



Original Article

Effect of calf muscle electrical stimulation on rostral fluid shift, snoring and obstructive sleep apnea

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ABSTRACT

Study objectives: Overnight fluid shift from the legs into the neck may contribute to the pathogenesis of snoring and obstructive sleep apnea (OSA). The present study investigates the effects of calf muscle electrical stimulation (ES) on reducing leg fluid accumulation while seated, subsequent rostral fluid shift on lying down, and the impact on snoring and OSA.

Methods: Sixteen non-obese, normotensive men with OSA participated in the study. On the first study day, participants sat for 150 min receiving either active or sham ES through random allocation, then lied supine for 60 min. While seated and supine, leg and neck fluid volumes were measured using bioelectrical impedance to determine the magnitude of fluid shift. On the night of the study day, participants wore a portable sleep apnea diagnostic device overnight to measure snoring and sleep apnea severity. One week later, participants crossed over to the other study condition.

Results: Active calf muscle ES reduced leg fluid accumulation by 46% while seated. Upon lying supine, active ES reduced fluid shift out of the legs by 17% and reduced neck fluid accumulation by 31%. This led to a 15% reduction in snoring index, but did not alleviate OSA.

Conclusions: One session of calf muscle ES was effective at reducing leg fluid accumulation and rostral fluid shift, which led to a modest reduction in the snoring index, but not OSA. Despite this lack of effect of calf muscle ES in attenuating OSA severity, the reduction in the snoring index suggests that it did have an effect, albeit mild, on upper-airway mechanics.

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1. Introduction

Obstructive sleep apnea (OSA) is a common disorder that occurs in 10% of the population [1] and is characterized by intermittent narrowing or collapse of the pharynx during sleep. Pharyngeal collapse can occur due to multiple interacting pathophysiological mechanisms, which can vary across individuals [2]. Among the components predisposing to OSA, anatomical factors that narrow

the airway (eg, craniofacial abnormalities, enlarged peripharyngeal tissues, or excessive neck fat deposition), are well understood to interact with various other mechanisms and contribute to pharyngeal collapse. Through this same mechanism, nocturnal fluid shift from the legs to the neck can also contribute to pharyngeal narrowing and predispose to OSA. Specifically, overnight fluid shift increases mucosal water content in the peripharyngeal tissues [3], which can apply pressure to the pharynx, leading to pharyngeal narrowing [4], increased pharyngeal resistance [5] and collapsibility [6], as well as increased OSA severity [7].

Rostral fluid shift and its association with OSA present avenues for new therapies to treat OSA that target the fluid shift mechanism. Alternative therapies for OSA are of particular importance given that the most common therapy, continuous positive airway pressure, is poorly tolerated by patients [8]. Therapies aimed at reducing fluid

Abbreviations: AHI, Apnea-hypopnea index; BMI, Body mass index; ES, Electrical stimulation; LFV, Leg fluid volume; NC, Neck circumference; NFV, Neck fluid volume; OSA, Obstructive sleep apnea.

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retention and/or fluid accumulation in legs have been shown to reduce pharyngeal narrowing and OSA. For example, daily walking, wearing compression stockings during the day, ultrafiltration, and diuretics, reduce overnight rostral fluid shift in association with a 16–34% reduction in OSA severity [9–12]. Among these therapies, compression stockings and exercise are most practical for the general population, although both are associated with low adherence [13–15].

An alternative method for reducing leg fluid is involuntary activation of the calf muscle via electrical stimulation (ES) [16,17]. As a device-based therapeutic approach, calf muscle ES can be especially useful for individuals that are sedentary due to their occupation, aging, or mobility impairment. Calf muscle contractions via ES reduces leg fluid by activating the skeletal muscle pump, moving blood back to the heart, reducing hydrostatic pressure in the capillaries of the legs, and counteracting the filtration of fluid out of the capillaries into the interstitium [18,19]. Indeed, calf muscle ES has been shown to reduce leg fluid accumulation while seated [16,17]. However, to the best of our knowledge the effect of calf muscle ES on rostral fluid shift and the pharyngeal airway has never been investigated.

The present study is an observational trial that tests the hypothesis that calf muscle ES will reduce the rostral shift of fluid out of the legs and into the neck, reduce snoring and alleviate OSA. Therefore, the primary objective of this study was to examine the effect of calf muscle ES on leg fluid accumulation while seated, and its impact on rostral fluid shift when lying supine and subsequent snoring and OSA.

2. Methods

2.1. Participants

The research protocol was approved by the Research Ethics Board of the Toronto Rehabilitation Institute – University Health Network. Participants were recruited from the community through advertisement and written informed consent was obtained prior to participation. Criteria for study inclusion were adults with a body mass index (BMI) < 30 kg/m², blood pressure < 140/90 mmHg and the presence of sleep apnea (AHI ≥ 10) on a screening test which took place less than two weeks prior to the first study day. Participants were screened for sleep apnea using a portable sleep monitoring device previously described by Alshaer et al., [20–24] and described further in the Data Analysis section. If participants had positive screening for sleep apnea, they were provided with information about the disorder and told to speak to their family doctor about their positive screening. Participants were excluded if they had a history of treated sleep apnea, cardiovascular, renal, neurological, or respiratory disorders, and were taking prescribed medication for these conditions.

2.2. Fluid measurement

Leg fluid volume (LFV) and neck fluid volume (NFV) were measured by bioelectrical impedance, as described previously [25]. Neck circumference (NC) was measured at the level of cricothyroid cartilage, and calf circumference was measured around the largest part of the calf. On the first measurement, a line was drawn around the neck and calf to ensure repeated measurements were made at the same level.

2.3. Monitoring of activity and diet

Participants monitored their activity for five days leading up to the study day using a paper diary which required participants to

record every half hour whether they were sleeping, lying, sitting, standing, walking at a usual pace, walking briskly, or participating in vigorous physical activity. Time spent sedentary is described by the total time spent sitting, lying, and standing. Time spent active was described by the total time spent walking at a usual pace, walking briskly and performing physical activity. Diet was also monitored for three days leading up to the study day using a paper diary that required participants to record the names and amounts of food and drink consumed at every meal or snack. The nutrient content of foods and beverages were quantified with a specialized software package for dietary analysis (ESHA Food Processor SQL Version 10.14.1, ESHA Research Inc., Salem, OR).

2.4. Electrical stimulation protocol

A programmable 4-channel neuromuscular electrical stimulator (Complex Motion, SA, Switzerland) was used to deliver transcutaneous electrical stimulation to the gastrocnemius muscle group in the left and right leg using 9 cm by 5 cm StimTrove electrodes (Axelgaard Manufacturing, California, USA). Stimulation was applied using an asymmetrical biphasic waveform with 40 Hz frequency, and 300 μs pulse duration. This electrical stimulation protocol is similar to that used for contracting the calf muscle for deep vein thrombosis prophylaxis [26]. Calf muscle ES was applied to both calf muscles at a duty cycle of 2 s on, followed by 2 s off. The left and right calf muscles were stimulated out of sync, such that when the right calf muscle was contracted, the left was relaxed and vice versa. Stimulation amplitude was set to the maximally tolerated stimulation amplitude (typically between 20 and 40 mA).

2.5. Study protocol

The study was a randomized, single-blind, crossover protocol. Participants were blind, but the experimenter was aware of the study condition. As illustrated in Fig. 1, participants initially completed an activity and diet log prior to the study day. On the study day, participants arrived at 11:00 AM and were instrumented with bioelectrical impedance surface electrodes and calf muscle ES electrodes. Next, circumferences of the neck and leg were measured. Participants then lay still on a bed in the supine position without a pillow for 30 min. Next, participants sat for two and a half hours while active or sham ES was applied. Finally, participants again lay still on a bed in the supine position without a pillow for the final 60 min to evaluate the magnitude of rostral fluid shift. Participants were sent home with a portable acoustic sleep monitoring device

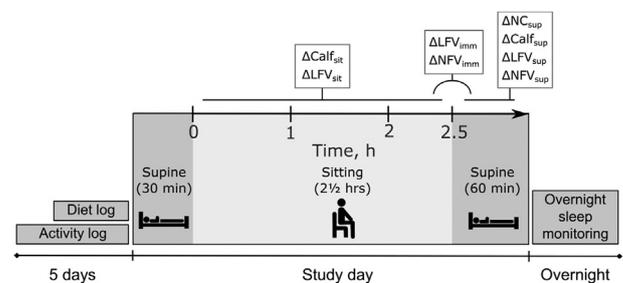


Fig. 1. Study protocol: an activity log and diet were completed for five and three days leading up to the study day. On the study day, participants initially lay supine for 30 min, sat for 2.5 h (with active or sham ES), and then lie supine for 60 min. The changes in leg fluid volume and calf circumference (ΔLFV_{sit} , $\Delta Calf_{sit}$) were measured over the seated period. The changes in leg and neck fluid volume were measured upon transitioning from sitting to supine (ΔLFV_{imm} , ΔNFV_{imm}). The changes in leg and neck fluid volume, neck circumference and calf circumference (ΔLFV_{sup} , ΔNFV_{sup} , ΔNC_{sup} , $\Delta Calf_{sup}$) were measured over the 60-min supine period. Participant's sleep was monitored on the night of the study day using a portable acoustic sleep monitoring device.

for use that night to measure snoring and sleep apnea severity. One-week later participants returned to the laboratory to participate in the other study condition.

2.6. Data analysis

2.6.1. Fluid measurements

To characterize fluid accumulation in the leg while seated, the change in LFV ($\Delta\text{LFV}_{\text{sit}}$) and calf circumference ($\Delta\text{Calf}_{\text{sit}}$) over the seated period were computed (Fig. 1). The immediate shift of fluid from the legs to the neck ($\Delta\text{LFV}_{\text{imm}}$ and $\Delta\text{NFV}_{\text{imm}}$, respectively) upon lying supine was calculated from fluid volumes measured from the end of sitting to the beginning of the supine period. Lastly, to characterize fluid shift over the 60-min supine period, the change in LFV ($\Delta\text{LFV}_{\text{sup}}$), calf circumference ($\Delta\text{Calf}_{\text{sup}}$), NFV ($\Delta\text{NFV}_{\text{sup}}$), and NC ($\Delta\text{NC}_{\text{sup}}$) were measured over the supine period.

2.6.2. Apnea-hypopnea index and snoring index

AHI and snoring index (number of snoring episodes per hour of sleep) were measured on the nights of the study days using a validated portable acoustic sleep monitoring device (BresoDx™, BresoTec, Toronto, Canada) [20–24]. The device is a self-contained, battery-operated, wireless device, consisting of an open face frame with an embedded microphone at a fixed distance (approximately 3 cm) in front of the participant's mouth, and an electronics compartment that contains a pre-amplifier, microprocessor, analog-to-digital converter, and a microSD card. Digitized breathing sounds are recorded on the microSD for up to 8 h at a sampling frequency of 16 kHz. Apneas and hypopneas are detected from the breathing sound data using highly accurate algorithms that have been validated against polysomnography and in the unattended home setting [20–23]. The device is also validated and highly accurate in the analysis of snoring [24]. The details of the analysis method have been described in detail elsewhere [24], but briefly, audio files were segmented in 64 ms overlapping (50%) windows. From each window, 10 mathematical features of breathing were computed, among which included signal energy (proportional sound amplitude), periodicity of the sound (quantifies turbulence of breathing), ratio of frequencies (identifies the dominant frequencies of the sound), and flatness of the frequency spectrum. Features were used as inputs to a machine learning algorithm which classified each window as “snoring” or “not snoring”.

2.7. Statistical analysis

Differences in activity levels and diet outcomes, as well baseline blood pressures, heart rate, LFV, calf circumference, NC and NFV at the start of sitting between the active and sham ES study conditions were evaluated using the paired t-test or Wilcoxon signed-rank test. Changes in fluid measurements over the seated and supine period were assessed using the paired t-test or Wilcoxon signed-rank test. To evaluate differences in fluid measurements over the seated and supine periods between active and sham ES study conditions, a repeated-measures ANOVA with time and study condition as factors was performed. A significant interaction effect (time \times condition) indicated a difference between the active and sham ES study conditions. A two-sided P-value < 0.05 was considered significant for the statistical tests conducted. To assess the AHI as the main outcome of the study, a sample size of 13 was selected to observe a 30% reduction in the AHI with a standard deviation of 35% as previously reported [10], with a two-tailed α of 0.05 and β of 80%. Statistical analyses were conducted using R open source statistical software version 3.2.1 (<http://www.r-project.org>). Data are presented as mean \pm SEM.

3. Results

3.1. Participants

Of the 137 pre-screened participants, 50 were eligible and were screened for sleep apnea. From this group, 17 participants were found to have an AHI ≥ 10 and were willing to participate in the full study. One participant was lost to follow-up for a final sample size of 16. Thirteen of the participants were included in a previous study (10 of whom were assessed for sleep apnea) that investigated the effect of calf muscle ES on seated leg fluid accumulation [17]. Three participants were newly recruited to meet the required sample size of the present study. As described in the recruitment flow diagram (Fig. 2), three participants did not correctly use the portable sleep monitoring device on the second study night and refused to repeat the study protocol. Five and two participants did not complete the diet and physical activity record, respectively, and refused to repeat the study protocol.

Mean age of the participants was 51.3 ± 7.5 years. All participants were non-obese men with a mean BMI of 26.3 ± 2.7 kg/m². Participants were all normotensive with mean systolic blood pressure of 117 ± 11 mm Hg, diastolic blood pressure of 80 ± 8 mm Hg and heart rate were of 68 ± 10 bpm. Mean AHI was 19.0 ± 3.2 events/hr. Sleep apnea severity was mild (AHI ≥ 10 , but < 15 events/hr) in nine participants, moderate (AHI ≥ 15 , but < 30 events/hr) in four participants and severe (AHI ≥ 30 events/hr) in three participants.

Baseline characteristics, shown in Table 1 were comparable between the two study conditions. Baseline LFV, NFV, and NC measured at the start of sitting were similar between the active and sham ES conditions ($P > 0.10$). However, calf circumference measured at the beginning of sitting was slightly smaller in the sham ES condition, compared to the active ES condition ($P = 0.03$). Blood pressures and heart rate were similar between the active and sham ES conditions (all $P > 0.10$). Time spent sitting, time spent sedentary and time spent active in the days leading up to study days were similar between the active ES and sham ES condition (all $P > 0.50$). In addition, average water and caloric intake were similar between the active and sham ES conditions (all $P > 0.10$). However, average sodium intake was greater in the active ES condition, compared to the sham ES condition ($P = 0.02$).

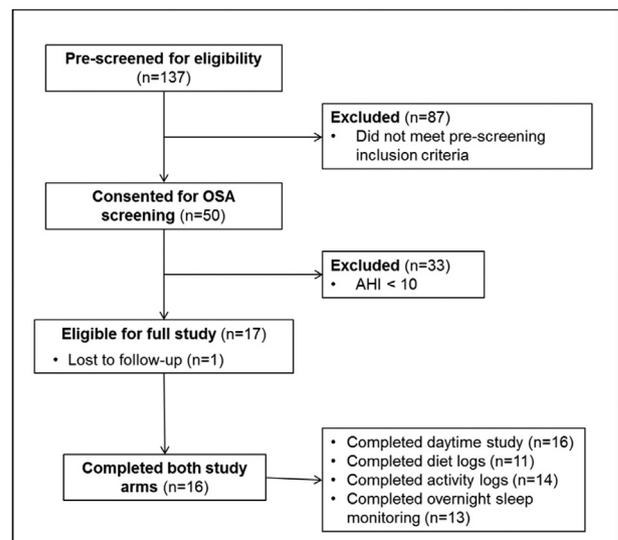


Fig. 2. Flow diagram of participants recruitment.

Table 1

Baseline characteristics. P-value represents the difference between the study conditions.

Variable	Sham ES	Active ES	P-value
Leg fluid volume (ml)	1333.3 ± 54.3	1394.5 ± 48.5	0.59
Calf circumference (cm)	39.1 ± 0.7	39.5 ± 0.7	0.03
Neck fluid volume (ml)	487.2 ± 45.8	483.0 ± 26.6	0.88
Neck circumference (cm)	41.1 ± 0.7	41.6 ± 0.9	0.11
Systolic blood pressure (mmHg)	113.6 ± 3.2	114.6 ± 2.6	0.60
Diastolic blood pressure (mmHg)	77.1 ± 2.8	79.1 ± 1.7	0.32
Heart rate (beats/min)	66.3 ± 2.2	66.3 ± 2.8	0.37
Percent Time Sitting (%)	36.6 ± 4.2	37.6 ± 12.4	0.63
Percent Time Sedentary (%)	87.4 ± 14.1	85.7 ± 12.2	0.55
Percent Time Active (%)	12.5 ± 4.5	14.3 ± 5.8	0.40
Calories (kcal)	2069 ± 205	2073 ± 217	0.75
Water (ml)	2817 ± 398	2554 ± 372	0.81
Sodium (g)	2056 ± 172	2696 ± 192	0.02

3.2. Seated leg fluid accumulation

Over the two-and-a-half hour seated period, LfV increased significantly in both the active ($P < 0.001$) and sham ES conditions ($P < 0.001$). However, the increase in LfV while seated was significantly lower when using active ES (51.7 ± 7.2 ml) compared to sham ES (95.5 ± 8.5 ml, $P < 0.001$, Fig. 3a). While calf circumference increased significantly over the seated period in the sham ES condition (0.80 ± 0.07 cm, $P < 0.001$), it did not change in the active ES condition (0.11 ± 0.07 cm, $P > 0.10$), and this difference between study conditions was significant ($P < 0.001$, Fig. 3b).

3.3. Fluid shift while supine

The immediate shift of LfV upon lying supine was statistically significant in both the active ES (101.4 ± 7.5 ml, $P < 0.001$) and sham ES conditions (132.7 ± 12.5 ml, $P < 0.001$), with significantly less fluid shifting out of the legs after using active ES ($P = 0.02$, Fig. 4a). The shift in LfV over 60 the minute supine period was also significant in both the active ES (62.5 ± 5.3 ml, $P < 0.001$) and sham ES (68.1 ± 5.0 ml, $P < 0.001$) conditions, but the LfV shift was not

different between the study conditions ($P > 0.10$, Fig. 4a). Similarly, over the supine period, calf circumference decreased significantly in both the active ES (0.41 ± 0.1 cm, $P < 0.001$) and sham ES (0.49 ± 0.1 cm, $P < 0.001$) conditions, but these changes were not different between the study conditions ($P > 0.10$, Fig. 4b).

The immediate accumulation of fluid into the neck was also significant in both the active ES (44.6 ± 8.4 ml, $P < 0.001$) and sham ES conditions (56.6 ± 12.4 ml, $P < 0.001$), but less fluid accumulated in the neck after using active ES ($P < 0.01$, Fig. 5a). Similarly, over the supine period the accumulation of neck fluid in both the active and sham ES conditions was significant (both $P < 0.001$). However, after using active ES, neck fluid accumulation was halved (19.6 ± 2.5 ml), compared to the sham ES condition (38.3 ± 5.3 ml, $P < 0.001$, Fig. 5a). NC also increased significantly over the supine period in both the active ($P < 0.05$) and sham ES conditions ($P < 0.001$). However, after using active ES, the increase in NC was about three times smaller (0.34 ± 0.1 cm), compared to sham ES (1.2 ± 0.2 cm, $P < 0.001$, Fig. 5b).

3.4. Apnea-hypopnea index and snoring index

Calf muscle contraction by active ES did not reduce overall AHI (active ES: 18.3 ± 3.6 and sham ES: 20.2 ± 3.8 events/hr, $P > 0.10$), supine AHI (active ES: 29.5 ± 6.5 and sham ES: 31.4 ± 5.6 events/hr, $P > 0.10$) or non-supine AHI (active ES: 16.1 ± 3.3 and sham ES: 18.4 ± 3.7 events/hr, $P > 0.10$). Conversely, active ES did reduce the snoring index (active ES: 266.4 ± 52.7 vs. sham ES: 313.1 ± 60.9 episodes/hr, $P = 0.03$), as illustrated in Fig. 6.

4. Discussion

The present study demonstrates that repeated activation of the calf muscles by ES reduces the accumulation of fluid in the legs by 46% and rostral shift of fluid from the legs by 17% and into the neck by 31% when lying down. This led to a reduction in the snoring index by 15%, but no change in the OSA severity. These findings support the proof of concept that calf muscle ES can potentially

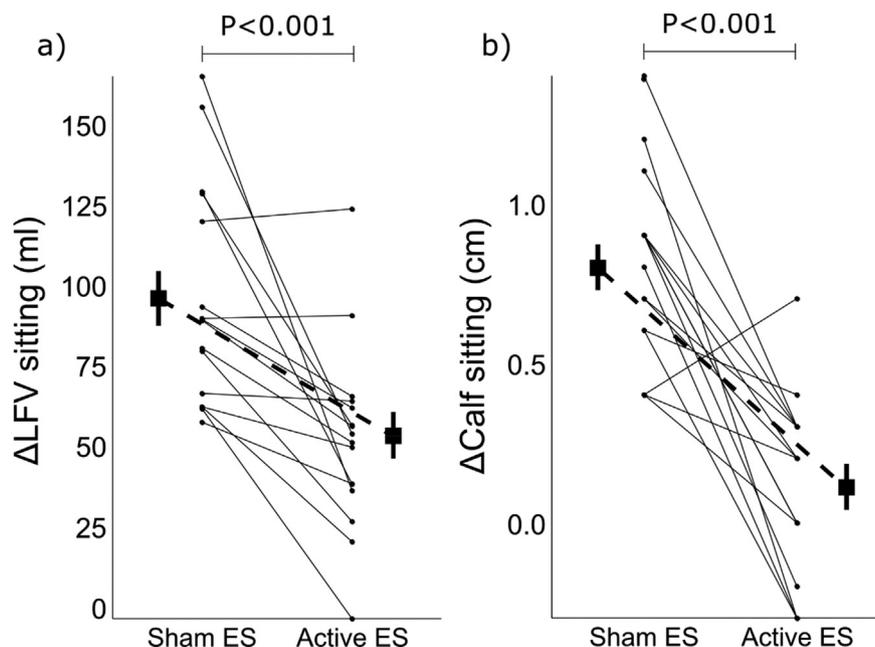


Fig. 3. Change in leg fluid volume (LfV) (a) and calf circumference (b) over the period sitting in the sham and active ES conditions. The amount of fluid accumulation in the legs was reduced in the active ES condition compared to the sham ES condition. P-values reflect the results of the interaction effect indicating differences of fluid accumulation between the study conditions.

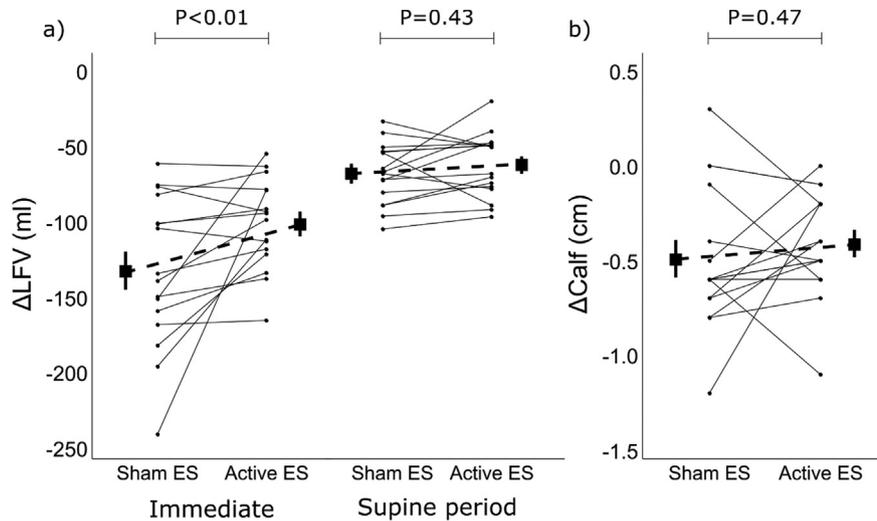


Fig. 4. Change in leg fluid volume (LFV) immediately upon lying down and over the supine period (a) and change calf circumference over the supine period (b). The immediate shift of fluid out of the legs was reduced after using active ES, compared to the sham ES condition. However, there was no difference between study conditions in the change in LFV and change in calf circumference over the supine period. P-values reflect the results of the interaction effect indicating differences of fluid accumulation between the study conditions.

reduce rostral fluid shift and merits further study into the long-term effect of calf muscle ES on overnight rostral fluid shift and OSA.

Despite not alleviating OSA, snoring index was reduced. The reduction in snoring observed was small, decreasing from 313 to 266 events/hr, and therefore not clinically significant. But despite this small magnitude, reducing the snoring index still suggests a possible effect of calf muscle ES on upper-airway mechanics. Snoring is a manifestation of breathing through a narrowed pharynx with increased resistance, leading to vibration of the soft tissues of the pharynx, soft palate and uvula, which generate acoustic characteristics [27,28]. Past research has demonstrated that shifting fluid out of the legs and into the neck, using lower body positive pressure, narrows the pharynx [4] and increases pharyngeal resistance [5] during wakefulness. Furthermore, preventing overnight rostral fluid shift through four weeks of daily walking significantly reduced the degree of overnight pharyngeal narrowing, compared to the

control period [10]. It therefore follows that calf muscle ES may have reduced the overnight rostral fluid shift and prevented neck fluid accumulation to reduce pharyngeal narrowing, pharyngeal resistance, and associated snoring.

The efficacy of calf muscle ES to reduce snoring, but not OSA, is potentially related to the acute application of the therapy. A single session of calf muscle contractions may not sufficiently reduce overnight neck fluid accumulation to effectively prevent pharyngeal collapse and reduce OSA severity. A study similar in design to the present study also explored a single session of calf muscle activation using a seated stepping device and reported similar results [29]. Compared to quiet sitting, 4 h of seated stepping in patients with OSA did not reduce OSA severity. However, in a subgroup of patients ($n = 5$) that were Mallampati IV, snoring index and snore duration reduced by 57% and 65%, respectively. Conversely, studies that investigated therapies to prevent leg fluid accumulation for a longer duration, such as four weeks of 45 min daily walking [10] or one

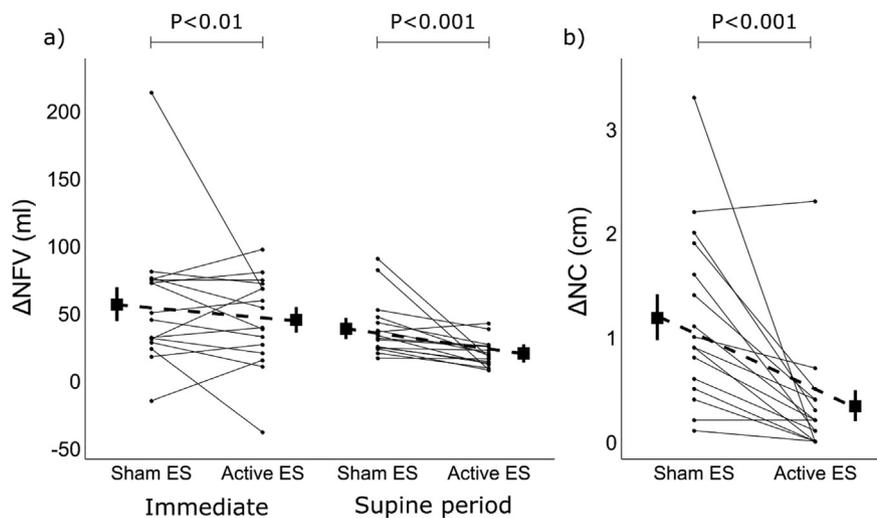


Fig. 5. Change in neck fluid volume (NFV) immediately upon lying down and over the supine period (a) and change neck circumference over the supine period (b). Neck fluid accumulation was reduced immediately upon lying down and over the supine period after using active ES, compared to the sham ES condition. Similarly, over the supine period the change in NC was significantly reduced after using active ES, compared to the sham ES condition. P-values reflect the results of the interaction effect indicating differences of fluid accumulation between the study conditions.

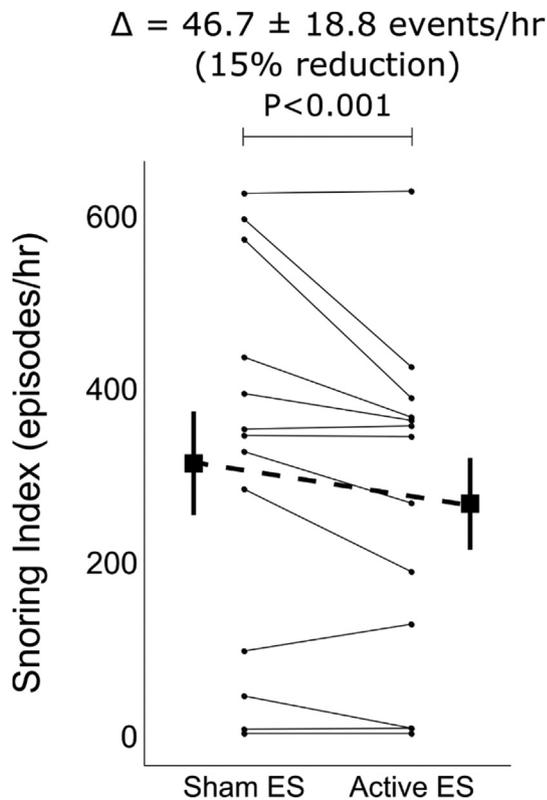


Fig. 6. Difference in the snoring index between the sham and active ES conditions. Snoring index reduced significantly by 15% after using active ES, compared to the sham ES condition.

week of 45 min twice daily walking [30], reduced the AHI by 34% and 30%, respectively. Given that longer periods of treatment for reducing daytime leg fluid accumulation have been more successful than single day treatments, it is plausible that long-term interventions for preventing leg fluid accumulation, versus acute, have a different effect on fluid redistribution, and the associated rostral fluid shift and OSA. Yet, to the best of our knowledge this has never been explored. As such, future studies investigating the effects of interventions aimed at reducing daytime leg fluid accumulation, overnight rostral fluid shift and OSA should utilize a longer-term treatment protocol.

It is somewhat surprising that calf muscle ES might not have led to a reduction in overnight neck fluid accumulation, given that calf muscle ES reduced NFV by 19 ml and NC by 0.8 cm over the 60-min supine period that followed the treatment session. By comparison, 45 min daily walking for four weeks reduced the overnight change in NFV and NC by 10 ml (not significant) and 0.5 cm, respectively [10]. Additionally, one week of twice daily walking reduced overnight change in NC by 0.7 cm (overnight NFV not measured) in non-obese men (only one woman in the sample) [30]. Meanwhile, two weeks of wearing compression stockings in men and women did not affect overnight change in NFV or NC [9]. The inclusion of women in their study potentially impacted the change in NC, since women tend to have less fluid accumulation in the neck via rostral fluid shift, despite the same volume of fluid leaving the legs [25]. While there is considerable variability in the neck fluid outcomes across studies, the present study reports values within the range of the previous work. However, despite a comparable reduction in neck fluid accumulation, calf muscle ES did not reduce AHI, whereas the previous studies did, as described. This is likely because in the present study, rostral fluid shift was examined immediately following the treatment session, which we used a

surrogate measure for overnight rostral fluid shift. Therefore, measuring rostral fluid shift immediately following the treatment is possibly an overestimate of overnight rostral fluid shift.

The benefit of calf muscle ES as therapy is that it can be developed into a convenient wearable platform that can apply calf muscle ES during prolonged sedentary periods (ie, sitting at a desk) when leg fluid is accumulating at a rapid rate. A device-based approach to reducing leg fluid will ensure consistency in both contraction strength and frequency. This benefit can be seen when comparing to the efficacy of seated stepping [29]. Compared to 4 h of stationary sitting, seated stepping reduced fluid accumulation in both legs by 54 ml. This reduction was approximately 40% lower than the present study, where calf muscle ES reduced leg fluid accumulation in both legs by an estimated 88 ml (44 ml in one leg). Calf muscle ES was likely more effective at reducing leg fluid accumulation due to the consistent regular intervals at which contractions were elicited by the device (every 2 s). In contrast to the prior study, where participants stepped at a self-selected pace which averaged to about 20 contractions per minute on each side – two-thirds the rate of contraction of the present study.

A device-based approach to preventing leg fluid accumulation can also improve upon the challenges associated with other competing therapies, such as physical activity and compression stockings. With respect to physical activity, compliance is low in the general population with only one in five adults achieving the recommended 150 min of weekly physical activity [31] due to factors including cost, lack of time or motivation, and illness or disability [32]. Furthermore, physical activity is less accessible than calf muscle ES for individuals with mobility limitations, which might be the cause of their sedentary lifestyle. Compression stockings are limited by their discomfort and difficulty to apply and remove, also leading to low patient adherence [13,14]. Compression stockings also increase risk of thrombosis [33] and exudative skin lesions [34] due to improper fit and use. Conversely, calf muscle ES under the protocol described in the present study, has been demonstrated to be comfortable over the short- and long-term [26,35]. Utilizing a device-based approach with calf muscle ES can potentially address the issues of compliance to therapies currently available for preventing excessive daytime leg fluid accumulation as a means of reducing overnight rostral fluid shift and treating OSA.

It is necessary to point out that sodium intake was significantly higher in the days leading up to the active ES study day, which can increase body fluid retention and diminish the effect of interventions on reducing body fluid. Additionally, calf circumference was also significantly larger at baseline on the active ES study day, indicating that participants may have started the study day with a higher volume of fluid in the legs. However, despite this increased sodium intake and larger calf circumference on the active ES study day, calf muscle ES was still effective at reducing rostral fluid shift. It is therefore plausible that the effect of calf muscle ES on rostral fluid shift may have been underestimated in the present study given the evidence of higher pre-treatment fluid retention on the active ES study day.

There are several limitations in the present study. First, only small sample of 13 participants underwent overnight sleep monitoring, which powered our main outcome of AHI. Although, given the modest reduction in snoring index, the effect of calf muscle ES on snoring should be confirmed in a follow-up study with a larger sample. In addition to measuring fluid volumes with bioelectrical impedance, calf and neck circumferences were measured using a tape measure. However, measurement error associated with calf circumference measurements is approximately 0.5 cm [36], which is greater than the differences observed between conditions. Despite this, we included the circumference measurements because many past studies, and possibly future studies, use circumferences as their

standard measurements for changes in leg and neck fluid volumes. Including these measurements allows for comparisons across studies. Furthermore, participants in the present study were all men, non-obese and without co-morbidities. Obesity and co-morbidities were exclusion criteria because of their potential confounding effect with rostral fluid shift on upper-airway mechanics. As a result, the study findings are not generalizable to typical sleep apnea patients who are often obese with cardiovascular co-morbidities [37]. Lastly, sleep apnea and snoring were measured using automated algorithms to detect apneas, hypopneas and snores using acoustic breathing data collected during sleep. While these algorithms have been validated and demonstrated high correlation with ground truth measures of apneas, hypopneas, and snores [20–24], there is still some degree of error that could over- or under-estimate the efficacy of calf muscle ES as a treatment for OSA. These limitations could be addressed in a follow-up study investigating the effect of long-term use of calf muscle ES on daytime leg fluid accumulation, overnight rostral fluid shift, as well as OSA and snoring.

In conclusion, the present study demonstrates that compared to a 150-min period of quiet sitting, repeated activations of the calf muscle by ES reduces leg fluid accumulation and the rostral shift of fluid out of the legs and into the neck upon lying supine. This led to a modest reduction in the snoring index, but no change in the OSA severity. Despite this lack of effect of calf muscle ES in attenuating OSA severity, the reduction in the snoring index suggests that it did have an effect, albeit mild, on upper-airway mechanics.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2019.01.035>.

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