Reversal of Lower Limb Edema by Calf Muscle Pump Stimulation

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■ **BACKGROUND:** Peripheral edema (PE) is commonly coupled with heart failure, restrictive cardiomyopathy, nephrotic syndrome, renal failure, and hypoproteinemia. Diuretics and/or limb elevation, although commonly prescribed to treat PE, are often insufficient to remove sufficient fluid to prevent complications. We assessed the ability of the calf muscle pump (CMP) stimulation to reverse PE.

■ **METHODS:** Fluid volume was evaluated by air plethysmography in the right legs of 54 adult women (mean age 46.7 ± 1.5 years) following venous status assessment. Change in calf volume was assessed during 30 minutes of quiet sitting, followed by 30 minutes of sitting with CMP stimulation via micromechanical stimulation of the plantar surface.

■ **RESULTS:** Leg volume changes demonstrated a bimodal distribution. Leg volume decreased during quiet sitting in 56% of the study group, whereas in 44% of the group, significant lower leg fluid pooling was evident (increase in calf volume of 14.0 ± 0.3 mL/h). CMP stimulation reversed the fluid pooling in the edematous group (−2.7 ± 0.1 mL/h) and was able to accelerate fluid removal in the nonedematous group.

■ **CONCLUSIONS:** Approximately two fifths of adult women experience substantial pooling when their lower limbs are maintained in a dependent position. Lower-extremity edema exhibited by these women may primarily be due to inadequate calf muscle tone because exogenous stimulation of the CMP was sufficient to halt and reverse fluid pooling. Whether CMP stimulation would provide a means to treat PE in individuals with edema-related health complications, such as congestive heart failure, merits further investigation.

K E Y W O R D S

air plethysmography

calf muscle pump

edema

micromechanical plantar stimulation

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Peripheral edema (PE), the excessive accumulation of fluid in the interstitium of the limbs, is associated with cellulitis, leg ulcers, heart failure, constrictive pericarditis/restrictive cardiomyopathy, nephrotic syndrome, renal failure, and hypoproteinemia.[1–3] Increased venous pressure during upright posture (orthostasis) arising from gravitational influences leads to increased fluid extravasation from the circulatory system. An overwhelmed lymphatic system can then result in the sequestration of the extravasated fluid in the dependent tissues. At its simplest, PE can only influence individual mobility, whereas at its most complex, it can be life-threatening. Edema-related disorders including venous leg ulcers and cellulitis carry direct costs in excess of $1 billion in the United States, with indirect costs estimated at 2 million workdays per year. In addition, the physical and psychological impact of decreased mobility and the adverse psychological manifestation of fear, anger, depression, and social isolation can be substantial.[4–6]

Although the occurrence of PE is widespread, treatment options are currently limited and there has been little progress in the development of new therapeutic approaches, which can ensure sufficient lymphatic fluid return to alleviate elevated vascular pressure and inhibit capillary damage.[7–9] The most commonly employed symptomatic relief options for benign cases of PE involve lifestyle and dietary modifications such as recumbency, patient mobilization, restricted fluid, and sodium intake as well as compression garments (stockings).[10,11] Increased PE severity generally requires therapeutic approaches, commonly in the form of diuretics. However, the development of diuretic resistance is common, leading to exacerbation of the PE[11–13] and necessitating the administration of potent loop diuretics or extracorporeal mechanical ultrafiltration techniques.

Operating in conjunction with the lymphatic system, a critical "anti-edema" mechanism in the lower limbs is the calf muscle pump (CMP). In individuals with intact venous and lymphatic valves, tonic contraction of the calf muscles, in particular the soleus, serves to compress the tissue, enhancing fluid convection to the lymphatics and, as importantly, the deep veins, driving fluid forward to the heart, thereby reducing tissue pressures. In individuals with lower limb edema, the interstitial fluid return is inadequate, implicating the calf muscle pump. Supporting this premise is recent work showing that activation of the CMP by micromechanical stimulation of the plantar surface is capable of significantly reducing lower limb interstitial pressures.[14] These data lead to the suggestion that micromechanical stimulation of the plantar surface may be effective in preventing or reversing lower limb edema. To address this possibility, we investigated the efficacy of plantar stimulation to reverse gravitational edema in adult women.

METHODS

The study was approved by the Binghamton University institutional review board and performed at Binghamton University's Clinical Science and Engineering Research Center during February through September 2006.

Participants

Adult, healthy (no self-reported acute or chronic conditions), white women aged between 20 and 80 years, who were capable of understanding and following the protocol and providing informed consent, were eligible for the study. Women who were pregnant, hypertensive (ie, systolic blood pressure greater than 150 mm Hg after 30 minutes of quiet sitting), or using hypertension and/or cardiac medication were excluded from the study. Individuals with a history of back injury, or any condition that precluded continuous sitting, were also excluded from the study. The subject pool was composed predominantly of university staff whose job involved limited physical activity and long-term sitting. Participants were recruited through flyers on the campus of Binghamton University and advertisement through university staff mailing service and face-to-face discussion. Participants' weight and height were obtained, permitting calculation of the body mass index (BMI [kg/m^2]). The distance from the head of the fibula to the lateral malleolus, in conjunction with calf circumference measurements, was used to select the appropriate air chamber (cuff) size for the plethysmographic recordings and for calf volume calculations.

Laboratory Evaluations

Edema Measurement

Volume changes in the right leg of each participant were measured using air plethysmography (APG) (Model APG-1000, ACI Medical Inc, San Marcos, California). In accordance with the methods described by Nicolaides[15] and Faghri et al,[16] a tubular polyurethane air cuff was placed around the right leg of the participant between the knee and ankle and inflated to a bias pressure of 6 mm Hg. Cuff pressure data were digitized at 1 sample per second (Biopac Systems, Inc, Goleta, California) and recorded. The system was calibrated by the injection of 25-mL and 50-mL air boluses into the inflated cuff, thereby facilitating the conversion of pressure changes to calf fluid volume changes in milliliters. Venous filling index (VFI, in milliliters per second) and calf ejection fraction (EF, percentage of functional venous volume) were assessed as measures of lower limb venous status.

Calf Muscle Pump Activation

Plantar reflex–based stimulation was employed to activate the CMP. A custom device (Juvent Medical, Inc, Somerset, New Jersey) capable of stimulating the frontal aspect of the plantar surface with a 50-μm sinusoidal displacement at 45 Hz was used to activate mechanoreceptors on the plantar surface. Contraction of the soleus muscle as a result of the plantar stimulation is believed to arise through both short- and long-loop reflex arcs.[17,18]

Experimental Design

After informed consent was obtained, participants were seated in a remote-controlled recliner to permit repositioning of the participant into a supine position without voluntary contractions of the leg musculature. The right leg was instrumented with the APG air cuff, and spacers were positioned behind the participant's back as necessary to ensure sufficient clearance around the leg cuff to avoid any mechanical disturbance. The duration of the study protocol was approximately 90 minutes, involving 15 minutes of thermal equilibration, approximately 15 minutes for venous status assessment, and 30 minutes of quiet sitting followed by 30 minutes of sitting with plantar stimulation. Measurements were recorded at a room temperature of 70°F to 72°F.

During the venous assessment segment of the protocol, each participant was reclined to the supine posture and the right leg elevated to facilitate venous emptying. This was followed by a period of 1-legged standing, using a walker for support and prevention of leg muscle contractions while bearing weight on the left leg, which permitted venous refilling and assessment of the participant's VFI, a measure of deep venous status. The participant then stood on both legs and performed a series of 3 tiptoe maneuvers. This provided a measure of the expelled volume (in milliliters) from which calf EF was calculated, an indicator of superficial venous status. In the context of this study, EF refers to the ejection capabilities of the CMP rather than the heart.

Following venous status assessment, each participant was instructed to sit down and maintain a relaxed posture and minimize extraneous movement for the duration of the edema assessment. The frontal aspects of the participant's feet were positioned on the plantar stimulation device (tilted to a 15° angle) with the heels supported by a nonconducting block. Recording of calf volume began immediately after taking a seated position so that the fluid volume shifts associated with moving from a standing to a seated position could be assessed. Following 30 minutes of recording during quiet sitting, the plantar stimulation device was activated and recording of calf volume continued for another 30 minutes.

Data Analysis and Statistics

To permit averaging of the time series data, all recordings were referenced to the start of plantar stimulation (onset of stimulation = time 0). Similarly, volume changes were normalized to a value of 0 at the zero time point. Effects of age, weight, height, and BMI on PE were assessed using multiple regression analysis, and time-dependent rates of fluid volume change were obtained by linear regression. Analyses were performed using Origin, version 7.0 (Origin Lab, Inc, Northampton, Massachusetts) and SPSS for Windows, version 13.0. A $P < .05$ was applied to establish statistical significance. All data are expressed as mean ± SEM.

RESULTS

Fifty-four healthy female participants were recruited and completed the protocol. The study cohort was composed of 54 women of mean age 46.7 ± 1.5 years, with BMIs ranging from 19 to 39 kg/m^2 (mean BMI = 27.0 ± 0.7 kg/m^2). Venous assessment demonstrated that 47 women had venous filling indices less than 2 mL/s, consistent with sufficient venous function (absence of venous reflux) whereas 7 women demonstrated VFI between 2 and 4 mL/s, consistent with reference values indicative of minor venous reflux.[15] Calf EFs averaged 61.5% (Table 1).

During quiet sitting, the calf fluid volume (average of all participants in the study) did not change significantly over the first 30 minutes of quiet sitting, with only a slight increase of 0.99 ± 0.2 mL/h being evident (Fig 1). However, on commencement of plantar stimulation, an abrupt decrease in calf fluid volume of approximately 2 mL was observed, followed by a sustained decrease in calf volume at a rate of approximately 4.3 ± 0.1 mL/h.

To further investigate the influence of plantar stimulation on reduction of lower limb edema, the change in calf volume during the initial 30 minutes of quiet sitting was determined for each individual in

Table 1 • DEMOGRAPHIC DATA[a]

Participants	*n* (%)	Age, y	Weight, kg	Height, m	BMI, kg/m^2	Calf EF, %	VFI, mL/s
Total	54 (100)	46.7 ± 1.5	72.5 ± 2.0	1.64 ± 0.01	27.0 ± 0.7	61.5 ± 5.1	1.1 ± 0.1
Nonedematous	30 (55.6)	46.8 ± 2.0	69.5 ± 2.5	1.63 ± 0.01	26.0 ± 0.9	59.0 ± 5.9	1.0 ± 0.2
Edematous	24 (44.4)	46.5 ± 2.2	76.3 ± 3.0	1.64 ± 0 .01	28.2 ± 1.0	64.7 ± 9.0	1.2 ± 0.2

Abbreviations: BMI, body mass index; EF, ejection fraction; VFI, venous filling index.
[a]All data are presented as mean ± SEM.

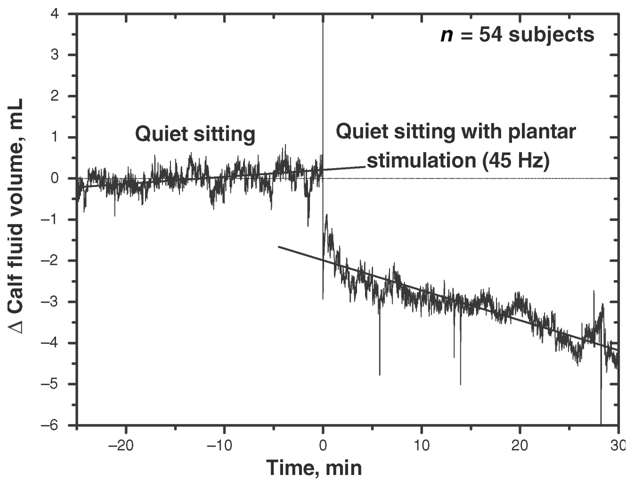

Figure 1. Calf fluid volume changes in participants while quietly sitting. Thirty minutes prior to time 0, participants were instructed to move from a standing position to a seated position. At time 0, stimulation of participant plantar surface was initiated, resulting in a rapid decrease in calf volume followed by a sustained volume decrease of 4.31 mL/h. Each data set was normalized such that the relative calf fluid volume at time 0 was equal to zero.

the study. Histogram analysis of calf fluid volume rate changes during this unstimulated period demonstrated a distinct bimodal distribution (Fig 2). Gaussian curve fitting identified 2 peaks at approximately −8.0 ± 1.1 mL/h and at 11.7 ± 1.6 mL/h ($R^2 = 0.63$). We used these data to divide the total study cohort into a "nonedematous" group (those with a decreasing calf volume during quiet sitting; ie, less than 0 mL/h) and an "edematous" group (those with increasing calf volume during quiet sitting; ie, greater than 0 mL/h).

Using this method, approximately 44% of the participants were categorized as having edematous lower limbs. On average, these participants were of similar age, weight, and stature to the nonedematous group (Table 1). Time course analysis of lower limb pooling in this group demonstrated a relatively linear increase in calf volume (14.0 ± 0.3 mL/h) throughout 30 minutes of quiet sitting (Fig 3). Commencement of plantar stimulation resulted in a rapid ejection of approximately 3 mL of fluid, followed by a sustained decrease in calf volume at an average rate of 2.7 ± 0.1 mL/h. In comparison, the nonedematous segment of the cohort, comprising the remaining 56% of the participants, demonstrated a relatively constant rate of decrease in calf volume for at least the first 30 minutes of quiet sitting (−8.9 ± 0.2 mL/h; Fig 4). Plantar stimulation resulted in accelerated fluid ejection for the first 5 minutes (~36 mL/h), followed by a lower, sustained level of ejection, averaging 5.7 ± 0.1 mL/h over the remainder of the 30-minute stimulation period.

DISCUSSION

Lower limb edema can be a manifestation of numerous physiologic conditions, including increased capillary pressure secondary to elevated venous pressure during orthostasis, venous obstruction, increased capillary permeability, decreased plasma oncotic pressure, or inadequate muscle tone.[19] The role of the

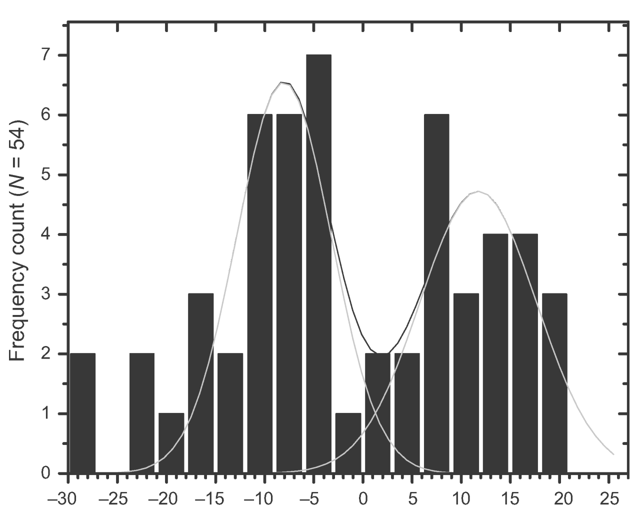

Figure 2. Rate-of-change analysis of calf fluid volume during 30 minutes of quiet sitting following 5 minutes of standing. Bimodal Gaussian fitting revealed peaks at approximately 11.7 mL/h and −8.0 mL/h ($R^2 = 0.63$). The resulting bimodal distribution facilitated the classification of the study cohort into edematous and nonedematous on the basis of location in this distribution.

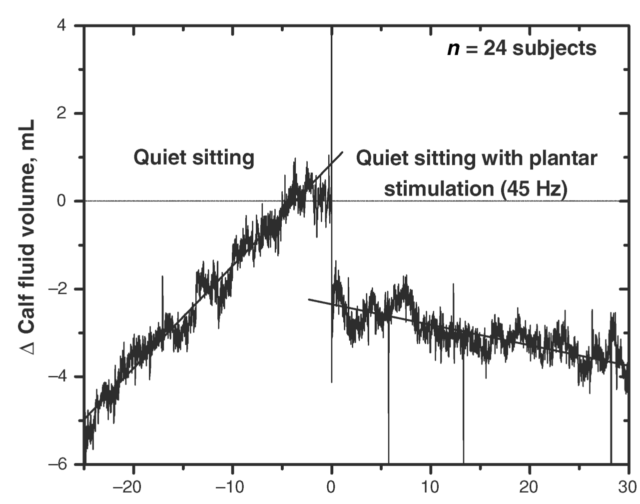

Figure 3. Calf fluid volume changes of lower leg edematous participants during quiet sitting. Pooling was observed at a rate of 14.0 mL/h. At time 0, stimulation of participant plantar surface was initiated, resulting in a reversal of fluid pooling as reflected by a rapid fluid ejection followed by a sustained fluid volume decrease at a rate of 2.73 mL/h and reversal of pooling.

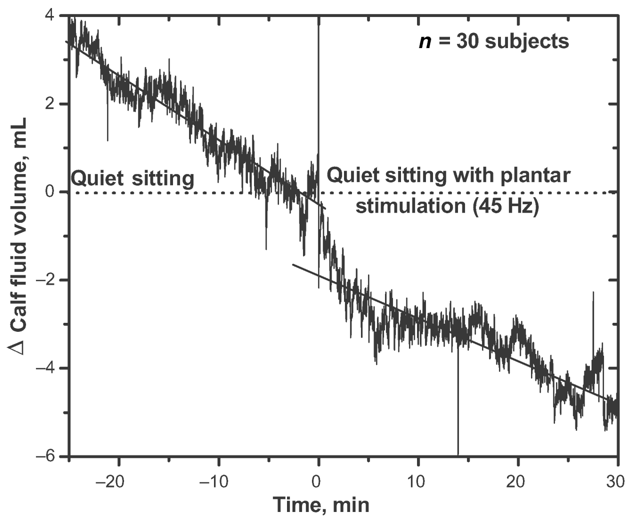

Figure 4. Calf fluid volume changes in nonedematous participants during quiet sitting. At time 0, stimulation of participant's plantar surface was initiated, resulting in accelerated fluid volume reduction followed by sustained fluid volume decrease at a rate of 5.73 mL/h.

CMP in preventing lower limb edema has been largely neglected because edema is generally viewed as a venous insufficiency problem.[20] However, in this study, we found that none of the women who demonstrated gravitational edema of the lower limbs had measurable venous insufficiency. Venous assessment did identify 7 participants (~13% of the study cohort) as having venous filling indices between 2 and 5 mL/s, but these values are considered as being indicative of only minor reflux by Nicolaides,[15] and so we did not categorize these participants as having chronic venous insufficiency (CVI). The EFs among the edematous and nonedematous participants were not significantly different and indicated the absence of venous disease. Although the edematous segment of our study cohort demonstrated EFs indicative of limbs without venous disease[15] during voluntary muscle contraction, this group demonstrated significant lower limb fluid pooling during quiet sitting. Because the EFs for this group indicate sufficient venous valve function, the sitting-induced edema would seem to arise because of a lack of involuntary CMP activity.

Forty-four percent of the women in this study were found to develop gravitational edema of the lower leg while seated. Although we established a minimum swelling rate of 0 mL/h as a cutoff for including participants in the edematous group, some participants experienced a swelling rate exceeding 20 mL/h. Because the APG cuff assesses approximately 1.5 L of calf volume,[21] the average change in calf volume for this group would be approximately 8 mL/L/h. Considering that lower limb volume ranges from 20 to 30 L in adult women, the total lower limb pooling in this group may have been approaching 150 to 250 mL/h. Given that we observed no evidence of slowing of the interstitial fluid buildup over 30 minutes of quiet sitting, it is possible that this group of women experienced an accumulation of several liters of fluid in their lower body during the course of a day.

Exogenous stimulation of the CMP, through micromechanical stimulation of the plantar surface, was found to be effective in reducing calf volume in both edematous and nonedematous participant groups. For those in the nonedematous group, CMP stimulation appeared to accelerate fluid removal, whereas for those in the edematous group, CMP stimulation reversed the fluid pooling. These results lead to the suggestion that a significant, if not dominant, contributing factor leading to edema in women with competent venous valves is inadequate calf muscle tone. It is interesting to note that although the edematous group appeared to lack sufficient involuntary soleus muscle activity to prevent edema, upon stimulation of the plantar surface, sufficient soleus activity could be achieved to reverse the edema. This would seem to suggest that the plantar reflex pathway is not the normal means by which the soleus is activated to prevent pooling.

The effect of the plantar stimulation on the edematous participants appears to occur in 2 phases. Within seconds, the buildup of fluid is terminated, and in addition, an abrupt reduction in leg volume was observed. This is likely due to enhanced clearance of fluid in the veins and lymphatics of the calf as a result of the initial contractions of the soleus muscle initiated by the plantar stimulation. Over longer time periods (tens of minutes), a sustained decrease in leg volume was observed, consistent with the time required for the convection of interstitial fluid from the tissue to the lymphatics from which it could be cleared.

Because the study cohort consisted solely of adult, white women, the ability of micromechanical stimulation to enhance CMP activity, and reverse edema, may not be representative for men or for individuals of non-white origin. Additional factors such as time of day of the measurements as well as participant activity level and diet before arrival at the research facility may have influenced the degree of fluid pooling during sitting; otherwise, our study cohort appeared to represent a typical female demographic because weight, height, and BMI were typical for women in this age range. Our participants did appear to have a lower distribution of venous disease than that described in the literature.[22–24] Rates of CVI in women have been reported to be in the range of 5%, and so we anticipated 2 to 3 CVI cases but found none. That most of the participants in this study were employed in office work rather than in occupations requiring extended standing may explain this reduced (<2%) rate of CVI.

These results confirm that the CMP plays an important role in preventing edema and exogenous stimulation of the pump can significantly enhance the mobilization of sequestered lower limb fluid in ambulatory individuals without apparent cardiovascular disease. These results may have important clinical implications because inadequate venous and lymphatic return, when coupled with cardiac disease, results in increased mortality in comparison with cardiac disease in the absence of PE (25% vs 8% at 2 years, $P < .01$, $n = 243$).[25] Furthermore, the association of PE with leg ulcers and cellulitis fosters delayed healing and increases recurrence rates.[4,5] Because the management of edema and coupled pathologies (heart failure, leg ulcers, and cellulitis) remains a clinical challenge,[2,9,26] incorporation of CMP stimulation techniques, such as the micromechanical stimulation utilized here, into patient care may be a useful adjunctive therapy and potentially preemptive therapeutic strategy.

In summary, we have shown that gravitational edema is common in this study cohort (nonhypertensive, white women with sedentary jobs), with a prevalence exceeding 40%. This finding is consistent with the existing literature that describes lower-extremity edema as a common medical problem experienced by every second person.[5] Moreover, such gravitational edema has been shown to be readily reversed through CMP stimulation. By enhancing fluid return from the lower limbs, it is possible that atrial refilling may be enhanced. Given the results of this study, investigation of the influence of fluid mobilization on study cohorts with edema-linked pathologies appears to be worthwhile. Such studies would provide insight into the capabilities of exogenous micromechanical plantar stimulation to serve as a complementary therapy in the management of patients with PE sufficiently severe to influence their health and well-being.

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