

Attenuation of Obstructive Sleep Apnea by Compression Stockings in Subjects with Venous Insufficiency

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Rationale: Fluid accumulation in the legs and its overnight redistribution into the neck appears to play a causative role in obstructive sleep apnea (OSA) in sedentary men. Chronic venous insufficiency (CVI) promotes fluid accumulation in the legs that can be counteracted by compression stockings.

Objectives: To test the hypotheses that, in nonobese subjects with CVI and OSA, wearing compression stockings during the day will attenuate OSA by reducing the amount of fluid displaced into the neck overnight.

Methods: Nonobese subjects with CVI and OSA were randomly assigned to 1 week of wearing compression stockings or to a 1-week control period without compression stockings, after which they crossed over to the other arm. Polysomnography and measurement of overnight changes in leg fluid volume and neck circumference were performed at baseline and at the end of compression stockings and control periods.

Measurements and Main Results: Twelve subjects participated. Compared with the end of the control period, at the end of the compression stockings period there was a 62% reduction in the overnight leg fluid volume change ($P = 0.001$) and a 60% reduction in the overnight neck circumference increase ($P = 0.001$) in association with a 36% reduction in the number of apneas and hypopneas per hour of sleep (from 48.4 ± 26.9 to 31.3 ± 20.2 , $P = 0.002$).

Conclusions: Redistribution of fluid from the legs into the neck at night contributes to the pathogenesis of OSA in subjects with CVI. Prevention of fluid accumulation in the legs during the day, and its nocturnal displacement into the neck, attenuates OSA in such subjects.

Keywords: obstructive sleep apnea; treatment; fluid; chronic venous insufficiency

Obstructive sleep apnea (OSA), characterized by repetitive collapse of the upper airway during sleep, is a common disorder that has important cardiovascular consequences (1). Continuous positive airway pressure (CPAP) alleviates OSA, but it is not easily tolerated by many patients (2). A better understanding of the mechanisms underlying OSA might lead to new and better treatments. In general, upper airway occlusion is due to a sleep-induced reduction in dilator muscle tone superimposed on an

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In previous studies, we showed that the apnea-hypopnea index is strongly linked to the volume of fluid shifting from the legs into the neck overnight, suggesting that such a mechanism plays a pathophysiological role in obstructive sleep apnea (OSA).

What This Study Adds to the Field

In subjects with OSA and venous insufficiency, wearing compression stockings during the day attenuates OSA by reducing fluid accumulation in the legs and its overnight redistribution into the neck. Reducing overnight rostral fluid displacement is therefore a new means of attenuating OSA.

upper airway that is anatomically narrowed due to a mismatch between the space occupied by soft tissue and that available within the bony envelope surrounding it. As a consequence, most research on the pathophysiology of OSA has focused on the neural activity of the upper airway muscles and the anatomy of the upper airway, especially fat deposition in the neck and skeletal space limitations. Soft tissue factors have been considered relatively fixed, with the exception that weight loss could reduce fatty deposition in the neck and improve upper airway patency (3, 4). Another potentially reversible soft tissue factor that has received little attention is accumulation of fluid around the upper airway. Indeed, fluid displaced from the legs by inflation of anti-shock trousers increases neck circumference, narrows the upper airway, and increases its collapsibility in awake healthy subjects (5–7).

In humans, the bipedal upright posture promotes gravitational fluid accumulation in the legs. This is normally counteracted by leg muscle contractions that squeeze the veins, within which unidirectional valves ensure anterograde flow to the heart (i.e., a musculovenous pump) (8). When such contractions become infrequent, as during prolonged sitting, fluid may accumulate in the legs in a quantity that is proportional to the time spent in this position (9). This fluid shifts rostrally when moving from the sitting to the recumbent position at bedtime (10) in a quantity that is also proportional to the time spent sitting during the previous day (11, 12). In otherwise healthy subjects, in patients with heart failure, and in patients with hypertension, the amount of this overnight rostral fluid shift is strongly correlated with the degree of overnight increase in neck circumference and with the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index, AHI) (11–13). This led to the conclusion that a portion of the fluid accumulated in the legs during the day was redistributed into the neck at night and

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contributed to upper airway obstruction. However, because of the observational nature of these studies, a causative relationship between overnight rostral fluid shift and OSA remained to be established.

Elastic stockings that apply a compressive force of 20 to 30 mm Hg are effective in preventing dependent fluid accumulation in the legs (14). They increase the interstitial hydrostatic pressure of the tissues of the legs, thereby counteracting the filtration of fluid outside of the capillaries to the interstitium, in accordance with Starling's equation (15). In an uncontrolled pilot trial involving six sedentary nonobese men with OSA, prevention of fluid retention in the legs by wearing compression stockings for 1 day reduced the overnight displacement of fluid from the legs into the neck. This was accompanied by a corresponding reduction in the AHI. These observations suggested a causative relationship between overnight fluid displacement into the neck and OSA but were limited by the small number of subjects and the uncontrolled study design (16). Therefore, to further establish the pathophysiological role of fluid displacement into the neck in patients with OSA, we tested the hypothesis that compression stockings would reduce the AHI in subjects with chronic venous insufficiency (CVI) who should be particularly prone to the postural fluid shift phenomenon because of the compromise of the musculovenous pump (17). Some of the results of this study have been previously reported in the form of an abstract (18).

METHODS

Subjects

Subjects were drawn from a CVI clinic at Pitié-Salpêtrière hospital, Paris, France. Inclusion criteria were: (1) nonobese (body mass index [BMI] < 30 kg/m²) men and women; (2) at least 18 years of age; (3) established CVI; (4) suspicion of OSA based on the presence of at least two of habitual snoring, nocturnal dyspnea, nocturia, morning headaches, restless sleep, or excessive daytime sleepiness; and (5) OSA defined as an AHI greater than or equal to 15 on an overnight polysomnogram (*see below*). The diagnosis of CVI was established at the department of vascular surgery of Pitié-Salpêtrière hospital by Doppler examination conducted by expert phlebologists. The color flow duplex technique was used to detect obstruction or reflux and to determine their anatomic extent in the deep, superficial, and perforating veins (19). Exclusion criteria were: (1) tonsillar hypertrophy, (2) current history of smoking or alcohol abuse, (3) history of hypertension or other chronic disease, (4) use of prescribed medications, and (5) previously treated OSA.

Polysomnography

Overnight attended polysomnography was performed in the sleep laboratory of Pitié-Salpêtrière Hospital on a standard working day in all subjects using standard techniques and scoring criteria for sleep stages and arousals (20, 21). All subjects slept with one pillow and with the bed flat. Thoracoabdominal movements were measured by piezo bands and airflow by nasal pressure cannulae (22). Arterial oxyhemoglobin saturation was monitored by oximetry. Obstructive apneas were defined as cessation of airflow and hypopnea as a 50% or greater reduction in airflow from baseline but remaining above zero lasting 10 or more seconds with out-of-phase thoracoabdominal motion or flow limitation on the nasal pressure tracing associated with either an oxygen desaturation of greater than 3% or an arousal. Apneas were classified as central if there was no motion of the rib cage and abdomen. The AHI was calculated. All sleep studies were scored by the same physician, who was blinded to the use of or nonuse of compression stockings and to the measurements of leg fluid volume and ankle and neck circumferences.

Weight, Total Body Fluid, Leg Fluid Volume, Ankle and Neck Circumferences, and Overnight Water Balance

Weight was measured just before bedtime and within 30 minutes of waking in the morning. The total body fluid and the fluid volume of each leg

were measured by bioelectrical impedance (Hydra 4200; Xitron Technologies, San Diego, CA) after subjects had been instrumented for the sleep study while lying awake and supine with the legs straight as previously described (5–7, 11–13). This well-validated technique uses impedance to electric current within the body or a body segment to measure its fluid content. The mean fluid volume of the two legs, referred to as leg fluid volume, was used in the analysis. Measurements of ankle circumferences and of neck circumferences above the cricothyroid cartilage were made with a tape measure immediately before and after measuring leg fluid volume, respectively (11–13). Marks were drawn on the skin with an indelible pen to ensure that subsequent measurements were made at exactly the same level. Subjects then went to sleep.

Total body fluid, leg fluid volume, and ankle and neck circumferences were measured again within 15 minutes after awakening the next morning before subjects got out of bed. Overnight urine excretion and water intake were measured, and the water balance was calculated as the difference between water intake and urine volume. The differences between total body fluid, leg fluid volume, and ankle and neck circumferences after and before sleep were calculated as the overnight changes in these variables. The differences between leg fluid volume and ankle circumferences before sleep after compression stockings and control periods were used to evaluate compression stocking efficacy in prevention of dependent fluid accumulation in the legs. Total body fluid, leg fluid volume, and ankle and neck circumferences were measured by an operator before scoring of the polysomnogram, who was therefore blinded to the AHI.

Assessment of Sitting Time

The day of the polysomnogram, subjects filled in an hourly diary indicating how much time they spent in the sitting, standing, and lying positions from the time they arose in the morning up to the time they laid down in the sleep laboratory.

Compression Stockings

Off-the-shelf thigh-length compression stockings exerting an ankle pressure of 20 mm Hg or more were fitted according to the subjects' leg dimensions. The subjects slipped their stockings on immediately after awakening in the morning and wore them throughout the day until bedtime in the evening, when they removed them only after retiring to bed.

Protocol

This was a 1-week, single-center, randomized, controlled, open-label double-crossover trial. After acquisition of baseline data, subjects were randomly assigned by a computer-generated randomization schedule in a 1:1 ratio to 1 week of wearing compression stockings during the day (compression stockings period) or to 1 week during which they did not wear compression stockings (control period), after which they crossed over to the other arm of the study for 1 week. Baseline measurements were repeated at the end of each of the compression stockings and control periods. The protocol received legal and ethical clearance from the appropriate local authority (Comité de Protection des Personnes Ile-de-France 6, Pitié-Salpêtrière), and all subjects provided written informed consent before their participation.

Statistical Analysis

Data distribution passed a Shapiro-Wilk normality test, and data are thus summarized in terms of mean \pm SD. Student paired *t* tests were used to compare values obtained at the end of the control period with those obtained at the end of compression stockings period. Potential relationships between variations in overnight leg fluid volume change and the AHI were examined by Pearson correlation. A *P* value of less than 0.05 indicated statistical significance. Statistical analyses were performed using Statistix version 9.1 (Statistix Inc., Tallahassee, FL).

RESULTS

Between March 2009 and January 2010, 16 eligible subjects were invited to undergo polysomnography. Among these, 12 had an

AHI of 15 or greater, without any other sleep disorders. They were consecutively enrolled and randomized. The venous insufficiency involved the superficial and perforating veins in three subjects and was limited to the superficial veins in nine. In six subjects the dysfunction was bilateral and in six unilateral. Clinically, all subjects complained of legs heaviness and nine of feet swelling. None of them was using compression stockings at the time OSA was diagnosed. Table 1 shows that the subjects were equally divided between men and women and were generally middle-aged and nonobese. Their lifestyle could not be qualified as sedentary because they spent less than 10 hours a day sitting. A substantial reduction in leg fluid volume occurred overnight at baseline, with a pronounced overnight increase in neck circumference. They had severe OSA as indicated by the high AHI. All patients had less than five central apneas per hour of sleep after both the control and compression stockings periods.

At the end of the compression stockings period, no change in weight was noted compared with the end of the control period, but the total body fluid measured before sleep was reduced by 0.6 kg (Table 2). Moreover, the leg fluid volume and the ankle circumferences measured before sleep were reduced by 150 ml and 0.5 cm, respectively, demonstrating the effectiveness of compression stockings in reducing dependent fluid accumulation in the legs. There was no difference in sitting time during the control and compression stockings periods. There was a 5 and 3% reduction in total body fluid overnight, respectively, after the control and compression stockings periods, which was, in part, attributable to the overnight negative water balance and in part to the insensible fluid loss. As shown in Figure 1, a substantial reduction in leg fluid volume did occur overnight at the end of the control period. This reduction corresponded to 12% of the leg fluid volume before sleep, and it was accompanied by a pronounced increase in neck circumference. The average AHI values indicate that these patients had severe OSA. One week of wearing compression stockings reduced the overnight change in leg fluid volume by 154 ml on average (62%, $P < 0.001$). A concomitant 0.7-cm reduction in the overnight change in neck circumference (60%, $P < 0.001$) also occurred. These changes were accompanied by a significant decrease in the AHI (36%, $P = 0.002$) as compared with the control period. We did not find any significant correlation between the

TABLE 1. BASELINE CHARACTERISTICS OF THE SUBJECTS (N = 12)

Sex, men/women	6/6
Age, yr	59 ± 5
Body mass index, kg/m ²	26.4 ± 4.0
Neck circumference before sleep, cm	39.1 ± 4.3
Sitting time, h/day	7.9 ± 1.5
Overnight change in leg fluid volume, ml	-268 ± 89
Overnight change in neck circumference, cm	1.1 ± 0.4
Apnea-hypopnea index, no./h of sleep	48.6 ± 26.0

Values are expressed as mean ± SD. Leg fluid volume is the mean of the volumes of the two legs.

reduction in leg fluid volume change and the reduction of the AHI. The reduction in overnight change in leg fluid volume was consistent with a significant reduction in overnight change in ankle circumferences (from 0.6 ± 0.4 to 0.2 ± 0.4 cm, $P = 0.013$ for the left ankle and from 0.6 ± 0.5 to 0.2 ± 0.4 , $P = 0.006$ for the right ankle). There were no differences in sleep time spent in the supine and nonsupine positions or in sleep stage distribution after the control and compression stockings period (Table 2), demonstrating that the change in AHI is not attributable to changes in these variables.

DISCUSSION

This double-crossover randomized study sheds light on the relationship between overnight displacement of fluid from the legs into the neck and OSA. Indeed, in subjects with CVI and severe OSA, wearing compression stockings for 1 week reduced dependent fluid accumulation in the legs and reduced the volume of fluid displaced overnight from the legs into the neck (Figure 1). The attenuation of the overnight rostral fluid displacement from the legs caused a significant reduction in the AHI. These findings therefore firmly establish the causative relationship between overnight rostral fluid displacement from the legs and OSA that was hinted at by our previous report (16). They also demonstrate that wearing compression stockings during the daytime can contribute to attenuate the severity of OSA in subjects with both severe OSA and CVI. This provides proof of principle that reducing overnight rostral fluid displacement is a new

TABLE 2. MEASUREMENTS PERFORMED BEFORE SLEEP AND THEIR OVERNIGHT CHANGES, SITTING TIME, OVERNIGHT WATER BALANCE, TOTAL SLEEP TIME, AND SLEEP POSITIONS AND STAGES AFTER CONTROL AND COMPRESSION STOCKINGS PERIOD

	Control Period	Compression Stocking Period	P Value
Body weight before sleep, kg	80.2 ± 14.0	80.0 ± 14.4	0.704
Total body fluid before sleep, kg	39.1 ± 7.0	38.5 ± 7.5	0.026
Leg fluid volume before sleep, L	4.47 ± 0.70	4.32 ± 0.71	0.003
Left ankle circumference before sleep, cm	23.1 ± 2.1	22.5 ± 2.1	<0.001
Right ankle circumference before sleep, cm	23.0 ± 1.8	22.6 ± 1.8	0.001
Sitting time, h/d	7.4 ± 1.4	7.7 ± 1.3	0.509
Change in body weight overnight, kg	-1.0 ± 0.5	-0.8 ± 0.7	0.339
Change in body fluid overnight, kg	-1.9 ± 0.8	-1.3 ± 1.7	0.247
Overnight fluid intake, ml	172 ± 213	181 ± 252	0.721
Overnight urine volume, ml	545 ± 334	331 ± 225	0.007
Overnight water balance, ml	-373 ± 238	-150 ± 138	0.011
TST, min	450 ± 51	414 ± 61	0.062
Sleep time in supine position, % of TST	56 ± 34	55 ± 35	0.853
Sleep time in nonsupine position, % of TST	44 ± 34	45 ± 35	0.858
REM sleep, % of TST	18 ± 6	19 ± 6	0.416
Non-REM sleep, % of TST	82 ± 6	81 ± 6	0.403

Definition of abbreviation: TST = total sleep time.

Values are expressed as mean ± SD. Leg fluid volume is the mean of the volumes of the two legs. Overnight water balance is the difference between water intake and urine volume during the night.

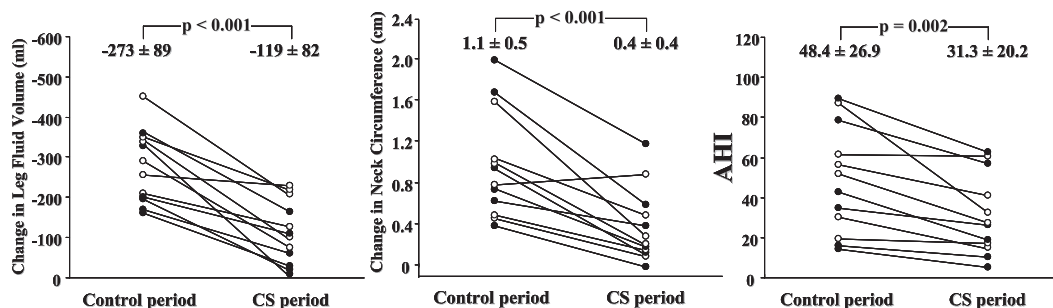


Figure 1. Influence of compression stockings (CS) on overnight changes in leg fluid volume and neck circumference and on the apnea-hypopnea index (AHI) in the 12 subjects (solid circles = 6 men; open circles = 6 women).

means of attenuating OSA. Whether this holds true outside the CVI population and whether or not this has clinical implications will have to be determined.

We have previously shown in an uncontrolled study involving six sedentary nonobese men with OSA that 1 day of wearing compression stockings reduced the amount of fluid retained in the legs during the daytime and its overnight rostral displacement in association with a corresponding reduction in the AHI (16). The present study confirms those findings and extends them by demonstrating in the more rigorous setting of a double-crossover, randomized protocol that wearing off-the-shelf thigh-length compression stockings for 1 week reduced daytime fluid accumulation in the legs by 300 ml, overnight rostral fluid displacement by 308 ml (60%), and overnight change in neck circumference by 0.7 cm, with a consequent 36% reduction in the AHI in nonobese subjects with CVI and moderate to severe OSA. Whether more optimal fitting of compression stockings (i.e., custom made) or a longer treatment period might cause more pronounced reductions in fluid accumulation in the legs during the day, rostral fluid displacement during the night, and severity of OSA merits further exploration.

CVI of the lower limbs is characterized by structural or functional abnormalities of venous valves of the legs leading to venous hypertension. The consequent higher capillary hydrostatic pressure results in higher transcapillary fluid filtration and accumulation into the interstitial tissue space of the legs (17). When moving to the recumbent position at bedtime, this interstitial fluid accumulated in the legs is reabsorbed into the intravascular compartment and is redistributed into the upper body in relation to gravitational forces (10). A portion of the fluid displaced from the legs via the abdomen is redistributed into the neck at night (11–13). Whether it accumulates in the blood vessels or in the interstitial spaces is unclear, but in either case it leads to narrowing of the upper airway, probably due to increasing extraluminal tissue pressure that predisposes to its collapse during sleep (5–7). In keeping with those findings, the present study demonstrates that reduction of fluid retention in the legs and its overnight shift into the neck attenuates OSA. Hence, fluid accumulation in the legs and its redistribution into the neck at night can now be considered a mechanism for OSA. The therapeutic effect of compression stockings is based on countering this mechanism. Accordingly, compression stockings can serve as an adjunctive measure for the management of the OSA, at least in subjects with CVI. Larger, longer trials are needed to determine whether this effect can be enhanced to more completely alleviate OSA and improve clinical outcomes.

In a recent study, the absence of an increase in the severity of OSA from the first to the second half of the night has been advanced as an argument against the role of the rostral overnight fluid displacement in the pathogenesis of OSA (23). However, because overnight leg fluid volume changes were not measured in that study, no conclusions about the role of overnight fluid shifts in the pathogenesis of OSA could reasonably have been

drawn from this observation. In addition, it has been shown that on the transition from the standing to the supine position, most of fluid displacement from the legs to the upper body occurs within 30 to 60 minutes (24). Consequently, a rapid fluid shift might induce a relatively quick change in upper airway characteristics at the beginning of the night without further significant changes overnight. If so, the AHI may not progress overnight as a result of continued fluid shift.

To avoid the potential confounding influence of obesity on the AHI, we confined our study to nonobese subjects. Thus, our findings may not be applicable to obese subjects. Nevertheless, CVI is common in obese subjects, and they are often sedentary. The possibility that rostral fluid redistribution at bedtime might contribute to OSA and compression stockings might attenuate OSA in obese subjects therefore warrants testing. Whether prevention of overnight rostral fluid displacement can attenuate OSA in other patient populations is an important issue that remains to be addressed in future studies.

It has been shown that approximately one-third of patients with OSA have leg edema (25) and that 70% of patients with leg edema have OSA (26). Although these studies show an association between OSA and leg edema, they did not demonstrate causality. In another study, the same authors showed that, in seven of eight patients with OSA and leg edema, CPAP reduced the amount of leg edema (27). These results led them to conclude that OSA causes leg edema. On the other hand, the present study provides evidence for a causative role of leg fluid retention in OSA pathogenesis. Even though the conclusions are seemingly the opposite of one another, one does not exclude the other. In fact, it is possible that leg edema causes OSA and OSA causes leg edema in a vicious cycle, which might be interrupted both by treating leg edema and by CPAP therapy.

Our study is subject to some limitations. The number of subjects was small, and the intervention period was short. Nevertheless, because our study was performed according to a very stringent clinical trial design—a randomized, controlled, double-crossover study—and because the effects of compression stockings on overnight changes in rostral fluid displacement and neck circumference and on the AHI were very consistent, we can conclude that compression stockings worn during the daytime reduced the AHI (Figure 1). In this, as in previous studies, we did not measure the overnight increase in neck fluid volume consequent to rostral fluid shift directly owing to the technical difficulties of doing so. Rather, we used changes in neck circumference as a surrogate measurement, which may be subject to some inconsistencies. Future studies will therefore be required to better quantify the actual changes in fluid content or volume and of the neck peripharyngeal tissues using, for example, computed axial tomography or magnetic resonance imaging techniques. In addition, in this study we did not measure the upper airway caliber or its resistance and collapsibility, but, considering the results of our previous studies (5–7), we can infer from the reduction in overnight increase in neck

circumference and reduction in the AHI that they were favorably altered by compression stocking usage. There was no significant correlation between the reduction in leg fluid volume change and the reduction of the AHI. This was probably because rostral fluid shift participates in the pathogenesis of OSA along with other factors, and its relative role may vary among different patients. The reduction in AHI was modest, and its clinical significance was not determined. Off-the-shelf compression stockings were used that may not be as effective as custom-made stockings. Thus, future studies should involve more subjects over longer periods using custom-made compression stockings, and clinical outcomes, such as sleepiness and neurocognitive function, should be assessed.

In conclusion, our findings provide proof of principle that among subjects with CVI, overnight rostral fluid displacement is a mechanism of disease for OSA. The effect of compression stockings on OSA is based on counteracting this fluid displacement, and prevention of dependent fluid accumulation could constitute a new therapeutic approach to OSA. Accordingly, these findings provide a strong rationale to test other interventions targeting fluid retention and its overnight rostral redistribution, such as diuretics and exercise, as novel therapies for OSA.

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