (ΔSBP=22.8±3.9mmHg, P=.003) and DBP (ΔDBP=20.9±3.3mmHg, P=.002).

Conclusions: About 25% of the adult women studied showed delayed OH during quiet sitting and the proximate cause appears to be neuromuscular in origin, specifically inadequate calf muscle tone, because venous and microvascular filtration status is normative in the delayed OH subpopulation and CMP stimulation reverses the hypotension.

Key Words: Orthostatic hypotension; Rehabilitation; Women.

DELAYED ORTHOSTATIC hypotension has recently been identified in 40% of people with symptoms such as lightheadedness, dizziness, and syncope, but with no evidence of acute OH.[1] Unlike acute OH, which is defined by a drop in SBP of 20mmHg or a DBP of 10mmHg or more within 3 minutes of standing or 60° head-up tilt,[2] delayed OH is characterized by a progressive decline in blood pressure occurring beyond 3 minutes after exposure to an orthostatic stress.[1,3] Although acute OH is generally associated with rapid, uncontrolled venous sequestration in the lower extremities,[4,5] delayed OH appears to arise from slower physiologic processes, although its etiology is unclear.[1,6] Not only is the underlying etiology of delayed OH unclear, but, given the very recent demonstration of this condition, its prevalence in the population remains unknown. However, delayed OH may be of significant medical interest because people with this condition are more likely to experience undiagnosed chronic hypotension, and numerous recent large-scale epidemiologic investigations have linked increased morbidity and mortality to chronic hypotension, specifically sustained DBP values below 70mmHg.[7-11]

Three mechanisms have been proposed to explain delayed OH: increased peripheral venous pooling, increased microvascular filtration, and gradual failure of the humoral and neuromuscular mechanisms that counteract the gravitational redistribution of fluid.[1] Upright posture serves to significantly increase the static fluid pressures in the circulatory system because of the gravity-driven hydrostatic pressures on the blood column. Venous vessels, like all biologic tissues, are viscoelastic so that under sustained static pressure the vessels walls will creep permitting increased pooling in the vessel over time.[12,13] Prolonged orthostasis also results in increased microvascular filtration of fluid from the capillaries into the dependent tissues, resulting in a 20% or greater decrease in plasma volume, even in young healthy people.[14] To counterbalance these processes, sustained orthostatic stress is typically associated with increased muscle sympathetic nerve activity.[15] These regulatory responses stimulate vessel constriction and increased muscle tone, which in healthy individuals serves to maintain or even increase blood pressure when upright. Of particular importance in this process is the tonic activity of the soleus muscle because it serves both as the primary means for maintaining upright stance and the primary lower leg muscle pump, which returns venous and lymphatic fluid from the dependent tissues back to the circulatory system.[16]

Recent studies on the stimulation of postural reflex pathways have shown that CMP activity can be exogenously enhanced, thereby assisting in the maintenance of blood pressure during

List of Abbreviations

BMI	body mass index
CMP	calf muscle pump
DBP	diastolic blood pressure
OH	orthostatic hypotension
SBP	systolic blood pressure

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orthostasis. Stimulation of the CMP can be achieved through micromechanical stimulation of the plantar surface, which activates the cutaneous mechanoreceptors used in postural maintenance.[17,18] Plethysmographic techniques have been used to show that reflex-mediated CMP stimulation approximately doubles the lymphatic return pressure in the leg.[19] Correspondingly, cardiovascular monitoring has shown that plantar stimulation is capable of limiting the acute blood pressure drop associated with orthostasis.[20] These observations suggest an approach for assessing the physiologic contributions to delayed OH. Specifically, techniques such as air plethysmography can be used to assess venous status and microvascular filtration rates in combination with plantar micromechanical stimulation to evaluate the role of calf muscle tone. In this study, we used these modalities to address the relative contributions of venous pooling, microvascular filtration, and CMP activity to the development of delayed OH during quiet sitting.

METHODS

The procedures in this study were conducted in accordance with the standards set by the 2000 version of the Declaration of Helsinki. The study protocol was approved by the Institutional Human Subjects Research Review Board at Binghamton University (State University of New York), and written informed consent was obtained from each participant before the session. All experiments were performed at Binghamton University's Clinical Science and Engineering Research Center from mid-March 2006 through late July 2006.

Participants

The study focused on adult women because this population shows the highest risk for the long-term complications associated with the sustained effects of chronic hypotension.[21,22] Nonpregnant women between the ages of 30 and 65 who were capable of understanding and following the study protocol and providing informed consent were recruited for the study. Individuals being treated for hypertension or with a previous diagnosis of hypertension were excluded from the study, as well as people with a history of deep vein thrombosis or who were lacking sensation on the plantar surfaces. During screening, the subjects' age, height, and weight were ascertained. BMI was determined as weight in kilograms divided by the square of body height in meters. Additionally, the distance from the head of fibula to the lateral malleolus was obtained to determine the appropriate cuff size for air plethysmography evaluation. After the initial screening, subjects with previously diagnosed hypertension or who were under therapy for hypertension were excluded from further testing.

Laboratory Evaluations

Air plethysmography. The quantification of venous status was performed through air plethysmography measurements of the right calf. The air plethysmography system[a] uses a tubular, polyurethane air cuff to surround the leg from knee to ankle so that changes in volume as a result of fluid volume changes in the calf produce changes in air chamber pressure. The leg cuff was inflated to a bias pressure of 6mmHg to ensure good contact between the cuff and the leg, and the system was calibrated by infusing 25 and 50mL of air into the cuff via a graduated syringe. Functional venous volume (in milliliters), venous filling index (in milliliters per second), and ejection fraction (percentage of total venous volume) parameters were assessed by methods previously described.[23,24] Briefly, the venous filling index was assessed by determining the venous filling rate as a function of venous volume after emptying the large veins by elevating the leg at a 45° angle for 60 seconds. Ejection fraction was assessed by determining the fluid volume ejected from the leg during a tip-toe stand as a fraction of the total venous volume. Peripheral pooling was calculated by linear regression analysis of the change in calf volume during 30 minutes of quiet sitting.

Continuous blood pressure acquisition. A servo-controlled, infrared plethysmographic, beat-to-beat, automated finger arterial blood pressure monitoring system (Portapres Model 2)[b] was used for continuous cardiovascular monitoring. Portapres uses a volume clamp method that dynamically unloads the arterial wall by using a pneumatic microcuff placed around a finger of the hand.[25,26] A height correction sensor detects height changes of the measured finger relative to the heart. Although peripheral blood pressure values measured by Portapres are typically 5 to 10mmHg lower than brachial pressures, they are in good concordance with invasively measured values[27-31] and are highly reproducible.[32,33]

Muscle pump activation by plantar stimulation. CMP stimulation was obtained through micromechanical stimulation of the mechanoreceptors of the plantar surface. The stimulation was achieved by using a custom device[c] that delivers sinusoidal 45-Hz, 50-μm mechanical displacement to the frontal portion of the plantar surface. This stimulus is sufficient to activate the fast-adapting mechanoreceptors on the plantar surface, with subsequent reflex-mediated activation of the calf muscles.[17,18,20,34]

Experimental Design

The examinations were conducted in a quiet, moderately lit, temperature-controlled room and were conducted between midmorning and early evening. After obtaining informed consent, the subjects removed their footwear and bracelets, rings, and wristwatches if they interfered with the placement of the blood pressure sensor. The subjects were subsequently instrumented with the air plethysmography leg cuff and Portapres blood pressure finger cuffs, with the height correction sensor placed over the sternum between the levels of the second and the third left intercostal space to provide the cardiac level calibration for the blood pressure measurements. A remote-controllable power recliner was used to lower the subjects into the supine position and raise them to the seated position without muscular effort.

Each subject served as her own control in the study. The overall duration of each session was approximately 90 minutes. After instrumentation, each subject underwent 20 minutes of quiet sitting, representing a controlled, extended orthostatic exposure. After 20 minutes of quiet sitting, venous status was assessed by elevating the right leg to empty the major veins of the leg followed by a transition to a 1-legged (left leg) stand to permit venous refilling and determination of the venous-filling index (primarily a measure of deep vein sufficiency). Subsequently, 3 toe stands, each separated by 10 seconds, were performed by the subject, permitting evaluation of the ejection fraction, a measure of CMP status. The subjects were then immediately returned to a seated position, and each subject completed an additional 60-minute quiet sitting session. During the first 30 minutes of this session, the swelling rate of the calf was monitored. In the course of the second 30 minutes of this session, the plantar surface of the subject was stimulated; calf volume continued to be monitored. The subjects were advised to relax and minimize any unnecessary motion of the left hand that could interfere with the blood pressure data collection; music was typically played during the recording session. Subject's breathing rate was not controlled. Blood pressure data collection was initiated at the start of the seated condition and

was continued throughout the protocol. Experimental criteria included termination of plantar micromechanical stimulation if the subject reached second-stage hypertension values corresponding to an SBP of 180mmHg or higher or a DBP of 110mmHg or higher, consistent with the exercise termination criteria of the American College of Sports Medicine.[35]

Data Acquisition and Analysis

Air pressure data from the air plethysmography, SBP, DBP, and heart rate signals from the Portapres units were continuously monitored with 24-bit resolution at a 1-Hz sampling rate (Biopac MP35/BSL Pro software).[d] Acute OH is defined, per consensus, as a 20-mmHg drop in SBP or 10-mmHg decrease in DBP after standing for 3 minutes or a 60° head-up tilt.[2] Because upright sitting is hydrostatically equivalent to a 50° head-up tilt, we applied this consensus definition to identify acute OH subjects. Furthermore, subjects who experienced a sustained and significant decline in their DBP after a minimum of 15 minutes of quiet sitting (ie, in the 15–30min interval) were categorized into the delayed OH group. Subjects with no change or an increase in DBP were categorized into the normotensive group. To determine the effect of calf muscle pump stimulation, the average of 120 measurements of blood pressure values collected over the last 2 minutes of the sitting regimen and the last 2 minutes of quiet sitting with plantar stimulation were also calculated.

Statistical Analysis

All data are expressed as means ± standard error of mean. The effects of age, height, and BMI on blood pressure were assessed using multiple regression procedures. Linear regression was performed on the beat-to-beat blood pressure spectra with a statistically significant negative slope used to identify delayed OH subjects. Pre- and poststimulational blood pressure values were compared by the Student *t* test. Inter- and intragroup analyses for both normotensive and delayed OH groups were determined by analysis of variance. Analyses were performed by using Origin[e] and SPSS[f] for Windows. A *P* value less than .05 was required to declare statistical significance.

RESULTS

Adult white women (N=33) residing in the Greater Binghamton Region of New York State were screened for this study. Three screened subjects were found to be on medication for the treatment of hypertension and so did not undergo any further study. Ten women reported noncardiovascular-related health conditions. The subjects who completed testing in this study (N=30) ranged in age from 34 to 62 years (mean age, 50.3±1.4y), with a mean BMI of 27.3±0.9kg/m^2 (table 1). The average SBP and DBP values for the total study population measured during the first 2 minutes of the quiet sitting protocol were 112.7±2.4 and 60.5±2.0mmHg, respectively. Although blood pressure has been reported to be correlated to age, height, and BMI, in this population none of these parameters approached statistical significance when included in multiple-regression analyses against SBP and DBP.

Table 1: Subject Anthropometric Data

Variable	Total Group (N=30)	Normotensive Group (n=21)	Delayed OH Group (n=9)
Age (y)	50.3±1.4	50.2±1.7	50.5±2.3
Height (cm)	163.6±1.0	165.0±1.0	160.3±2.0
Weight (kg)	73.4±2.7	72.6±3.3	74.8±5.3
BMI (kg/m^2)	27.3±0.9	26.6±1.1	28.8±1.3

NOTE. Values are mean ± standard error of mean.

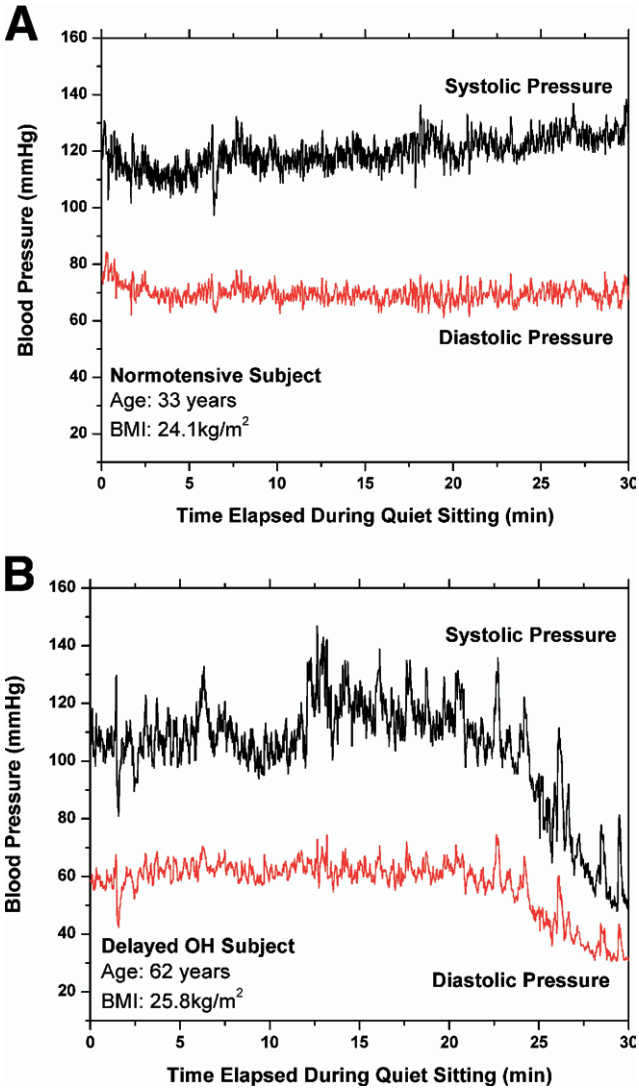

Fig 1. A representative SBP and DBP profile obtained by continuous blood pressure monitoring during 30 minutes of quiet sitting from a (A) normotensive subject and (B) delayed OH subject.

The majority of subjects showed a rise in both SBP and DBP after taking a seated position (fig 1A). Twenty-one subjects showed this normotensive response. No subjects showed a classical acute OH (20-mmHg drop in SBP or 10-mmHg drop in DBP after 3 minutes of quiet sitting). Delayed OH (defined as a statistically significant fall in DBP after at least 15 minutes of quiet upright sitting) was observed in 9 subjects (fig 1B).

The normotensive group (n=21) had an average initial DBP of 63.9±0.4mmHg that increased to 65.3±0.9mmHg after 15 minutes of quiet sitting. At the end of the 30-minute sitting regimen, this group's mean DBP was significantly elevated to 71.6±1mmHg (*P*=.001) (fig 2). In contrast, the delayed OH group (n=9) had an initial resting DBP value of 54.2±0.3mmHg that increased to 58.8±0.4mmHg within 15 minutes but was followed by a significant decline to 52.9±0.9mmHg at the completion of the 30-minute quiet sitting regimen (*P*=.02).

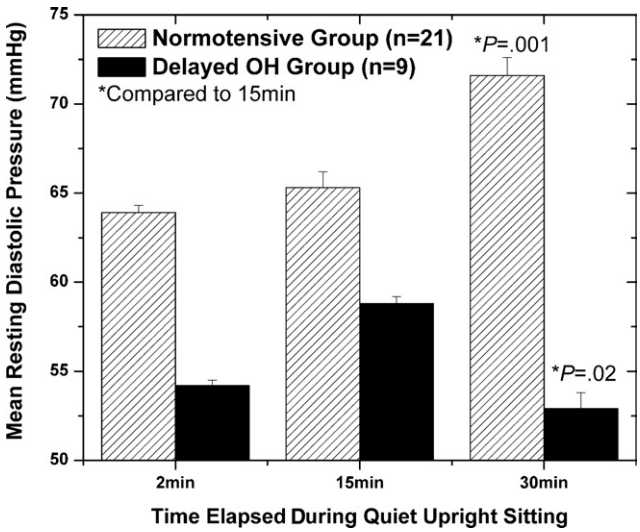

Fig 2. The mean resting DBP of the study population 2 minutes, 15 minutes, and 30 minutes after sitting. The normotensive group (n=21) exhibited a significant increase in DBP (*P*=.001) during 30 minutes of quiet upright sitting (71.1±1.0mmHg) in comparison to the 15-minute time point (64.2±0.9mmHg). The delayed OH group (n=9) experienced a significant decrease in resting DBP (53.1±0.9mmHg, *P*=.02) compared with the 15-minute time point (59.8±0.4mmHg).

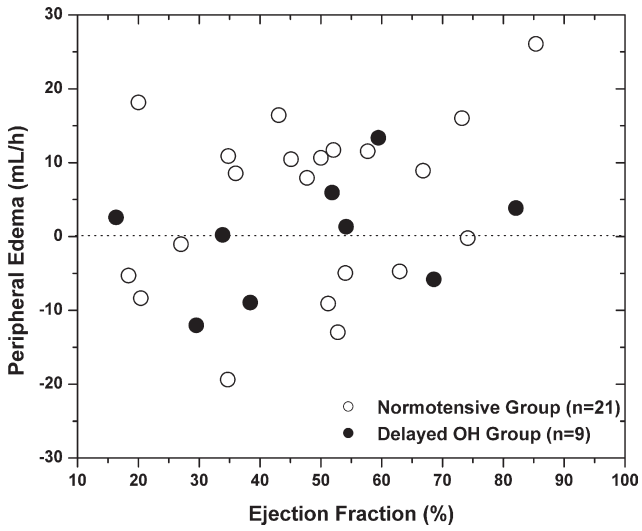

Fig 4. Peripheral edema (index of microvascular filtration) and venous ejection fraction after 30 minutes of upright sitting. Six subjects (4 from the normotensive group; 2 delayed OH group) had an ejection fraction less than 30%. Four normotensive subjects showed higher peripheral edema rate than any of the delayed OH subjects. Legend: ●, delayed OH group; ○, normotensive group.

Venous and microfiltration status assessment of the study subjects indicated that none of the subjects showed excessive venous or interstitial fluid pooling after 20 minutes of quiet sitting. Venous volume and venous filling index values were in the normative range of 20 to 80mL and less than 2.5mL/s, respectively (fig 3). The peripheral pooling values for the delayed OH group ranged between −12 and 13mL/h, whereas the normotensive group were in the range of –20 to 26mL/h. Six subjects were observed to have an ejection fraction 30% or less (the threshold for diagnosing venous varicosity), with 2 subjects from the delayed OH group and 4 from the normotensive group (fig 4).

For the overall population, CMP stimulation resulted in a consistent and significant increase in SBP and DBP. The average increase in SBP and DBP in all the subjects was 13.1±2.4 and 9.7±2mmHg, respectively. Within the delayed OH group, the increase in DBP ranged from 6 to 44mmHg (mean, 20.9±3.3mmHg; *P*=.002), whereas the increase in SBP caused by the stimulation ranged from 7 to 39mmHg (mean, 22.8±3.9 mmHg; *P*=.003) (fig 5).

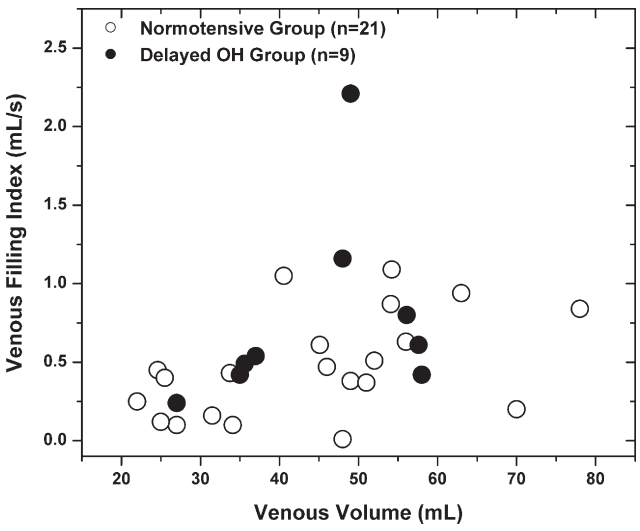

Fig 3. The venous-filling index and calf venous volume for all study subjects. The venous-filling index was in the normative range (≤5mL/s) for all the subjects, as was calf venous volume (20–80mL). Legend: ●, delayed OH group; ○, normotensive group.

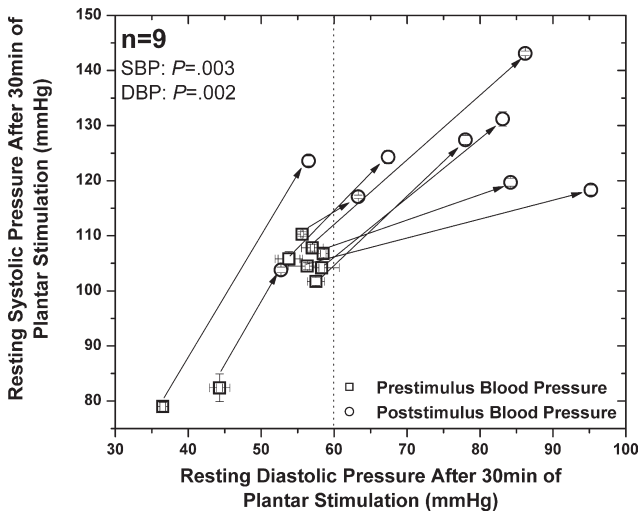

Fig 5. Effect of 30 minutes of plantar micromechanical stimulation on both SBP and DBP of 9 subjects in the delayed OH group. Both SBP (*P*=.003) and DBP (*P*=.002) values were significantly increased because of stimulation in comparison to values observed after 30 minutes of quiet upright sitting. Legend: □, blood pressure after 30 minutes of upright sitting; ○, blood pressure values after 30 minutes of plantar-based stimulation.

DISCUSSION

Because chronic hypotension and its complications are more common in women, we focused on women in this initial study of delayed OH. Preliminary data from our laboratory suggest that the prevalence of delayed OH among white adult males below 75 years of age is less than 10%, although it may be more common in older men. Furthermore, in this investigation, we used prolonged quiet sitting as a means to provide an orthostatic challenge to our study subjects. Although tilt table studies are commonly used for orthostatic investigations, recent work has shown that tilt table testing can cause psychologic[36] and physiologic stresses leading to blood pressure changes unrelated to orthostasis.[37] Correspondingly, tilt table challenge leading to autonomic responses correlates poorly with postural blood pressure measurements.[38] Hence, quiet sitting was used both for experimental convenience and as a nonpsychologically stressful means of producing orthostatic hemodynamic stress equivalent to 50° head-up tilt.[39] In our laboratory, this technique is associated with an intrasubject coefficient of variation of 10% for orthostatically induced changes in SBP and DBP. Although delayed orthostatic hypotension is typically defined as OH developing well after the 3-minute cutoff used to distinguish acute OH, by using an orthostatic challenge extending for 30 minutes,[1] this study design provided adequate time to detect a sustained blood pressure drop and therefore adequate power (>98%) and sensitivity (α=.001) to detect subjects with delayed OH even for the relatively small number of delayed OH subjects (n=9) identified in this study.

Although we identified no subjects with acute OH, 1 subject showed a drop in DBP of 12mmHg within 6 minutes of taking a seated position, although her blood pressure recovered within 10 minutes. Because the prevalence rate for acute OH has been estimated to be less than 7%, this result is consistent with our expectations for a population drawn from a pool of healthy working women.[40] That our 1 subject with transient OH had a BMI of 35kg/m^2 is also consistent with the higher prevalence of acute OH episodes in individuals with high BMI.[41]

Recent work[1] has suggested that delayed OH is likely to be a consequence of venous insufficiency, excessive microvascular filtration, or inadequate CMP activity. Venous status measurements in our study population, however, did not indicate that venous impairment was playing any significant role in delayed OH because the venous filling index and venous volume values for our study subjects were all within the normative range. One delayed OH subject had the highest venous-filling index value (2.25mL/s) observed in our study population, but this value is still well below the diagnostic cutoff of 2.5mL/s for venous insufficiency.[42] Furthermore, microvascular filtration assessment through the evaluation of peripheral edema did not substantiate its role in the development of delayed OH. Four subjects in the normotensive group had higher levels of peripheral edema than any of the delayed OH subjects, suggesting that excessive capillary transudation of fluid is not a significant factor in the development of this condition.

Because CMP activation served to reverse the delayed drop in blood pressure, essentially returning both SBP and DBP to the levels observed in the normotensive population after 30 minutes of sitting, we suggest that delayed OH may primarily be the result of loss of tonic calf muscle activity resulting in inadequate fluid return to the heart. However, given that we were able to stimulate CMP activity through a postural reflex pathway seems to suggest that this reflex arc mechanism, as well as the muscle itself, is functionally intact. That in the absence of exogenous stimulation this muscle group is not performing adequately leads to several hypotheses as to the specific physiologic failure in delayed OH. One possibility is that an alternative (nonpostural) reflex pathway that normally provides the CMP activation has failed in the delayed OH population. Alternatively, it is possible that the plantar-based postural reflex is involved but that the activation thresholds for the plantar mechanoreceptors have increased to the point in which only exogenous stimulation is adequate to activate these receptors. Finally, it may be that the difference between the normotensive and delayed OH population is a difference in muscle fiber distributions, with the delayed OH group having lost the majority of their type IIA fibers and, therefore, they could not sustain extended CMP function. If this is the case, then it may be that training up of the calf muscles, either through postural exercises or through exogenous muscle-stimulation techniques, may be sufficient to ameliorate the complications of delayed OH through stimulation of a reconversion of type IIB fibers back to type IIA fibers.[43,44]

Perhaps the greatest medical concern with respect to delayed OH is that it places the individual at an increased risk of chronic hypotension and the associated risks of cerebrovascular degeneration and dementia, and this potential link served as the primary motivation for undertaking this study. The relationship between low blood pressure and dementia has been observed in several large-scale epidemiologic studies, including the Chicago Health and Aging Project,[45] the East Boston Project,[9] the Bronx Aging Study,[11] and others.[10] In these studies, chronic low DBP (between 60–70mmHg) was found to be associated with a 2- to 6-fold increase in risk for the progression of dementia, vascular dementia, and Alzheimer's disease. The cerebral hypoperfusion resulting from chronic hypotension has also been implicated in diminishing functional status, concentration, and cognitive function, particularly in the elderly.[7] In addition, chronic hypotension is a significant early predictor of the development of depression[46] and chronic fatigue,[8,47] a condition that is approaching epidemic status with reports of prevalence ranging from 10% to 40% in primary care patients,[48-51] with 75% of the afflicted being women.[21,52] For these reasons, we have focused primarily on DBP in this study, although we recognize that relying on DBP to make a clinical diagnosis of delayed hypotension may be inappropriate.

In this context, it is interesting to note that CMP stimulation was observed to significantly increase the DBP levels in all the subjects within the delayed OH group. Indeed, in 7 of 9 subjects with delayed OH, DBP values were elevated beyond 60mmHg. In 2 delayed OH subjects, DBP was substantially elevated by CMP stimulation but remained below 60mmHg after 30 minutes of stimulation. It is possible that a longer duration of stimulation may have elevated these individuals' DBP beyond the 60-mmHg threshold. Nonetheless, it is important to point out that this study did not address the question of whether these subjects with delayed OH were, in fact, chronically hypotensive.

Study Limitations

Limitations of this study include both technical and demographic factors. Although Portapres provides a convenient means for recording beat-to-beat blood pressure in a noninvasive manner, it does tend to report values below brachial pressures and has been reported to drift over extended (multiple hours) recording times. We limited our study to 90 minutes to minimize the influence of drift, and, by using a threshold for clinically significant low DBP of 60mmHg rather than the 70mmHg reported in the literature, we compensated for the fact that our finger blood pressure recordings may be lower than brachial blood pressures.

We have also relied on quiet, upright sitting to provide the orthostatic stress to initiate the delayed hypotension. Although upright sitting is hydrostatically equivalent to a 50° head-up tilt, there are differences in hydrostatic pressure distributions between these 2 interventions. Specifically, although the orthostatic pressures at the ankle will be the same in both cases, orthostatic pressures will be higher at the hip and lower at the knee in the seated position in comparison to 50° tilt. Because the pelvic region represents the largest volume in the body for fluid pooling, this may mean that quiet sitting presents a somewhat greater stress on the cardiovascular system than a 50° head-up tilt.

From a demographic perspective, because we studied only women, our results do not necessarily apply to men. If previous results from our laboratory on low failure rate of the CMP in men can be extrapolated to delayed OH, we would anticipate a much lower prevalence of delayed OH in men. Furthermore, the generalizability of these results to the larger female population is not clear because our subject group was composed of white women actively employed in office work. According to the U.S. Bureau of Labor Statistics, such a group represents about 20% of American women.[53] Women of a different racial background or different daily activity pattern may be more or less prone to delayed OH. Beyond demographic issues, our protocol did not involve the acquisition of data on factors such as meal consumption, prior exercise or physical activity, or the hormonal status of our subjects. However, recent investigations[54,55] on the influence of the menstrual cycle on orthostatic tolerance seem to rule out this latter factor. Similarly, different socioeconomic (educational and occupational), environmental, emotional, and psychosocial backgrounds may alter the proportion of delayed OH women in a population.

CONCLUSIONS

About 25% of healthy adult women in our study population showed delayed orthostatic hypotension. Because our subjects showed normal vascular and microvascular performance, the predominant cause of their delayed OH appears to be inadequate calf muscle tone because CMP stimulation was sufficient to reverse this hypotension.

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Suppliers

a. ACI Medical Inc, 1857 Diamond St, San Marcos, CA 92078.
b. Portapres model 2; TNO-BMI, Paasheuvelweg 34a, NL-1105 Amsterdam ZO, The Netherlands.
c. Juvent Medical Inc, 300 Atrium Dr, Somerset, NJ 08873.
d. Biopac Systems, 42 Aero Camino, Goleta, CA 93117.
e. Version 7.5; Origin Lab Inc, One Roundhouse Plz, Ste 303, Northampton, MA 01060.
f. Version 13.0; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.