Role of overnight caudo-rostral fluid shift in the pathogenesis of sleep apnea

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Summary

The prevalence of obstructive sleep apnea (OSA) is higher in patients with fluid-retaining states, such as chronic heart failure (CHF), than in the general population. In patients with CHF, central sleep apnea (CSA), which is rare in the general population, is also common. Although OSA and CSA pathogenesis is multifactorial, these observations suggest that fluid retention may contribute to the development of both types of sleep apnea in CHF and in other fluid-retaining states. In particular, excess fluid accumulated in the legs while upright during the day because of gravity, is redistributed rostrally overnight on lying down, again due to gravity. Some of this fluid may reach the neck, increasing tissue pressure around upper airway and thereby predisposing to OSA. In CHF patients, with increased rostral fluid shift, fluid may additionally accumulate in the lungs, provoking hyperventilation, driving $PaCO_2$ below the apnea threshold and thereby triggering CSA. This article will review the evidence supporting overnight rostral fluid shift as a potential contributor to the development of both OSA and CSA.

KEY WORDS: sleep apnea; fluid shift; pathogenesis.

Introduction

Obstructive sleep apnea (OSA), is more prevalent in patients with fluid-retaining states, such as chronic heart failure (CHF) (1,2), end stage renal disease (ESRD) (3), drug-resistant hypertension (4) and idiopathic peripheral edema (5), than in the general population (6). In patients with CHF, central sleep apnea (CSA), which is rare in the general population (7), is also common (1,2). Moreover, in CHF patients, both types of sleep apnea can be present, and the predominant type can shift from obstructive to central (8,9). These observations suggest that fluid overload might contribute to the pathogenesis of OSA in some patients and that, in CHF patients, the pathogenesis of OSA and CSA may be linked by fluid overload.

OSA is caused by repetitive collapse of the pharynx secondary to the reduction of pharyngeal dilator muscle tone at sleep onset, superimposed upon a narrowed or collapsible pharynx (10). In contrast, CSA is caused by intermittent cessation of central respiratory drive due to a fall in $PaCO_2$ below the apnea threshold during sleep (11). Therefore, it has been hypothesized that some of the fluid accumulated in the legs while upright during the day and redistributed rostrally overnight on lying down, may reach the neck, increasing fluid volume and tissue pressure around upper airway (UA) and predisposing to OSA, or accumulate in the lungs, causing pulmonary congestion, pulmonary C fiber stimulation, hyperventilation and a fall in $PaCO_2$, thus predisposing to CSA (Figure 1). The objective of this review is to summarize the evidence of the possible role of excessive fluid retention during the day and its nocturnal redistribution in the pathogenesis of OSA and CSA.

Sleep apnea prevalence in fluid-retaining states

Sleep apnea is present if the number of apneas and hypopneas per hour of sleep, the apnea-hypopnea index (AHI), is ≥5 and it is mild if the AHI is from 5 to 15, moderate if the AHI is from 15 to 30 and severe if the AHI is ≥30 (12). Moderate to severe OSA occurs in approximately 7% of adults from the general population (6) and its prevalence is four to five times higher in patients with the fluid retaining states of CHF (1,2) and ESRD (3), respectively. Moreover, patients with drug-resistant hypertension, another condition associated with fluid overload, have an extremely high prevalence of moderate to severe OSA of approximately 80% (4). In a non-randomized, uncontrolled study involving patients with diastolic CHF and OSA, intensive diuresis was accompanied by attenuation of OSA in association with an increase in UA caliber (13). Moreover, studies in patients with ESRD on dialysis revealed marked improvement of sleep apnea when fluid removal during the night was increased (14,15). A recent study demonstrated that

CHF patients with sleep apnea have greater sodium intake, which promotes fluid retention, than those without sleep apnea, and the AHI correlates with sodium intake.

spironolactone reduces the severity of OSA in patient with drug resistant hypertension (16). Finally, in patients with nephrotic syndrome, leg edema and OSA, treatment of the nephrotic syndrome with steroids resolved edema, decreased total body water, and reduced the AHI by 50% (17). On the other hand, while CSA is rare in the general population (prevalence of <1%) (7), it is common among patients with CHF (prevalence of 23-40%) (1,2). Moreover, CHF patients with sleep apnea have greater sodium intake, which promotes fluid retention, than those without sleep apnea, and the AHI correlates with sodium intake (18). All these observations suggest that fluid overload might contribute to the pathogenesis of both OSA and CSA in some patients. However, these studies did not examine overnight fluid redistribution nor the effect of reducing overnight rostral fluid shift on sleep apnea severity. Accordingly, while fluid overload has been shown to be associated with both OSA and CSA, the redistribution of fluid during sleep and the impact of its accumulation at different levels remained to be determined.

Effect of posture on body fluid distribution

When subjects assume the recumbent position at bedtime, excess fluid accumulated in the interstitial tissues of the legs is reabsorbed into the intravascular compartment and is redistributed towards the head and upper body because of gravity.

Body fluid distribution is influenced by body posture (19). During sitting or motionless standing, the height of the venous blood column to the level of the heart is higher than in the supine position. This greater gravitational force accumulates blood in the capacitance vessels of the legs. In accordance with Starling's equation (20), the consequent higher capillary hydrostatic pressure results, in higher filtration of fluid from the capillaries into the interstitial tissue spaces of the legs. As a consequence, there is an increase in extracellular fluid in the lower extremities (21). During walking, this is counteracted by leg muscle contraction that squeezes the veins, within which unidirectional valves ensure anterograd flow to the heart (i.e. a musculo-venous pump) (22-25). Accordingly, inactivity predisposes to fluid accumulation in the legs such that the amount of fluid accumulated in the lower extremities at the end of the day is proportional to the amount of time spent in the sitting position (22,23,26,27).

When subjects assume the recumbent position at bedtime, excess fluid accumulated in the interstitial tissues of the legs is reabsorbed into the intravascular compartment via Starling's forces (18) and is redistributed towards the head and upper body because of gravity (21,28,29). When healthy subjects move from the upright to the recumbent position, 240-360 ml of fluid is displaced from the legs to the upper part of the body (21), and most of this displacement occurs within 30-60 minutes (29). Fluid redistributed rostrally on lying down moves into the abdomen, thorax, neck and head (30,31).

Obstructive sleep apnea

Current understanding of the pathogenesis of OSA suggests that maintenance of UA patency during sleep depends on the balance of anatomical/structural factors and imposed mechanical loads versus compensatory neuromuscular responses (10). Anatomically, the UA is enclosed along its length by bones (nasal turbinates, hard palate, mandible, hyoid and cervical vertebrae) that envelop soft tissues surrounding the UA lumen (soft palate, uvula, tonsillar pillars, tongue, lymphoid tissue, UA muscles, pharyngeal fat pads and blood vessels). A mismatch between the space available within the bony envelope and that occupied by the soft tissues may decrease UA size and transmural pressure predisposing to the UA collapse. In contrast, the actions of UA dilator muscles counteract these collapsing forces to maintain UA patency. OSA develops when the structures surrounding the UA produce a collapsing force that cannot be adequately compensated by UA dilator muscles. Soft tissue factors have been considered relatively fixed, with the exception that weight loss could reduce fatty deposition in the neck and improve UA patency and collapsibility (32,33). Another potentially reversible soft tissue factor that has received little attention in the past is the accumulation of fluid around the UA.

Accumulation of fluid around upper airway

Systemic infusion of papaverine and nitroprusside cause a significant reduction of UA cross-sectional area in association with an increased thickness of the UA mucosa.

Accumulation of fluid around the UA has been demonstrated on tissue specimens and with MRI scanning in OSA patients (34,35). For example, pharyngeal mucosal water content, assessed by MRI of the UA, is greater in ESRD patients with, than in those without OSA (36). Edema of the soft tissues surrounding the UA could result from transudation of fluid into the interstitial space secondary to increased hydrostatic pressure in the neck veins, or from vascular congestion secondary to the trauma and/or inflammation caused by vibration of tissues during snoring. UA edema can contribute to soft tissue enlargement in OSA patients. In fact, it has been shown that systemic infusion of the vasodilators such as papaverine and nitroprusside caused a significant reduction of UA cross-sectional area in association with an increased thickness of the UA mucosa in cats (37). Conversely, topical application of a vasoconstrictor phenylephrine, to the pharyngeal mucosa decreased pharyngeal resistance in healthy humans (38). Pharyngeal mucosal water content also decreased after chronic application of continuous positive airway pressure (CPAP) in patients with OSA (39). In addition, distension of the jugular veins that are located adjacent to the lateral pharyngeal walls, is likely transmitted medially to the pharynx, narrowing its lumen, because the expansion of these vessels is limited by the mandible laterally and cervical spine posteriorly. The above mentioned observations strongly suggest that fluid accumulation around the UA may cause pharyngeal narrowing and increase the likelihood of UA collapse in patients predisposed to OSA. However, the role of caudo-rostral fluid redistribution in the causation of UA occlusion remained to be assessed.

Effect of induced rostral fluid shift on the upper airway

Considering that UA dilator muscle activity diminishes at the transition from wakefulness to sleep, it is likely that rostral fluid displacement would have had an even greater effect on the UA during sleep.

Shepard et al. (40) first proposed that fluid displacement from the lower extremities to the upper body during sleep could play a role in narrowing the UA, predisposing to its collapse. They tested the potential effects of shifting fluid into the neck by raising the legs for 10 minutes, and of reducing venous return to the upper body by applying venous occlusive tourniquets for 10 minute around the thighs in patients with OSA. Using computed tomography, they found a tendency for UA cross-sectional area to decrease and increase in response to leg raising and tourniquet application, respectively. However, they did not measure either the amount of fluid displaced out of or accumulated into the legs in response to these interventions, nor did they assess whether any fluid was displaced into or out of the neck. It is therefore possible that they did not find a significant reduction in UA size in response to leg raising because this intervention did not cause sufficient fluid displacement into the neck.

Excess fluid redistribution from the lower to the upper body occurring with recumbency during sleep has been effectively reproduced by the application of a positive pressure of 40 mmHg to the legs of healthy, non obese subjects for 5 minutes while awake by using medical antishock trousers. A 160 to 190 ml reduction in fluid volume of each leg, measured using bioelectrical impedance, was accompanied by a significant increase in neck circumference, measured using mercury strain gauge plethysmography at the superior border of the cricothyroid cartilage and used as a surrogate of fluid content change of the neck. This caused a significant reduction in UA calibre (41), as well as an increase in UA airflow resistance (42) and collapsibility (43), indicating that a portion of the fluid displaced from the legs reached the neck and influenced UA anatomy and function (Figure 1). The same experiment performed in patients with systemic hypertension and in CHF patients with OSA caused, respectively, a reduction in UA caliber and an increase in UA resistance to airflow which were strongly related to the amount of fluid displaced from the lower extremities by the application of positive pressure to the legs (44,45). These experiments were conducted during wakefulness, because it would not have been feasible for subjects to sleep uninterrupted with antishock trousers in the deflated and then in the inflated state. However, considering that UA dilator muscle activity diminishes at the transition from wakefulness to sleep, it is likely that rostral fluid displacement would have had an even greater effect on the UA during sleep.

Spontaneous rostral fluid shift during sleep and OSA

Overnight caudo-rostral fluid shift might not be a primary causal factor for OSA, but could be secondary to negative intrathoracic pressure generated by inspiratory efforts during obstructive apneas, drawing fluid from the legs into the neck.

Spontaneous fluid shift from the legs to the neck and its relationship with OSA has been demonstrated in a number of groups of patients. In non-obese men, severity of OSA, as assessed by the AHI, was highly related to the degree of overnight leg fluid volume reduction (Figure 2) which was in turn related to a concomitant increase in neck circumference (46). Indeed, the overnight increase in neck circumference correlated with the amount of fluid displaced from the legs overnight, supporting the con-

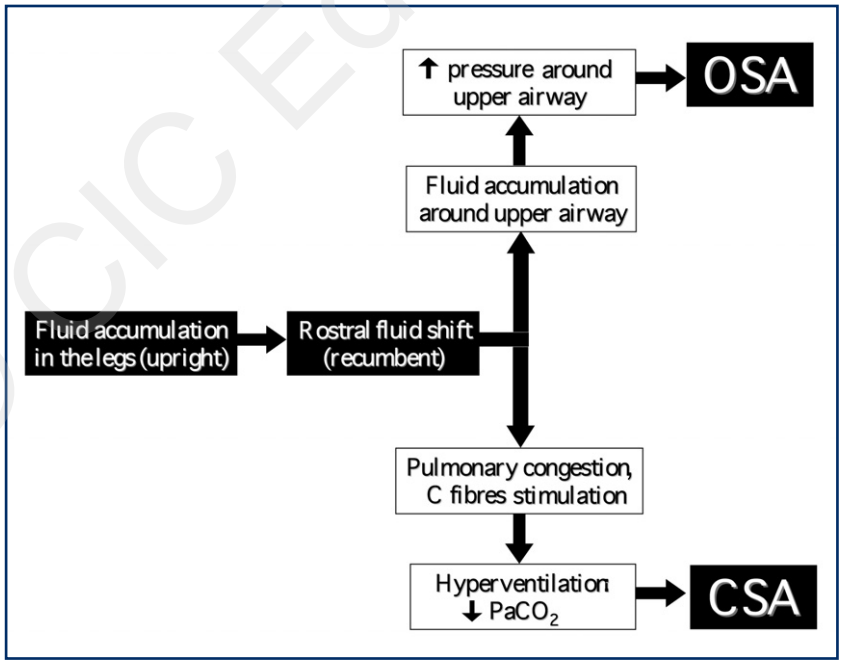

Figure 1 - The role of overnight rostral fluid shift in the pathogenesis of obstructive and central sleep apnea (OSA and CSA). $PaCO_2$: arterial partial pressure of carbon dioxide, UA: upper airway.

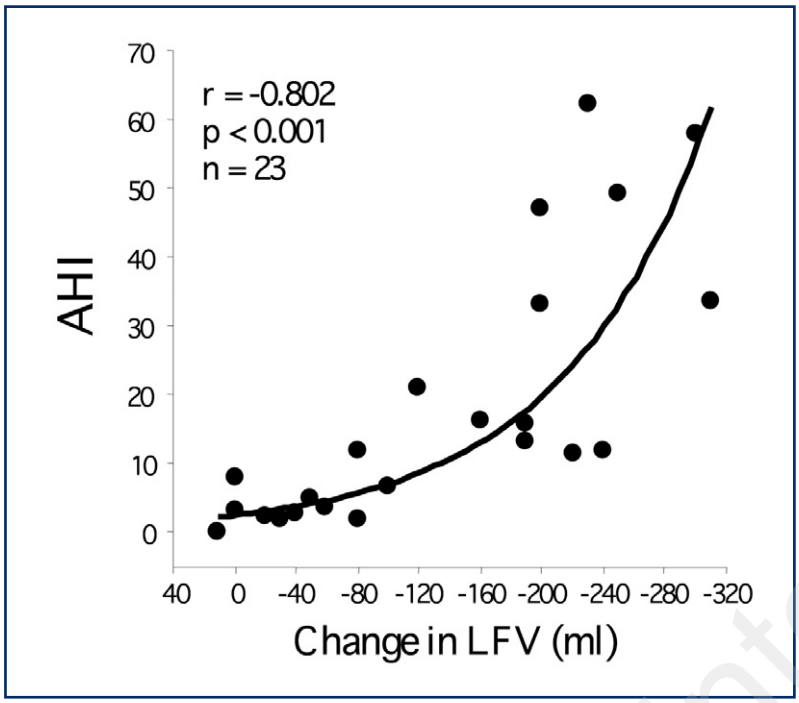

Figure 2 - Relationship between the overnight change in leg fluid volume (LFV) and the apnea-hypopnea index (AHI) in non-obese men.

cept that part of the fluid displaced from the legs was redistributed into the neck. Moreover, the reduction in leg fluid volume was the strongest correlate of the AHI and explained approximately 64% of AHI variability independently from other factors, indicating that the more fluid was displaced from the legs at night, the greater was the AHI. This relationship between the fluid displacement from the legs and the AHI was exponential, probably in relation to the fact that UA resistance to airflow increases to the fourth power of the decrease in the radius of a tube. Similar relationships were observed between overnight decrease in LFV and severity of OSA in patients with hypertension (47), men with CHF (48) and ESRD (49).

The observational nature of these studies does not prove a cause-effect relationship between overnight caudo-rostral fluid shift and OSA. In fact, overnight caudo-rostral fluid shift might not be a primary causal factor for OSA, but could be secondary to negative intrathoracic pressure generated by inspiratory efforts during obstructive apneas, drawing fluid from the legs into the neck. However, in CHF patients with OSA, CPAP, while preventing obstructive apneas, did not reduce overnight fluid movement out of the legs, suggesting that rostral fluid shift from the legs is a primary phenomenon (48).

Central sleep apnea

During sleep, ventilation is largely dependent upon $PaCO_2$. Central apnea occurs when $PaCO_2$ falls below the threshold required to stimulate respiration (i.e. the apnea threshold). CHF patients with CSA tend to chronically hyperventilate, with $PaCO_2$ closer to the apnea threshold than normal. Thus, even slight perturbations that augment ventilation, such as arousals from sleep, can drive $PaCO_2$ below the apnea threshold and trigger a central apnea. In fact, in CHF patients with CSA, the AHI is inversely proportional to $PaCO_2$ (50). In CHF patients, hyperventilation is caused by increased peripheral and central chemosensitivity, and stimulation of pulmonary C fibres by pulmonary congestion due to elevated pulmonary capillary wedge pressure (PCWP) (51-54). In fact, in CHF patients, $PaCO_2$ is inversely proportional to PCWP (55). In addition, CHF patients with CSA have higher PCWP than those without CSA and intensive medical therapy decreases both PCWP and AHI (56).

Therefore, it has been hypothesized that some of the fluid accumulated in the legs while upright during the day and redistributed rostrally overnight on lying down, may reach the lungs, leading to pulmonary congestion and C fibre stimulation. The ensuing hyperventilation and the decrease in $PaCO_2$ towards the apnea threshold may easily trigger CSA (Figure 1). Indeed, in awake CHF patients with CSA the rostral fluid shift induced by the application of positive pressure to the legs through antishock trousers induced a 1.4 mmHg reduction in transcutaneous PCO_2 ($PtcCO_2$), which is clinically significant since such a decrease is able to induce CSA during sleep in CHF patients (50), in association with a reduction in the UA resistance (45). This suggested that a portion of the fluid displaced from the legs shifted into the lungs, stimulated pulmonary C fibres and increased central respiratory drive, which caused hyperventilation. It is likely

Susceptibility to OSA increases in HF patients in whom rostral fluid shift induces an increase in UA resistance, whereas susceptibility to CSA increases in those in whom with increased respiratory drive and reduced UA resistance and $PaCO_2$

that the increased central respiratory drive simultaneously activated pharyngeal dilator muscles, stabilizing the UA. Moreover, the AHI in men with CHF and CSA was directly related to the degree of spontaneous overnight rostral fluid shift and inversely to the level of overnight $PtcCO_2$ (48). All these observations provide evidence that, in CHF patients, overnight rostral fluid shift can contribute to the pathogenesis of both OSA and CSA. In particular, these findings suggest that in HF patients in whom rostral fluid shift induces an increase in UA resistance, susceptibility to OSA will increase, whereas in those in whom it induces an increase in respiratory drive with reductions in UA resistance and $PaCO_2$, susceptibility to CSA will increase (Figure 1).

Shift in sleep apnea type in patients with chronic heart failure

In CHF patients, both OSA and CSA can co-exist, and the type can shift from predominantly obstructive to predominantly central from the beginning to the end of the night (8) and over longer periods of time (9). In both cases, this shift was associated with a decrease in $PaCO_2$ which is inversely related to the PCWP (55). In addition, the shift from OSA to CSA occurred in association with an increases in circulation time and apnea-hyperpnea cycle duration, both of which are indicative of a falling cardiac output (57). The implications of these findings are that the adverse mechanical and neuro-humoral effects of OSA on the failing heart aggravate cardiac dysfunction causing further declines in cardiac output and increases in PCWP that eventually drive $PaCO_2$ below the apnea threshold. Conversely, a shift from predominantly CSA to predominantly OSA over time was associated with a reduction in circulation time, apnea-hyperpnea cycle duration and an increase in left ventricular ejection fraction (58). Thus conversion from CSA to OSA occurs in association with improvement in cardiac function. Taken together, the above observations suggest that in CHF patients, nocturnal rostral fluid shift can play a role in both OSA and CSA, and the predominant type can shift in association with alterations in cardiovascular function and, probably, in relation to variations in the degree of nocturnal rostral fluid displacement.

On the other hand, in patients with OSA who do not have CHF, CSA is rare and OSA has not been shown to convert to CSA overnight or over time. It has been shown that in OSA patients both with and without CHF, the maximum fluid shift from the legs is about 300 ml, whereas in CHF patients with CSA, the maximum fluid shift is about 600 ml (46,48). Moreover, in OSA patients with CHF there is no correlation between overnight fluid shift and $PaCO_2$, unlike in those with CSA, where there is an inverse correlation (48). Thus, the degree of fluid shift associated with OSA, both in patients with and without CHF, appears to be insufficient to cause pulmonary congestion, pulmonary C fibres stimulation, hyperventilation and a fall in $PaCO_2$ below the apnea threshold. Furthermore, in the case of OSA patients without CHF, nocturnal fluid shift into the heart is probably insufficient to raise PCWP and lower $PaCO_2$ in the face of normal cardiac systolic and diastolic function.

Factors influencing fluid shift and sleep apnea

Physical activity

During walking dependent fluid accumulation is counteracted by the activation of the musculo-venous pump in the legs and calf contraction squeezes the veins ensuring anterograd flow to the heart because of unidirectional valves (24, 25, 59). In contrast, during sitting the inactivity of the musculo-venous pump allows dependent fluid accumulation in the legs (23, 24). As a consequence, low level of physical activity, which is becoming more and more common in modern society predisposes to greater fluid accumulation in the legs during the day, greater fluid displacement from the legs when lying down at night and greater movement of fluid in the chest and neck. Thus, inactive individuals may be predisposed to both OSA and CSA. In fact, in non-obese men the AHI was related to overnight decrease in legs fluid volume which was in turn proportional to the amount of time spent sitting during the day (47). Similarly, it was shown that in CHF patients with OSA or CSA, the AHI and overnight decrease in leg fluid volume were related directly to sitting time and inversely to physical fitness (49).

Epidemiological studies demonstrate that higher levels of physical activity are associated with reduced prevalence and incidence of OSA, independently of body mass index. Moreover, a modest reduction in OSA severity has been described after exercise interventions without concomitant change in body weight.

Epidemiological studies demonstrate that higher levels of physical activity are associated with reduced prevalence and incidence of OSA, independently of body mass index (60-62). Moreover, a modest reduction in OSA severity has been described after exercise interventions without concomitant change in body weight (62-64). Similarly, in CHF patients, exercise training caused a modest reduction in severity of OSA or CSA (65, 66).These observations provide evidence that exercise may protect against, or reduce severity of sleep apnea apart from any effect on body weight. However, the underlying mechanisms for this effect remains unknown. One possible mechanism is that exercise may prevent daytime fluid accumulation in the legs, and thereby reduce rostral fluid displacement into the neck or chest at night.

Age

Age may also be a factor affecting rostral fluid shifts. In fact, as people grow older, they lead an increasingly sedentary life (67). Moreover, daytime dependent fluid accumulation in the legs is more likely to occur in the elderly due to a compromised function of the venous valves of the legs that facilitates gravitational fluid accumulation (68). Indeed, in non-obese, otherwise healthy men with OSA, the de-

The fact that prevalence of both OSA and CSA increases progressively with age may be partly explained through the effect of age on daytime dependent fluid retention in the legs.

gree of overnight rostral fluid shift from the legs correlated directly with age independently of other factors, including sitting time (46). Hence, the fact that prevalence of both OSA and CSA increases progressively with age (1,6) may be partly explained through the effect of age on daytime dependent fluid retention in the legs.

Sex

In healthy men and women application of low body positive pressure caused a similar decrease in legs fluid volume, but UA collapsibility increased more in men than women.

In the general population, the prevalence of OSA is estimated at 3-14% in men and 4-9% in women (6). In CHF patients, male sex is a risk factor for both OSA and CSA (1). A number of potential explanations for the difference in prevalence of OSA between the sexes have been investigated, such as differences in UA length, responses to UA obstruction, UA collapsibility, genioglossus activity, body and neck fat distribution and hormonal status (69). Another potential mechanism contributing to the higher male prevalence of OSA may be differences in patterns of overnight rostral fluid shift between men and women. In fact, in healthy men and women, application of low body positive pressure caused a similar decrease in legs fluid volume, but UA collapsibility increased more in men than women (70). Moreover, despite similar overnight decreases in LFV in men and women with CHF, the overnight increase in neck circumference was much smaller in women and than in men, and the strong direct relationship between AHI and overnight rostral fluid shift observed in men was absent in women (48,71). These observations suggest that a greater proportion of the fluid shifting from the legs accumulates in the neck in men than in women, which may therefore result in increased peripharyngeal pressure and OSA. Reasons for differing patterns of overnight fluid redistribution between men and women are not clear and merit further investigation. Different patterns of overnight rostral fluid shift might also help to explain the higher prevalence of CSA in men than in women with CHF.

Obesity

The prevalence of OSA increases with increasing BMI and neck circumference, probably due to fat deposition in the soft tissue surrounding the pharynx, which narrows the UA lumen and increases its collapsibility (72,73). Nevertheless, considering that obese subjects are often sedentary and have increased circulating levels of mineralocorticoids that contribute to fluid retention and chronic leg edema, it is possible that rostral fluid redistribution at bedtime also contributes to the development of OSA in these individuals. This possibility requires further exploration.

Effect of manipulation of fluid shifts on sleep apnea

In patients with OSA and chronic venous insufficiency, wearing compression stockings for one day or one week, respectively, reduced AHI by a third, in association with a reduction in leg fluid volume at the end of the day, and attenuation in the overnight rostral fluid shift in the degree of increase in neck circumference overnight.

As indicated above, fluid retention and overnight rostral displacement appear to contribute to the pathogenesis of both OSA and CSA (1-4,18). Moreover, it has been shown in different pathologic conditions that fluid removal was accompanied by attenuation of OSA (13-17). However, in none of these studies was overnight fluid shift measured.

Wearing compression stockings prevents daytime fluid accumulation in the legs by reducing fluid filtration from the intravascular to the interstitial space due to an increase in tissue hydrostatic pressure. In otherwise healthy men with OSA (74), and in patients with OSA and chronic venous insufficiency (75), wearing compression stockings for one day or one week, respectively, reduced AHI by a third, in association with a reduction in leg fluid volume at the end of the day, and attenuation in the overnight rostral fluid shift and in the degree of increase in neck circumference overnight (Figure 3).

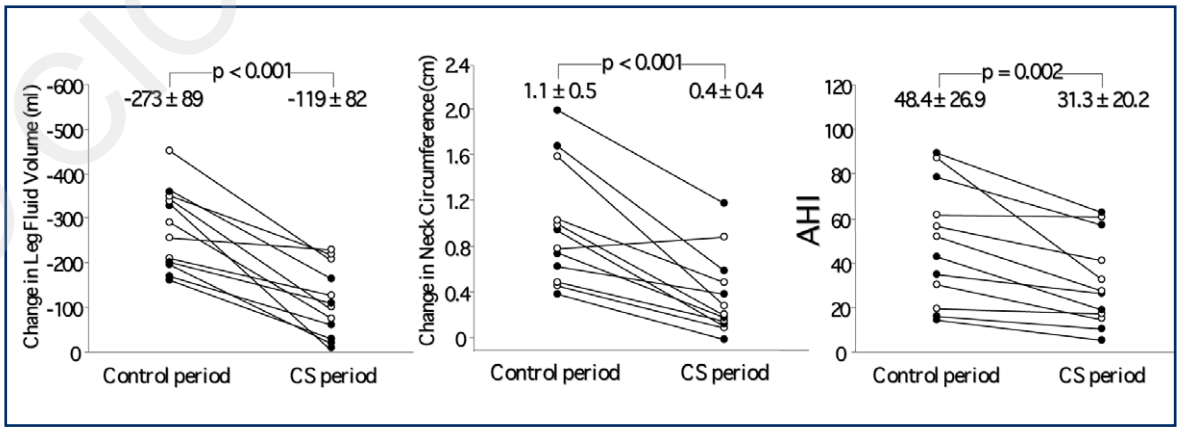

Figure 3 - Influence of compression stockings (CS) on overnight changes in leg fluid volume, neck circumference and the apnoea-hypopnea index (AHI) in the men (solid circles) and women (open circles) with chronic venous insufficiency and OSA.

Hence, interventions that reduce overnight fluid shift may attenuate sleep apnea.

Conclusion and perspectives

The evidence presented in this review consistently supports the idea that daytime fluid accumulation in the legs and its overnight rostral shift contribute to the pathogenesis of both OSA and CSA. Future studies are required to better characterise different patterns of fluid redistribution from the legs to abdomen, chest and neck in OSA and CSA, and in men and women.
Since sleep apnea remains largely undiagnosed, better risk stratification for sleep apnea could lead to a more rational approach to diagnostic testing. Thus, it is plausible that the presence of fluid retaining states, lower extremity edema, or a history of sedentary living would be one factor to take into consideration when deciding who should undergo polysomnography.
As shown above, counteracting fluid accumulation in the legs during the day and its overnight rostral shift can attenuate sleep apnea, but whether this effect is clinically significant remains to be seen. Therefore, considering that the standard treatment of sleep apnea through CPAP is poorly tolerated by many patients, this novel mechanistic approach to sleep apnea could serve as an adjunctive measure for its management. Accordingly, a strong rationale now exists to test other interventions targeting fluid retention and its overnight rostral redistribution as novel therapies for sleep apnea in the setting of large, long-term, randomised clinical trials. Potential interventions include diuretics, sodium restriction, compression stockings, elevating the head of the bed and interventions aimed to increase daytime physical activity.

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