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Cardiomyopathy in Women: Second Heart Failure

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1. Introduction

Heart failure is characterized by the inability of the heart to maintain sufficient cardiac output (CO) to meet the metabolic demands of the body. Reduced CO activates compensatory mechanisms directed towards reestablishing CO, thereby initiating a cycle which can lead to cardiomyopathy. Therapeutic strategies for addressing heart failure have been developed primarily based on studies of male populations; however, heart failure in women has a distinct phenotype. In women, heart failure develops later in life, generally presents with preserved systolic function, and is less commonly attributable to ischemic heart disease. In many women, the initiating event in heart failure is extrinsic, specifically, poor venous return resulting from inadequate calf muscle (soleus) pump activity during upright posture. Such “second heart” failure has been identified in approximately half of all adult women, an observation which helps to explain the fact that while women’s survival rate with heart failure is better than in men, their quality of life with heart failure is far worse. A determination that inadequate venous return is arising from calf muscle pump failure can permit effective early intervention to slow or reverse cardiomyopathy, while significantly improving quality of life in affected women.

2. Extrinsic cardiomyopathy

Cardiomyopathies are a group of diseases of the myocardium reflecting mechanical and/or electrical dysfunction of the heart [1], and can be delineated as being either intrinsic or extrinsic. Intrinsic cardiomyopathies are those which originate in the heart muscle cells, and includes both conditions which typically influence the cardiac muscle cells alone (primary cardiomyopathy) and systemic disorders which affect other tissues in the body in addition to cardiac muscle tissue (secondary cardiomyopathy). Primary cardiomyopathies are commonly genetic or acquired (e.g. inflammatory, physical stress, or physiologic stress induced). Secondary

cardiomyopathies span a broad spectrum of etiologies including inflammation, toxicity, infiltrative, endocrine, nutritional, autoimmune, electrolyte imbalance, and neuromuscular.

In contrast, extrinsic cardiomyopathies arise due to conditions which do not directly produce heart muscle cell abnormalities. These include the well known conditions of ischemia, hypertension, diabetes, and alcohol abuse, but also the less commonly considered condition of insufficient venous return. Insufficient venous return results in inadequate atrial filling and a correspondingly decreased CO. Decreased CO initiates a range of compensatory responses which eventually lead to progressive heart failure. Lower limb edema, as well as ascites development, are emblematic of inadequate fluid return to the right atrium, and fatigue is common as the heart cannot maintain sufficient CO to meet the body's metabolic needs. Nausea and loss of appetite arise as blood is shifted from the gastrointestinal tract to the vital organs, and palpitations occur as the heart adapts to reduced stroke volume by increasing the heart rate [2]. This latter compensatory mechanism induces cardiac stress and systolic hypertension, eventually leading to cardiomyopathy.

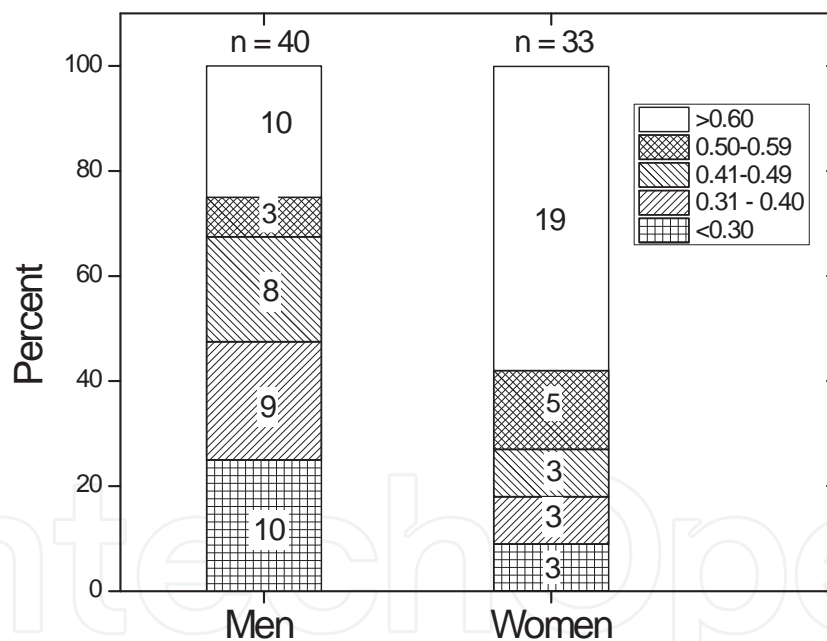


Figure 1. Left ventricular ejection fraction in men and women with congestive heart failure. *After Vasan, et al. 1999.*

Heart failure arising from inadequate fluid return to the heart is most commonly experienced by women. It is well recognized that while half of heart failure patients are women [3], the characteristics of heart failure in women differ substantially from those observed in men. Specifically, heart failure develops later in life in women, is commonly associated with preserved systolic function (Figure 1) [4], less commonly involves ischemia, and, while sur-

vival rates are higher than for men, women with heart failure have a far worse quality of life [5]. The crucial link between maintaining adequate fluid return, and therefore cardiac output, and heart failure is reflected in the ability of resting heart rate to strongly and independently predict coronary events in women [6]. In a recent study of over 100,000 postmenopausal women, resting heart rate was found to predict myocardial infarction or coronary death with a risk ratio of 1.6 (95% confidence interval of 1.49-1.89) when comparing the highest (>76 bpm) to the lowest (<62 bpm) quintiles of resting heart rate.

3. Anatomic and physiologic influences on venous and lymphatic return

When ventricular function is preserved, the critical factor regulating CO is end-diastolic volume, which, through the Frank-Starling mechanism provides a non-neural, non-humorally mediated, regulation of stroke volume. End-diastolic volume is a function of venous and lymphatic return to the heart, which correspondingly, are dependent on circulatory system volume and venous/lymphatic system pressure. The importance of lymphatic return is not widely appreciated in the context of maintenance of circulatory volume, and venous pressure is often considered only in the context of high venous pressure being an indicator of heart failure. However, to fully understand extrinsic heart failure it is necessary to consider the profound influence of upright posture on venous and lymphatic return.

In supine posture, fluid pressures in the arterial system are approximately 100 mmHg, and pressures in the venous system range from 15-20 mmHg in the smallest vessels to approximately 5 mmHg at the right atrium. The driving pressure to return venous blood back to the heart is therefore only 10-15 mmHg, or approximately 13-20 cm of water. Nonetheless, in the supine position this pressure is typically adequate to return venous blood from the lowest part of the body (typically the buttocks) back to the heart. In the upright position, however, hydrostatic forces (i.e. gravitational forces operating on the venous fluid column) add significantly to arterial, venous, and capillary pressures. At the right atrium, fluid pressure drops to zero. Above the atrium, venous pressures become negative, venous blood readily flows back to the heart and the veins collapse. At the same time, hydrostatic forces serve to reduce arterial pressures by 40mmHg at the top of the head, and if this reduces arterial pressure below 60 mmHg, regulation of cerebral perfusion can be significantly affected [7].

Below the heart, venous pressure increases progressively with distance below the heart such that at the level of the feet venous pressure can exceed 100 mmHg; yet the driving return pressure (i.e. capillary pressure) remains at approximately 20 mmHg. Moreover, blood return to the heart must take place through the highly distensible venous system so that the volume of the venous system has the potential to increase significantly in upright posture. Hydrostatic effects also increase pressures in the arterial system below the heart, though the thick walled structure of arteries prevents significant dilation. However, the increased pressures in the capillaries result in increased extravasation, resulting in significant pooling of interstitial fluid until interstitial fluid pressures increase to match capillary pressures (Figure 2) [8].

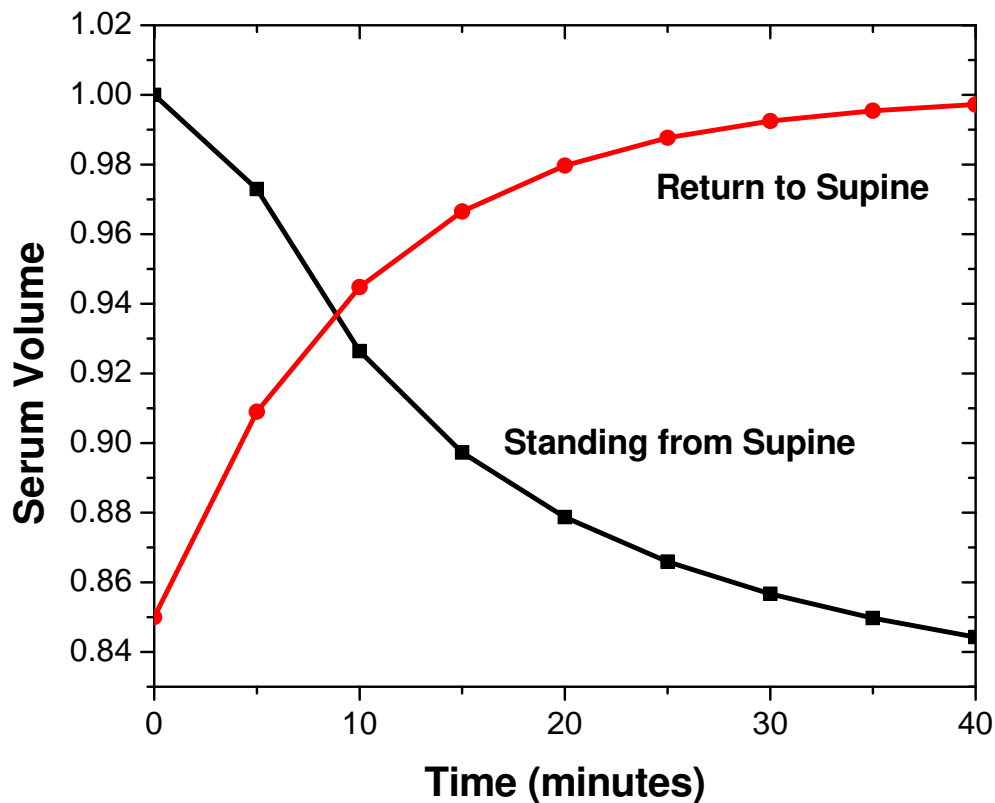


Figure 2. Fractional blood volume changes associated with postural shifts in young adult men. After Hagan, et al., (1978) *J. Appl. Physiol.* 45:414-417

The net effect of these various processes is that 500-600 ml of blood pools into the lower limb veins within 2-3 minutes after attaining upright posture, while increased filtration from the capillaries reduces blood fluid volume by an additional 750 ml over the following 30-40 minutes, resulting in well over 1L decrease in effective circulatory system volume. The upright human therefore is confronted with three significant challenges with respect to maintaining adequate CO. First, fluid pooling into the lower limb veins and dependent tissues rapidly reduces effective blood fluid volume. Second, the fluid pressure available to return blood to the heart from the lower extremities remains at little more than 20 mmHg, which is incapable of overcoming the 80 mmHg of hydrostatic pressure created by the venous fluid column. Third, the high compliance of human skin allows these conditions to become exacerbated over the course of the day through interstitial fluid build up. This stress of upright posture is particularly challenging for women in that they have both more compliant veins [9], and somewhat more compliant skin [10].

4. Soleus muscle anatomy/physiology

The cardiovascular challenges of upright posture are, in part, overcome by neuro-humorally mediated venoconstriction which limits venous pooling, though vasoconstriction has essen-

tially no effect on interstitial fluid pooling nor on venous and lymphatic return pressures. Further, during locomotion it is well recognized that skeletal muscle pumping serves to drive venous blood back to the heart; however, for most people, for the vast majority of the time they are in upright posture, they are either standing or sitting quietly, not in ambulation. Correspondingly, the essential features of human physiology which permits long-term upright posture are the second heart (soleus muscle) combined with competent venous and lymphatic valves. In upright posture (sitting or standing) venous pressure alone is sufficient to pump blood only one-third of the distance up the lower leg. This blood then collects in the venous sinuses of the soleus muscle. These sinuses are large, thin-walled veins which have the capacity to hold large volumes of blood and the soleus muscle can have up to 18 such sinuses [11]. While the sinuses themselves are valveless, the indirect perforating veins feeding the sinuses are valved, as well as the posterior tibial and peroneal veins into which the soleus sinuses drain. These valves play a crucial role in the effectiveness of the calf muscle pump (CMP), providing an opportunity for the pump to incrementally force venous blood back to the heart. Importantly, the soleus is a deep postural muscle, and correspondingly is composed of more than 70% slow-twitch muscle fibers [12]. Moreover, the soleus originates on the posterior tibia and fibula such that when either standing or seated the muscle is able to be active, producing slow, continuous rhythmic, involuntary contractions. During contraction, the soleus can generate venous driving forces exceeding 200 mmHg, more than sufficient to force the blood in the sinuses back to the heart [13].

The soleus also plays an essential role in ensuring lymphatic drainage back to the heart. Collecting lymphatics, which appear downstream in the lymphatic system, contain smooth muscle cells in the media and therefore the ability for spontaneous contractions sufficiently large to pump lymph fluid back to the heart (fluid pressures in the collecting lymphatics is relatively low as the fluid column is not continuous) [14]. However, the initial lymphatics, which are the site of interstitial fluid absorption, are non-muscular, and so require an extrinsic force in the surrounding tissue to create a periodic driving pressure gradient. This force can arise from arterial pressure pulsations and arteriolar vasomotion, and muscle contraction. In the lower limbs, the involuntary contractile activity of the soleus, which typically is the sole active muscle in the lower leg during quiet sitting or standing, therefore provides a critical extrinsic periodic compression of these lymphatics, driving the lymph fluid in the initial lymphatics upward toward the collecting lymphatics, relying on endothelial microvalves to ensure unidirectional flow.

5. Second heart failure in women

The essential role of non-locomotory based calf muscle pumping (i.e. second heart activity) in maintaining CO when individuals are in quiet upright posture, raises the question of the extent to which second heart activity varies within the population. Recent studies in our laboratory have focused on identifying the extent of second heart insufficiency in adults, with a particular focus on the prevalence of second heart failure in women. The predictive ability of resting heart rate in identifying women at greatest risk of experiencing coronary events suggests that

tracking heart rate during the transition from standing to quiet sitting should be an effective means to quantify second heart capability. Moving from a standing to seated position represents a decrease in both physical stress on the cardiovascular system (i.e. a reduction in the hydrostatic forces operating on the venous fluid column and therefore a reduction in pooling forces), and a reduction in physiologic stress (i.e. reduced metabolic activity). Quiet sitting, therefore, should result in a decrease in heart rate in otherwise healthy individuals.

We monitored heart rate in adult women (N=20) for 20 minutes following a transition from standing to quiet sitting [15]. Initial heart rate in this population of self-reported healthy women (average age = 52 ± 4 years) was 77.5 ± 3.5 bpm. In nine of these women (45%), heart rate decreased 1-8 bpm as expected (Figure 3) [15]. However, in 55% of the tested women (N=11), 20 minutes of quiet sitting led to a 6-12 bpm increase in heart rate (avg. 8.3 ± 0.5 bpm). Consistent with this increase in resting heart rate, brachial systolic blood pressure in this group of women was observed to fall by average 9.5 ± 1.8 mmHg from an initial average pressure of 122.4 mmHg (± 3.6 mmHg).

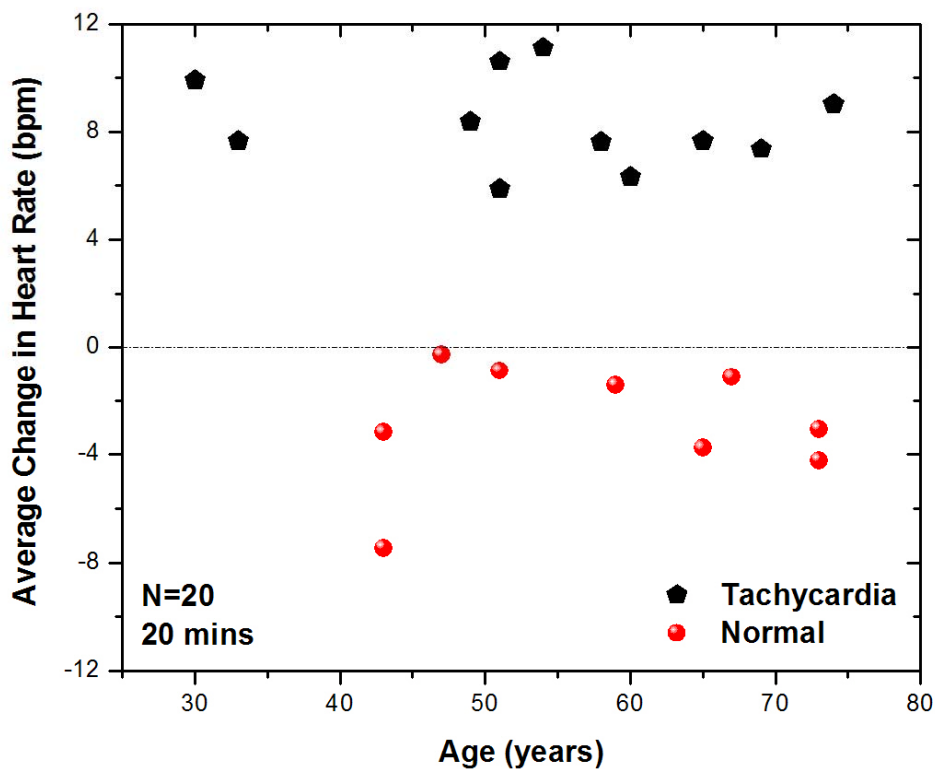


Figure 3. Change in systolic blood pressure in healthy adult women following 20 minutes of quiet sitting. From Madhavan, et al., 2005.

Though approximately 50 percent of women appear to be able to maintain adequate fluid return from the lower limbs to support CO during 20 minutes of quiet sitting, 20 minutes is a

relatively short time period in the context of typical durations of sitting which most individuals experience during the day, and so does not directly address the challenge women face during extended upright posture given the high venous and skin compliances previously discussed. To address the impact of extended orthostatic stress, we have monitored beat-to-beat blood pressure changes during quiet sitting periods of over 30 minutes [16]. This research was motivated by recent reports of delayed orthostatic hypotension (DOH), a condition observed in 40% of individuals with symptoms of orthostatic intolerance, but with no evidence of acute orthostatic hypotension as assessed through traditional tilt-table testing [17]. We have observed that among women who appear to be able to maintain CO during quiet sitting, for approximately 30% of such women this capability is transient. We observe in these women that following 20-30 minutes of sustained quiet sitting, fluid return to the heart rapidly falls and resting blood pressure cannot be maintained (Figure 4) [16]. This inability to maintain resting blood pressure is particularly striking with respect to diastolic pressure as the average diastolic pressure in this group was found to fall to an average of 53 mmHg (± 0.9 mmHg) after 30 minutes of quiet sitting (Figure 5) [16], a value well below that necessary to adequately regulate cerebral perfusion.

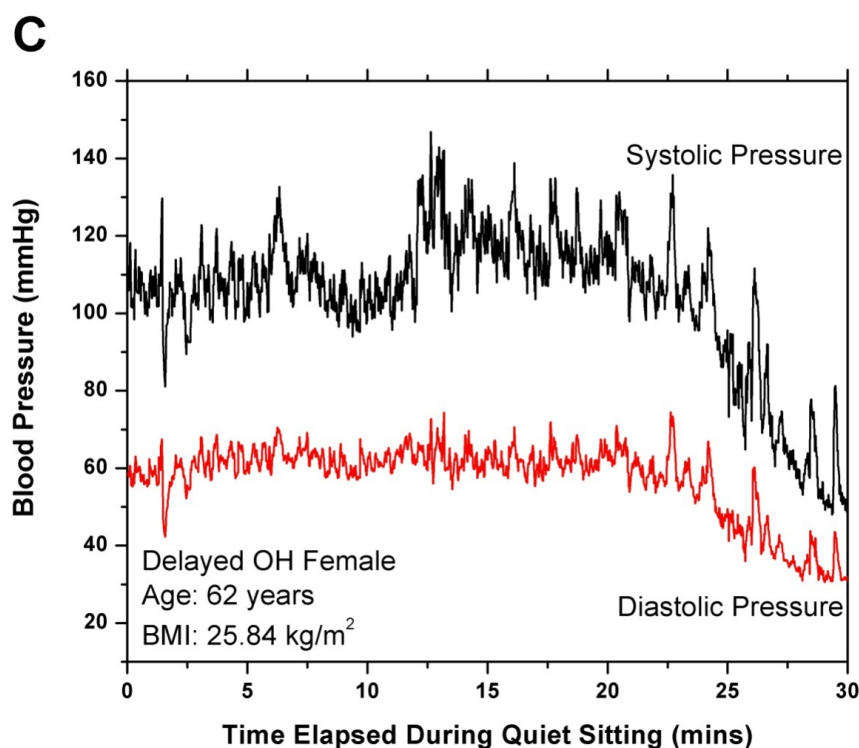


Figure 4. Typical blood pressure response to 30 minutes of quiet sitting in an adult woman with delayed orthostatic hypotension. From Madhavan et al., 2008.

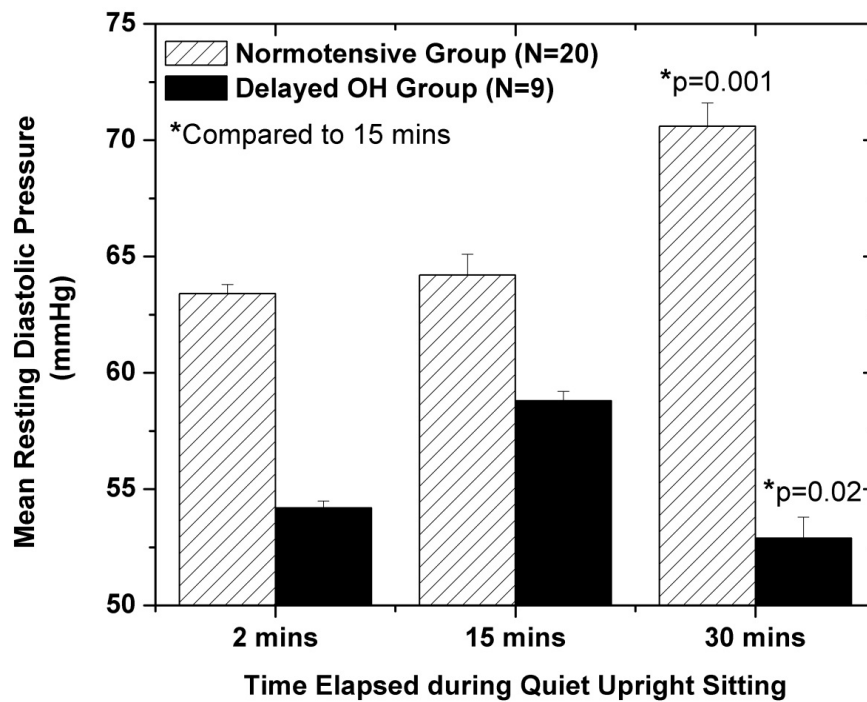


Figure 5. Time dependent changes in resting diastolic blood pressure in 29 adult women capable of maintaining HR and BP for the first 20 minutes of quiet sitting. Twenty women (70%) demonstrated a normotensive response to 30 minutes of the orthostatic stress of quiet sitting, while 9 (30%) demonstrated a distinct delayed orthostatic hypotensive response. *From Madhavan, et al., 2008.*

Similarly, a large fraction of women have been observed to experience extensive interstitial fluid pooling during quiet sitting. The high compliance of human skin, and women's skin in particular, creates a scenario in which extended duration orthostatic stress can permit extensive extravasation from the blood supply without the development of high tissue pressures which would inhibit this flow. To determine the extent to which this phenomenon could play a significant role in reducing fluid return to the heart, and correspondingly, maintaining CO, we utilized air plethysmography to follow calf volume over time in healthy adult women sitting quietly [18]. Fifty-four adult women (average age 46.7 ± 1.5 years) were recruited. After being placed in the supine position, the right calf was instrumented for air-plethysmographic recording and the recording system was allowed to equilibrate to body temperature (approximately 30 minutes). The subject was then transitioned to the upright seated position and calf

volume was continuously monitored for another 30 minutes. Two distinct subpopulations could be readily delineated according to their interstitial pooling behavior (Figure 6) [18]. Approximately half of the women experienced a significant decrease in calf fluid volume during the 30 minutes of quiet sitting at a median rate of 8 ml/hour, while half demonstrated significant calf swelling at a median rate of 12 ml/hour under these conditions.

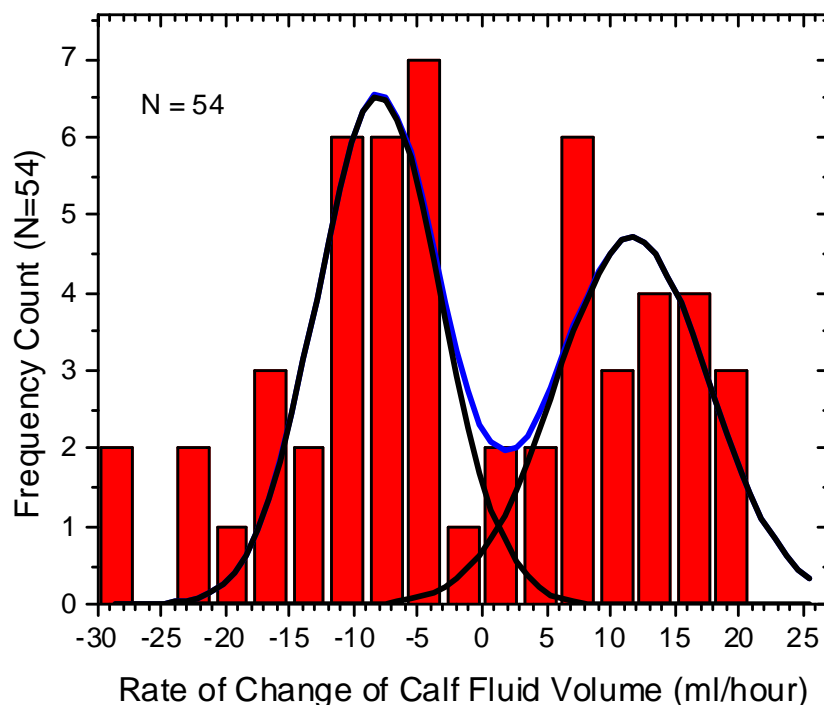


Figure 6. Interstitial fluid swelling of the calf during quiet sitting in a population (N=54) of healthy adult women. Bi-modal distribution of pooling responses indicates that 55% of the subjects experienced decreased calf fluid volume while 45% were found to pool interstitial fluid into the calf at an average rate of 12ml/Hr. *From Goddard et al., 2008.*

While women who experience increased venous and interstitial pooling tend to be somewhat heavier, on average, than those that maintained their HR, BP, and calf volume during extended sitting, no significant differences in age, weight, or BMI have been identified. Moreover, these individuals do not demonstrate any frank failure of the circulatory system as measured by microvascular filtration rate, venous ejection fraction, venous filling index, or calf venous volume. Importantly, these responses do not reflect the behavior of just a small subset of women, but rather 50% or more of an otherwise healthy population of women. The most likely explanation for these observations appears to be inadequate calf muscle pump (second heart) activity, though this can only be confirmed through direct intervention by second heart stimulation.

6. Intervention for second heart failure

The soleus muscle operates primarily as an involuntary postural muscle whose activity is mediated by two different reflex arcs. In addition to the stretch reflex associated with venous sinus filling and emptying, the soleus is the primary lower leg muscle supporting upright stance. As such, its activity is mediated by a postural reflex arc originating on the frontal plantar surface. That is, pressure on the frontal aspect of the plantar surface during standing results in contraction of the soleus which pulls the body in the posterior direction; this unloads the frontal plantar surface, resulting in the soleus relaxing, and the body stops its posterior motion and begins to sway forward. While the stretch reflex appears to fail in a large fraction of adult women, very few of these individuals have any difficulty standing upright, indicating that the postural reflex arc controlling soleus activity is intact. This observation sets the stage for a convenient method to exogenously activate the soleus muscle.

We have pursued this hypothesis that the postural reflex arc regulating soleus activity is intact in women with inadequate fluid return from the lower limbs, and our experimental results support both the contention that this postural reflex is operational, and that exogenous activation of this soleus reflex arc is sufficient to significantly increase venous and lymphatic return from the lower limbs. Initial work focused on identifying the characteristics of the stimulus necessary to activate the soleus reflex and we observed that a micromechanical stimulation of plantar surface at 45 Hz, with a magnitude of 10 micrometers or greater was sufficient. This observation is consistent with the activated mechanoreceptors on the foot being the Meisner corpuscles [19]. A stimulus of this nature applied to the frontal plantar surface was found to completely block the drop in BP and increase in HR observed in women who could not maintain fluid return from the lower limbs during quiet sitting (Figure 7) [15]. Further studies on the mechanism underlying these clinical observations have shown that the plantar reflex stimulation has no effect on lymphatic microfiltration rate, but rather increases the isovolumetric lymphatic pressure, as well as significantly enhancing perfusion in the lower leg, pelvic, and thoracic segments of the body [20].

As importantly, activation of the second heart (soleus) has been found to effectively inhibit interstitial fluid pooling in adult women [17]. Following a 30 minute quiet sitting period during which a population of women (N=24) were observed to pool extensively (using air plethysmography), the subjects were exposed to 20 minutes of continuous plantar stimulation sufficient to activate the soleus muscle. Activation of the stimulus was found to result in an immediate drop in calf volume, which is interpreted to be due to the rapid decrease in venous volume (Figure 8) [17]. This rapid volume decrease was then followed by a sustained slower decrease in calf volume consistent with interstitial fluid migration to the initial lymphatics with subsequent ejection to the collecting lymphatics and back to the heart. Sustained stimulation with continuous blood pressure monitoring confirms that the ejected fluid is returning to the heart per the associated increase in systolic blood pressure (Figure 9) [21].

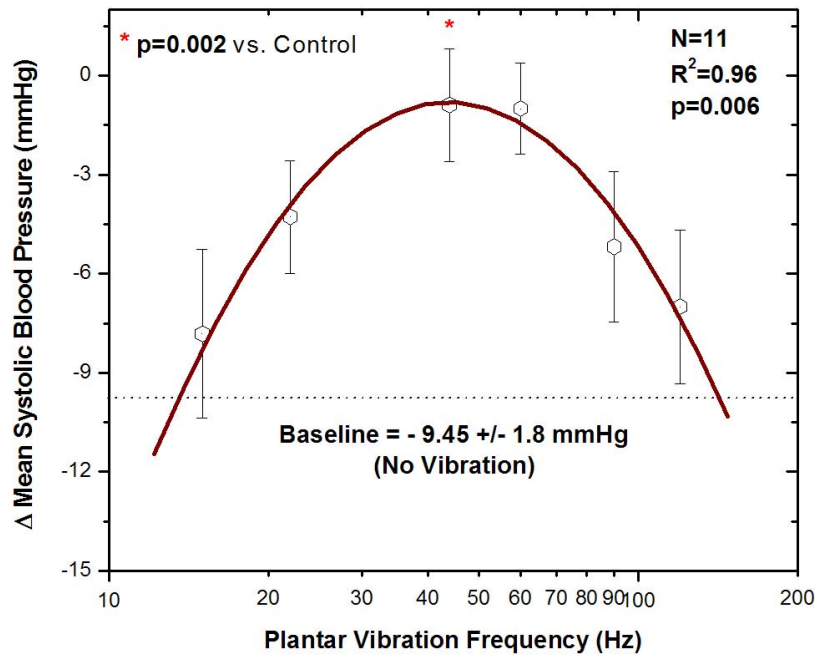


Figure 7. Efficacy of soleus muscle activation, through its postural reflex arc, to prevent blood pressure drop in adult women. From Madhavan, et al., 2005.

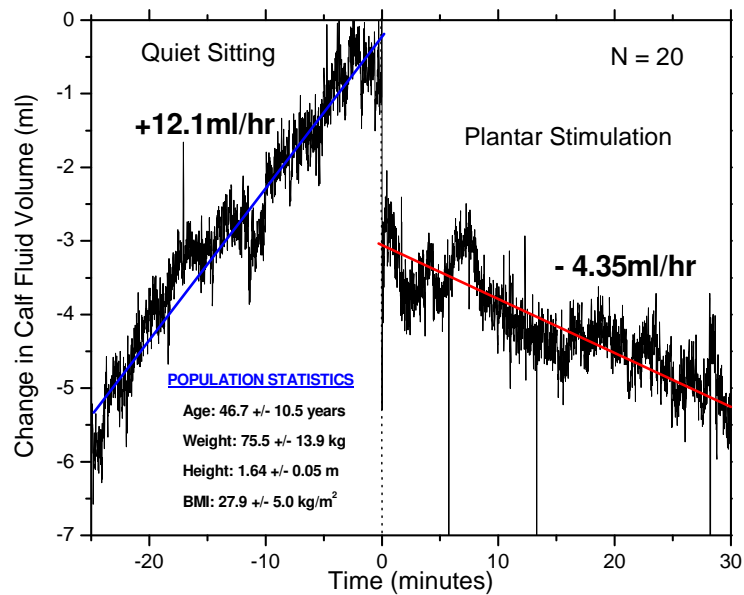


Figure 8. Efficacy of second heart stimulation, through the plantar reflex, to reverse interstitial fluid pooling in adult women. From Goddard, et al., 2008.

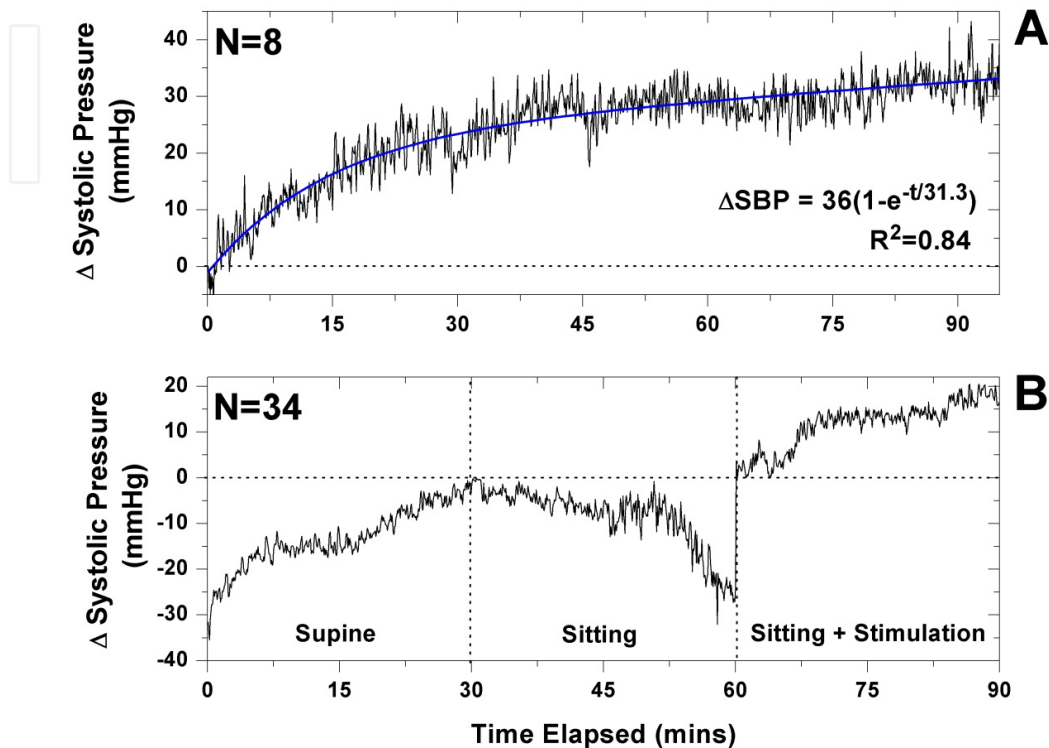


Figure 9. Influence of sustained second heart stimulation via the plantar reflex on systolic blood pressure during extended orthostatic stress associated with extended sitting. A) Time course of change in systolic blood pressure with transition from sitting to supine position. Time constant of 30 minutes suggests that close to three hours are necessary for interstitial fluid in the lower limbs to be recovered into the circulatory system following a transition to a supine position. B) Ability of second heart stimulation to accelerate fluid recovery from the lower limbs. Left panel: recovery rate associated with supine rest; Middle panel: Pooling associated with quiet sitting; Right panel: Influence of plantar reflex stimulation of the second heart. *From Madhavan, et al., 2009.*

The potential for second heart stimulation to assist individuals with diastolic heart failure, and at stage NYHA III has been tested in a pilot clinical study wherein individuals were provided with a plantar reflex stimulation device to use in their home for a four week period of time [22]. Three men and three women (average age 68 years) were recruited into the study with a group average LVEF of 49.8%. Lower limb water content was assessed using Dual Energy X-ray Absorptiometry (DXA). The average daily use of second heart stimulation ranged from 0.2 hours per day to 1.8 hours per day, and the change in retained lower limb water over the one month study period was associated with daily stimulation use (Figure 10). On average, a significant ($p=0.03$) decrease in lower limb water mass of 0.5Kg was observed, ranging from no decrease to over 1 liter.

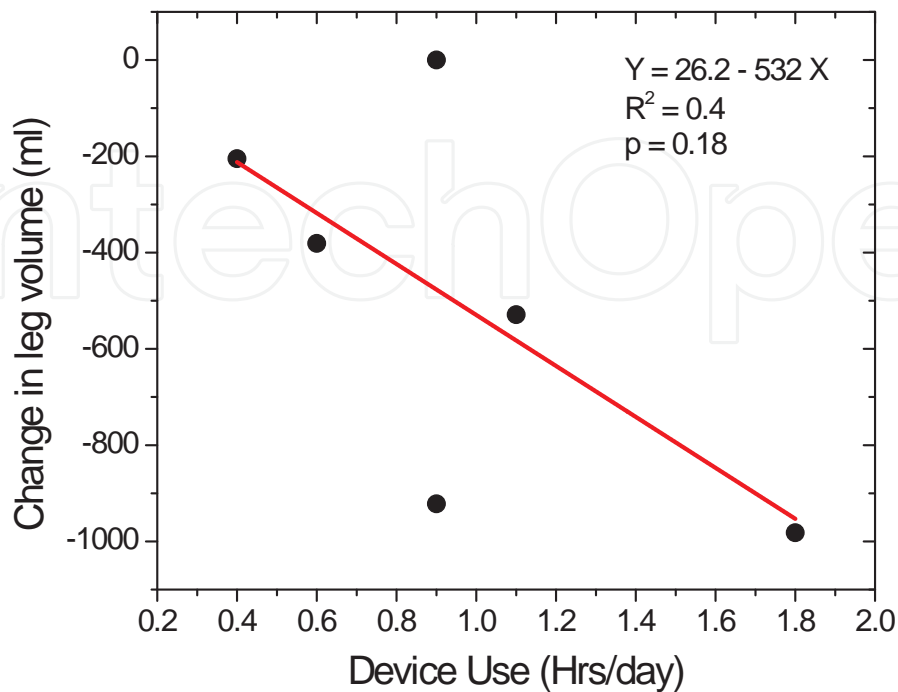


Figure 10. Change in lower limb body fluid over a one month time period as a function of average daily use of plantar reflex stimulation of the second heart. *After Pierce & McLeod, 2009.*

7. Differential diagnosis

The recent research on second heart activity has largely relied on measurements such as continuous (beat-to-beat) blood pressure monitoring, air plethysmography, electrical impedance plethysmography, and strain-gage plethysmography. However, none of these techniques represent a practical technique for the clinical environment. We would suggest that the critical factors in diagnosing inadequate second heart activity are the creation of an extended time period of orthostatic stress coupled with blood pressure monitoring and HR determination. These can be readily accomplished utilizing either upright standing or extended sitting, though as many older individuals have difficulty standing quietly for extended time periods, an extended sitting protocol is likely the most practical. A useful approach would be to obtain the BP and HR from a patient upon entering the examining room and first sitting down, then having them continue to sit for another 30 minutes or more with BP and HR obtained at the 15 and 30 minute time points. HR increases of more than 5 bpm, coupled to BP decreases of more than 10 mmHg, or more specifically, a diastolic BP dropping below 60 mmHg, should be considered a strong indication of inadequate fluid return to the heart, with long term implications for heart health and the development of extrinsic cardiomyopathy.

8. Summary and conclusions

Second heart failure, which occurs in close to 50% of women, represents a common etiology in extrinsic heart failure and cardiopathy. Clinical recognition of this condition opens the opportunity for early diagnosis and intervention, reducing the long term risk for this substantial subpopulation of women, with the potential to maintain a much higher quality of life into old age. Simple office tests of temporal changes in blood pressure and heart rate over 30 minutes of quiet sitting can reveal significant pooling associated with failed second heart activity. Augmenting venous return to the right heart to improve atrial refilling will allow for improved stroke volume and thus improved peripheral and cerebral blood flow. Early interventions can include specific exercises to train up the soleus muscle, lifestyle changes which challenge the postural reflexes; or utilization of extrinsic stimulation technology.

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