

Nocturnal Rostral Fluid Shift

A Unifying Concept for the Pathogenesis of Obstructive and Central Sleep Apnea in Men With Heart Failure

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Background—Obstructive sleep apnea (OSA) and central sleep apnea are common in patients with heart failure. We hypothesized that in such patients, severity of OSA is related to overnight rostral leg fluid displacement and increase in neck circumference, severity of central sleep apnea is related to overnight rostral fluid displacement and to sleep PCO_2 , and continuous positive airway pressure alleviates OSA in association with prevention of fluid accumulation in the neck.

Methods and Results—In 57 patients with heart failure (ejection fraction $\leq 45\%$), we measured change in leg fluid volume and neck circumference before and after polysomnography, and we measured transcutaneous PCO_2 during polysomnography. Patients were divided into an obstructive-dominant group ($\geq 50\%$ of apneas and hypopneas obstructive) and a central-dominant group ($> 50\%$ of events central). Patients with OSA received continuous positive airway pressure. In obstructive-dominant patients, there were inverse relationships between overnight change in leg fluid volume and both the overnight change in neck circumference ($r = -0.780$, $P < 0.001$) and the apnea-hypopnea index ($r = -0.881$, $P < 0.001$) but not transcutaneous PCO_2 . In central-dominant patients, the overnight reduction in leg fluid volume correlated inversely with the apnea-hypopnea index ($r = -0.919$, $P < 0.001$) and the overnight change in neck circumference ($r = -0.568$, $P = 0.013$) and directly with transcutaneous PCO_2 ($r = 0.569$, $P = 0.009$). Continuous positive airway pressure alleviated OSA in association with prevention of the overnight increase in neck circumference ($P < 0.001$).

Conclusions—Our findings suggest that nocturnal rostral fluid shift is a unifying concept contributing to the pathogenesis of both OSA and central sleep apnea in patients with heart failure. (*Circulation*. 2010;121:1598-1605.)

Key Words: heart failure ■ sleep ■ apnea, sleep

Obstructive sleep apnea (OSA) is caused by repetitive occlusion of the upper airway,¹ and central sleep apnea (CSA) is caused by intermittent cessation of inspiratory drive due to a fall in Paco_2 below the apnea threshold.² Compared with the general population, OSA and CSA are more prevalent in patients with heart failure (HF),³⁻⁵ in whom they are associated with increased mortality.^{6,7} Despite their differing pathologies, patients with HF can have both types of sleep apnea, and the predominant type can shift from obstructive to central in association with a fall in Paco_2 and an increase in circulation time, or vice versa.^{8,9} These observations suggest that in HF, mechanisms for development of OSA and CSA may be linked.

Editorial see p 1583
Clinical Perspective on p 1605

We demonstrated previously that fluid displacement from the legs by inflation of antishock trousers increased neck

circumference, narrowed the pharynx, and increased its collapsibility in awake healthy subjects.¹⁰⁻¹² We also observed, in men without HF, that the amount of fluid displaced from the legs overnight correlated strongly with an overnight increase in neck circumference and frequency of obstructive apneas and hypopneas per hour of sleep (ie, apnea-hypopnea index [AHI]).¹³ Hence, some of the fluid displaced from the legs moved into the neck and increased the propensity to pharyngeal obstruction. It is therefore possible that in patients with HF, a condition characterized by dependent fluid retention in the legs, overnight rostral fluid displacement into the neck could also contribute to the pathogenesis of OSA.

HF predisposes to CSA by provoking hypocapnia partly as a result of pulmonary irritant receptor stimulation by pulmonary congestion.¹⁴ In patients with HF, Paco_2 is inversely proportional to pulmonary wedge pressure,¹⁵ which is higher in patients with CSA than in those without CSA.¹⁶ Under these conditions, abrupt increases in ventilation can drive

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P_{aCO_2} below the apnea threshold, triggering central apnea.^{17,18} These findings raise the possibility that overnight rostral fluid shift may increase the risk of developing CSA if fluid accumulated in the lungs and provoked hypoxemia.

Continuous positive airway pressure (CPAP) is thought to reverse OSA by pneumatic splinting of the pharynx.¹⁹ Another mechanism, not previously considered, is that it may impede fluid accumulation in the neck by increasing intrathoracic and intrapharyngeal pressure.

We therefore tested 3 hypotheses in patients with systolic HF. First, the greater the amount of fluid displaced from the legs overnight, the greater is the severity of OSA in relation to an overnight change in neck circumference. Second, the severity of CSA is also related to the degree of overnight rostral fluid shift but is inversely related to P_{CO_2} during sleep. Third, CPAP alleviates OSA in association with prevention of fluid accumulation in the neck.

Methods

Subjects

We performed polysomnography on consecutive men with HF irrespective of symptoms or signs of sleep apnea between October 1, 2007, and December 1, 2008. Inclusion criteria were as follows: (1) men aged ≥ 18 years; (2) HF due to ischemic or nonischemic dilated cardiomyopathy for ≥ 6 months; (3) left ventricular ejection fraction (LVEF) $\leq 45\%$; (4) New York Heart Association (NYHA) class I to III; and (5) medically stable without medication changes for at least 1 month before sleep studies. Exclusion criteria were as follows: (1) acute decompensated HF; (2) treated sleep apnea; (3) tonsillar hypertrophy; and (4) unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months. The protocol was approved by the local Research Ethics Board, and all subjects provided written consent before participation.

Demographic characteristics, history, and medication use were recorded before polysomnography. LVEF, plasma creatinine concentration, estimated glomerular filtration rate, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were measured within 3 months before polysomnography. Just before polysomnography, subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale,²⁰ physical fitness was assessed by the Duke Activity Status Index,²¹ and leg edema was classified on a scale of 0, 1+, 2+, and 3+.²² Subjects also completed an hourly diary indicating the amount of time they spent sitting that day, from the time they arose until bedtime in the sleep laboratory.¹³

Weight, Leg Fluid Volume, and Neck and Calf Circumferences

Weight was measured just before bedtime and within 30 minutes of waking in the morning. With subjects instrumented for sleep studies, lying awake and supine with legs straight, leg fluid volume (LFV) of the right leg was measured by bioelectric impedance (Hydra 4200, Xitron Technologies Inc, San Diego, Calif).^{10–13} This well-validated technique (accuracy, 0.5%; repeatability, 0.3%) uses impedance to electric current within a body segment to measure its fluid content. Subsequently, we measured circumference of the neck above the cricothyroid cartilage and of the thickest portion of the right calf by tape measure.¹³ Lines were drawn at these levels to ensure that measurements before and after sleep were made at the same level. Subjects then went to sleep. On awakening the next morning and before patients got out of bed or urinated, measurements made before sleep were repeated before scoring of the sleep study or AHI. The differences between LFV and neck and calf circumferences before and after sleep were deemed the overnight changes in these variables. In patients with OSA who agreed to a trial of CPAP, these measurements were repeated at the second polysomnogram for CPAP titration. All aforementioned measurements were repeated,

and neck circumference was measured before CPAP application and immediately after its removal in the morning.

Polysomnography

All subjects underwent overnight polysomnography with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep.^{23,24} All subjects slept on a single pillow with the bed flat. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow was monitored by nasal pressure cannulae (Binaps model 5500, Salter Labs, Arvin, Calif). Arterial oxyhemoglobin saturation (SaO_2) was monitored by oximetry. Transcutaneous P_{CO_2} (P_{tCO_2}) was recorded with a capnograph (TCM4, Radiometer, Copenhagen, Denmark).¹⁷ Central apnea was defined as the absence of tidal volume for ≥ 10 seconds without thoracoabdominal motion, and central hypopnea was defined as a reduction of $\geq 50\%$ in tidal volume from baseline for ≥ 10 seconds with in-phase thoracoabdominal motion and without airflow limitation on nasal pressure. Apneas and hypopneas were classified as obstructive if there was out-of-phase motion of the rib cage and abdomen or airflow limitation on nasal pressure.^{13,25} The AHI was quantified. Patients were divided into an obstructive-dominant group ($\geq 50\%$ of events obstructive) and a central-dominant group ($>50\%$ of events central). In addition, patients in the obstructive- and central-dominant groups were considered as having an OSA or CSA disorder, respectively, if their AHI was ≥ 15 because this is a level above which mortality risk increases in HF.²⁶

Patients with OSA and an AHI ≥ 15 were offered CPAP because it has been shown that, in such patients, it improves cardiovascular function with a tendency to improved survival.^{6,27} CPAP was titrated to abolish OSA during a second polysomnogram. CPAP was not offered to the CSA group because we demonstrated, in such patients, no morbidity or mortality benefits related to its use.²⁵ Signals were recorded on a computerized sleep recording system (Sandman, Nellcor Puritan Bennett Ltd, Ottawa, Ontario, Canada) and scored by a technician blind to measurements of LFV, neck circumference, and calf circumferences. The latter measurements were made by another technician blind to scoring of polysomnograms.

Statistical Analysis

The 2 groups were compared by Student *t* test for normally distributed continuous variables and by Mann-Whitney *U* test for nonnormally distributed variables. The χ^2 or Fisher exact test was used to compare nominal variables. Relationships between dependent variables and single independent variables were examined by Pearson correlation coefficient. To identify factors that correlated independently with the AHI and with overnight change in LFV, multivariable analyses using stepwise linear regression with $P < 0.05$ to enter and $P > 0.1$ to remove were performed. In the multivariable analysis for the AHI, we included age, height, body mass index (BMI), neck circumference before sleep, NYHA class, LVEF, estimated glomerular filtration rate, NT-proBNP, Duke Activity Status Index, sitting time, degree of leg edema, mean P_{tCO_2} during sleep, overnight changes in neck and calf circumferences, and LFV. Because the relationship between AHI and change in LFV was exponential, change in LFV was introduced into the model after linearization by exponential transformation.

Independent variables considered in the analysis of the overnight change in LFV were age, BMI, NYHA class, LVEF, estimated glomerular filtration rate, NT-proBNP, Duke Activity Status Index, sitting time, and degree of leg edema. Comparison of LFV change between obstructive- and central-dominant groups was further evaluated by ANCOVA. The slopes of the relationship between change in LFV and the AHI in the obstructive- and central-dominant groups were also compared by ANCOVA including an interaction term after linearization by logarithmic transformation. The best cutoff values for variables predicting risk of sleep apnea with an AHI ≥ 15 were generated with receiver operating characteristic curves.²⁸ We also compared overnight change in LFV among those with an AHI < 15 (mild to no sleep apnea), those with an AHI ≥ 15 with predominantly OSA (OSA), and those with an AHI ≥ 15 with predominantly CSA (CSA). Comparisons of continuous variables before and while on

Table 1. Characteristics of the Patients

	Total (n=57)	Obstructive-Dominant (n=35)	Central-Dominant (n=22)
Age, y	60.6±12.4	59.3±11.6	62.7±13.5
BMI, kg/m ²	29.4±5.1	30.0±5.4	28.4±4.6
Neck circumference before sleep, cm	41.1±5.1	41.7±3.7	40.2±3.2
NYHA class	2.1±0.7	2.0±0.7	2.4±0.6*
Ischemic pathogenesis, %	42	37	50
LVEF, %	31.6±9.5	32.5±9.4	30.1±9.7
eGFR, mL/min per 1.73 m ²	75.2±23.9	76.7±25.6	72.6±21.0
NT-proBNP, pmol/L	221.4±269.6	160.0±140.0	322.6±385.2*
Epworth Sleepiness Scale score	5.7±3.8	6.5±4.1	4.5±2.9
Duke Activity Status Index	34.3±14.2	37.7±14.0	28.9±13.2*
Sitting time, h	7.3±2.8	6.6±2.8	8.5±2.5*
Thiazide or loop diuretics, %	74	69	82
ACE inhibitors and/or AT2 antagonists, %	95	97	91
β-blockers, %	84	80	91

Values are expressed as mean±SD unless indicated otherwise. eGFR indicates estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; and AT2, angiotensin-2 receptor.

* $P<0.05$ vs obstructive-dominant.

CPAP for patients with OSA were performed by paired *t* test. Data are mean±SD unless indicated otherwise. A value of $P<0.05$ was considered statistically significant. Analyses were performed with the use of SPSS 13.0.1 (SPSS Inc, Chicago, Ill).

Results

Characteristics of the Subjects

As shown in Table 1, we studied 57 men with HF: 35 in the obstructive-dominant group and 22 in the central-dominant group. The central-dominant patients had a higher NYHA class and NT-proBNP level, lower Duke Activity Scale Index, and higher sitting time than obstructive-dominant patients. There were no significant differences between the 2 groups in the remaining variables and no differences in medication use.

Sleep Study Data and Overnight Changes in Weight, LFV, and Neck and Calf Circumferences

Neither total sleep time nor AHI differed significantly between the obstructive- and central-dominant groups (Table 2). However, by design, the great majority of respiratory events were obstructive (85%) in the obstructive-dominant group and central (73%) in the central-dominant group ($P<0.001$). All central-dominant patients had a Cheyne-Stokes respiratory pattern of hyperpnea. Leg edema score before sleep was significantly higher and mean sleep Ptcco₂ was significantly lower in the central- than in the obstructive-dominant group.

Both groups experienced similar overnight reductions in weight and calf circumference, increases in neck circumfer-

Table 2. Sleep Study Data and Overnight Changes in Weight, LFV, and Neck and Calf Circumferences

	Total (n=57)	Obstructive-Dominant (n=35)	Central-Dominant (n=22)
Total sleep time, min	257.0±74.6	250.2±71.9	267.9±79.3
REM sleep, %	12	10	14
Supine position, %	46	57	27†
AHI, No. of hours of sleep	28.3±20.6	27.1±21.0	30.2±20.2
Obstructive, %	63	85	27%†
Central, %	37	15	73%†
Leg edema scale, 0-3+	1.2±0.9	1.0±0.8	1.5±0.9*
Mean Ptcco ₂ during sleep, mm Hg	42.8±6.4	44.7±6.4	39.8±5.4*
Overnight change in body weight, kg	-0.6±3.2	-0.7±0.3	-0.5±0.3
Overnight change in body weight, %	-0.7±0.4	-0.8±0.3	-0.6±0.3
Overnight change in LFV, mL	-240.2±146.9	-173.4±96.0	-346.4±153.2†
Overnight change in LFV, %	-4.8±2.9	-3.5±2.2	-6.7±3.0†
Overnight change in calf circumference, cm	-1.1±0.6	-1.1±0.7	-1.2±0.6
Overnight change in neck circumference, cm	0.8±0.6	0.7±0.6	1.0±0.6

Values are expressed as mean±SD unless indicated otherwise. REM indicates rapid eye movement.

* $P<0.05$, † $P<0.001$ vs obstructive-dominant.

ence, and frequency of nocturia ($0.77±1.2$ versus $0.82±0.95$ episodes of nocturia per patient per night in the obstructive-dominant and central-dominant groups, respectively; $P=0.821$). However, volume of urine excreted was not recorded. The overnight reduction in LFV was twice as high in the central- as in the obstructive-dominant group ($P<0.001$; Table 2). In both groups, the percent overnight reduction in LFV of 1 leg was much greater than the percentage of insensible overnight fluid loss assessed by the overnight reduction in body weight.

In the obstructive-dominant group, there was an inverse exponential relationship between overnight changes in LFV and neck circumference (Figure 1A) but not with mean sleep Ptcco₂ (Figure 2A). In the central-dominant group, the overnight change in LFV correlated exponentially and inversely with the overnight change in neck circumference (Figure 1B) and directly and linearly with mean sleep Ptcco₂ (Figure 2B). For the entire group, there was a significant linear relationship between change in LFV and lowest Sao₂ ($r=0.460$, $P=0.006$) but not mean sleep Sao₂.

Factors Related to AHI

Univariable analyses revealed that, in the obstructive-dominant group, the best correlate of the AHI was the

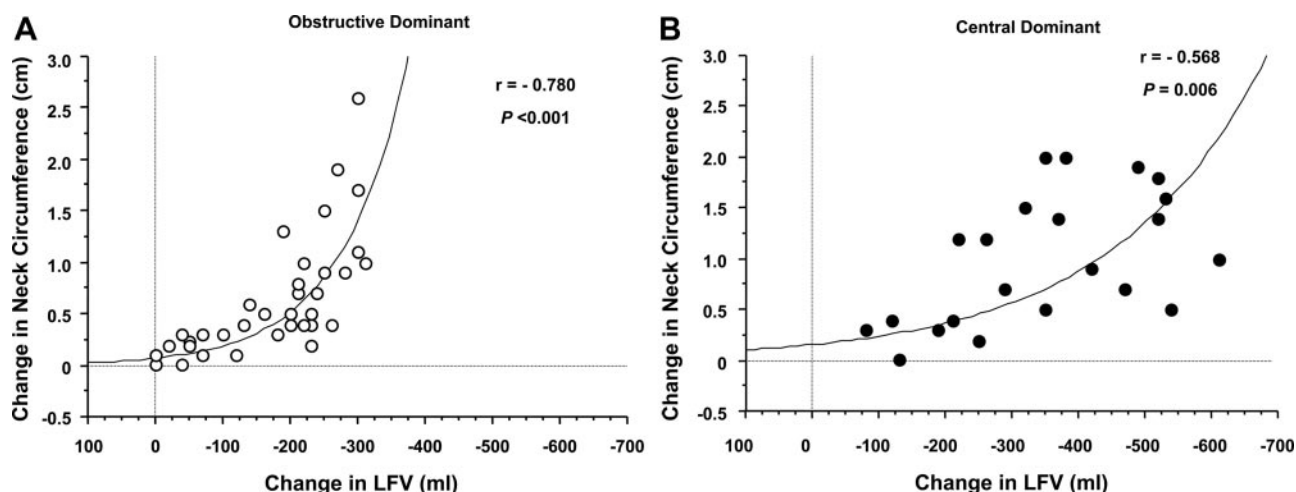


Figure 1. In both the obstructive- (A) and central-dominant (B) groups, there were inverse exponential relationships between overnight changes in neck circumference and LfV.

overnight change in LfV ($P < 0.001$; Figure 3). Other significant correlates were Duke Activity Status Index, sitting time, degree of leg edema, and changes in calf and neck circumference (Table 3). However, there was no significant correlation between the AHI and either BMI ($P = 0.451$) or mean sleep $PtCO_2$ ($P = 0.444$). Multivariable analysis revealed that the only significant independent correlate of the AHI in the obstructive-dominant group was the overnight change in LfV ($r = -0.881$, $P < 0.001$), which accounted for 78% of its variability.

In the central-dominant group, univariable analyses also revealed that the best correlate of the AHI was the overnight change in LfV ($P < 0.001$; Figure 3). Other significant correlates included sitting time, degree of leg edema, mean $PtCO_2$ during sleep, and change in calf circumference (Table 3). However, there was no significant relationship between the AHI and either BMI ($P = 0.706$) or overnight change in neck circumference ($P = 0.070$). Multivariable analysis revealed that the only significant independent correlate of the AHI in the central-dominant group was the overnight change in LfV ($r = -0.919$, $P < 0.001$), which accounted for 85% of

its variability. The slopes of the curves relating AHI to change in LfV differed significantly between the obstructive- and central-dominant groups ($P < 0.001$; Figure 3). In both obstructive- and central-dominant groups, there was no significant correlation between AHI and percentage of time spent in the supine position ($r = 0.213$, $P = 0.220$ and $r = 0.371$, $P = 0.089$, respectively).

There was a graded reduction in overnight LfV from patients with mild to no sleep apnea to OSA to CSA (from -98 ± 73 to -235 ± 47 to -404 ± 119 mL; $P < 0.001$; Figure 4). Receiver operating characteristic analyses revealed that an overnight reduction of ≥ 190 mL in LfV best predicted an AHI ≥ 15 among the entire group (area under the curve, 0.96 ± 0.02 ; $P < 0.001$; sensitivity, 92.1%; specificity, 89.5%), and a reduction of ≥ 320 mL best predicted an AHI ≥ 15 in the central-dominant group (area under the curve, 0.95 ± 0.04 ; $P < 0.001$; sensitivity, 76.5%; specificity, 100%).

Factors Related to the Overnight Change in LfV

For the entire group, multivariable analysis revealed that Duke Activity Status Index, sitting time, and degree of leg

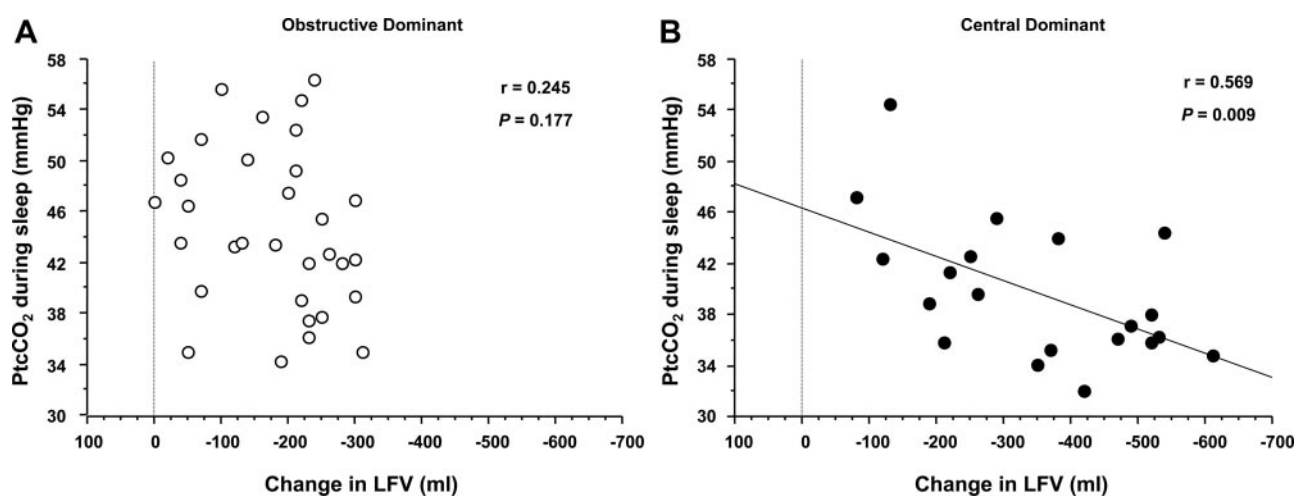


Figure 2. In the obstructive-dominant group, there was no significant correlation between mean $PtCO_2$ during sleep and overnight change in LfV ($n = 32$; A). However, in the central-dominant group, there was a significant correlation between mean sleep $PtCO_2$ and the overnight change in LfV ($n = 20$; B).

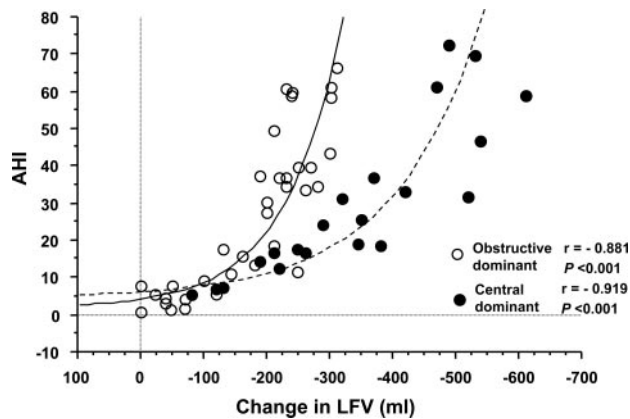


Figure 3. Relationship between change in LFV and AHI in the obstructive- and central-dominant groups. The open circles and solid line represent the relationship between the AHI and the change in LFV in the obstructive-dominant group [$y = 2.4 \cdot e^{(-0.011 \cdot x)}$]. The closed circles and dashed line represent the relationship between the AHI and the change in LFV in the central-dominant group [$y = 5.1 \cdot e^{(-0.004 \cdot x)}$]. The slopes of these curves differed significantly ($P < 0.001$).

edema correlated significantly and independently with the overnight change in LFV ($P = 0.009$, $P < 0.004$, $P < 0.001$, respectively), which together accounted for 61% ($r^2 = 0.610$) of the variability in the overnight change in LFV.

Effects of CPAP in Patients With OSA

Of the 21 patients with OSA (ie, $AHI \geq 15$), 20 (mean age, 60.0 ± 10.5 years; BMI, 30.3 ± 5.8 kg/m²; LVEF, $29.9 \pm 9.0\%$) agreed to a CPAP titration during a second polysomnogram. There were no significant differences in total sleep time (277.9 ± 53.8 versus 279.1 ± 96.0 minutes; $P = 0.963$), percentage of total sleep time spent in the supine position ($65.5 \pm 25.8\%$ versus $74.6 \pm 29.0\%$; $P = 0.166$), or percent REM sleep ($9.5 \pm 6.8\%$ versus $12.4 \pm 6.5\%$ of total sleep time; $P = 0.166$) between the baseline and CPAP titration sleep studies. The mean CPAP required to alleviate OSA was 6.7 ± 1.0 cm H₂O. Although CPAP reduced the AHI significantly ($P < 0.001$), it had no effect on the overnight change in LFV compared with the baseline study ($P = 0.862$; Figure 5).

Table 3. Variables Associated Significantly With AHI, Other Than Change in LFV, by Univariable Analyses

Variables	Correlation Coefficient (r)	R ²	P
Obstructive-dominant group			
Duke Activity Status Index	0.414	0.171	0.014
Sitting time	0.444	0.197	0.008
Leg edema	0.464	0.216	0.005
Change in calf circumference	-0.523	0.274	0.001
Change in neck circumference	0.623	0.388	<0.001
Central-dominant group			
Sitting time	0.514	0.264	0.014
Leg edema	0.509	0.259	0.016
Mean Ptcco ₂ during sleep	0.532	0.283	0.009
Change in calf circumference	-0.481	0.232	0.023

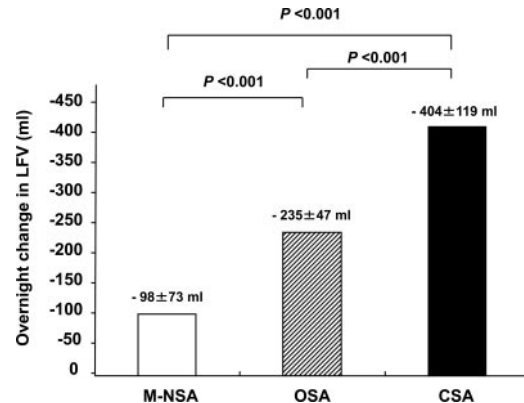


Figure 4. Demonstration of a progressively greater reduction in LFV from patients with mild to no sleep apnea (M-NSA) ($AHI < 15$; $n = 19$) to OSA ($AHI \geq 15$; $n = 21$) to CSA ($AHI \geq 15$; $n = 17$).

However, CPAP dramatically reduced the overnight increase in neck circumference ($P < 0.001$), and this was, in turn, related to the degree of decrease in the AHI ($r = 0.541$, $P = 0.009$).

Discussion

This study sheds new light on the pathogenesis of OSA and CSA in men with systolic HF. First, the only factor that correlated independently with the AHI in both obstructive- and central-dominant patients was overnight change in LFV. Receiver operating characteristic analysis revealed that an overnight LFV reduction ≥ 190 mL predicts the presence of an $AHI \geq 15$ for the entire group with very high sensitivity and specificity. Second, in both groups, there was an overnight increase in neck circumference of similar degree strongly related to the overnight change in LFV. This change in neck circumference correlated with the AHI in obstructive- but not in central-dominant patients. In central-dominant patients, the overnight fall in LFV correlated inversely with mean sleep Ptcco₂, which was inversely related to the AHI. However, in obstructive-dominant patients, no such relationships existed. Thus, in the central-dominant group, some fluid shifted into the neck, causing an increase in neck circumference. However, because the overnight reduction in LFV was

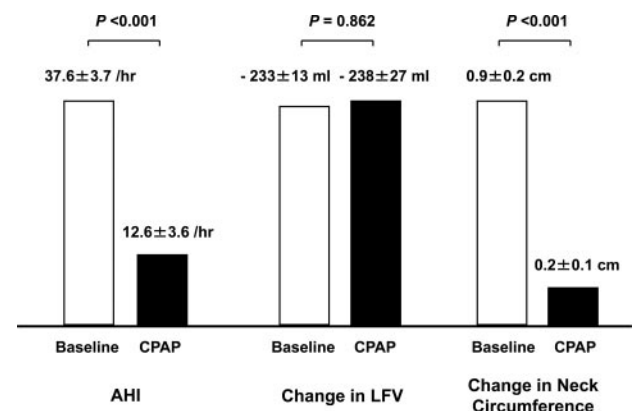


Figure 5. Effect of CPAP on OSA, overnight changes in LFV, and neck circumference. The AHI shown is the AHI during the entire polysomnogram at all CPAP levels. At the optimum CPAP level, the AHI was $8.2 \pm 2.8/h$. Data are mean \pm SE.

twice as high in the central-dominant as in the obstructive-dominant group, some of this additional fluid must have been redistributed elsewhere, possibly into the lungs,²⁹ where stimulation of irritant receptors likely contributed to their lower sleep P_{tCO_2} and predisposed to CSA.^{14–18} Third, the overnight change in LFV was proportional to the degree of leg edema and sitting time and inversely proportional to physical fitness. Finally, although CPAP alleviated OSA, it did not prevent fluid displacement from the legs but prevented fluid accumulation in the neck. This latter finding provides a new insight into the mechanisms by which CPAP reverses OSA.

In obstructive-dominant patients, there was an exponential relationship between the change in LFV and AHI whose position and slope [$y=2.4 \cdot e^{(-0.011 \cdot x)}$] were practically identical to those we described in otherwise healthy obstructive-dominant men [$y=1.9 \cdot e^{(-0.012 \cdot x)}$].¹³ This relationship is exponential probably because resistance to airflow increases to the fourth power of the reduction in radius of the pharynx.³⁰ Similarly, the maximum overnight reduction in LFV of -310 mL was identical to that reported in otherwise healthy men with OSA.¹³ The potential for patients with HF to experience, on average, greater dependent edema and rostral fluid shift overnight might explain, in part, the higher prevalence of OSA in these patients than in the general population, despite lower BMI.^{3,4,31} Two recent observations favor this possibility. First, in patients with diastolic HF and OSA, diuresis was accompanied by attenuation of OSA and increased pharyngeal caliber.³² Second, in patients with renal failure, conversion from nocturnal to continuous peritoneal dialysis was accompanied by worsening of OSA and a decrease in pharyngeal caliber associated with lower fluid removal during the night.³³ These data suggest a unifying concept that overnight rostral fluid displacement from the legs contributes to the pathogenesis of OSA in patients both with and without HF.¹³

With progressively greater LFV shift, there was a gradation from mild to no sleep apnea to OSA to CSA. The greater LFV shift in central- than in obstructive-dominant patients also related exponentially to the AHI but with a shallower slope. This exponential relationship is consistent with mathematical models demonstrating that as lung volume decreases and ventilation/perfusion matching worsens, owing to lung fluid accumulation, respiratory system gain and frequency of central apneas increase exponentially.³⁴ The overnight change in LFV that best predicted CSA with an AHI of ≥ 15 was a decrease of ≥ 320 mL, just beyond the maximum reduction in LFV of 310 mL seen in our obstructive-dominant subjects with and without HF.¹³ This greater LFV displacement helps to explain why CSA is far more common in HF patients than in the general population.^{3,5} In HF, P_{aCO_2} is inversely proportional to pulmonary capillary wedge pressure, which is higher in those with CSA than in those without CSA.¹⁶ Our central-dominant patients had greater signs of fluid overload, including more leg edema and higher NT-proBNP, than our obstructive-dominant patients. Because wedge pressure increases during sleep in patients with HF, in response to increased venous return,²⁹

consequent pulmonary congestion may cause greater ventilation/perfusion mismatch and stimulation of hyperventilation that drives P_{CO_2} below the apnea threshold and triggers central apnea.^{14–18} This is consistent with the observed inverse correlation between overnight change in LFV and mean P_{tCO_2} and lowest SaO_2 during sleep. Our findings also help to explain why OSA and CSA can coexist in HF patients and why the predominant type can change over time,^{8,9} possibly in relation to variations in the degree of fluid retention and overnight rostral fluid shift.

While a subject is sitting, gravity sequesters blood in the legs.³⁵ In HF, elevated venous pressure further contributes to leg edema.³⁶ Activation of the calf muscles during walking decreases venous pressure and prevents fluid accumulation in the legs.³⁷ We found that the amount of overnight LFV displacement related directly to the amount of leg edema and to sitting time, confirming our previous findings in men without HF.¹³ It was also inversely related to physical activity, consistent with the observation that severity of OSA is inversely related to physical activity.³⁸ Therefore, in men with HF, sedentary living combined with increased venous pressure leads to leg fluid accumulation during the daytime and to a large rostral LFV displacement during the night that likely predisposes to both OSA and CSA. Consistent with the above, exercise training attenuated OSA in patients without HF and CSA in patients with HF without concomitant weight change.^{39,40} Our results suggest that 1 mechanism for such effects could be prevention of daytime leg fluid accumulation and reduction of nighttime fluid displacement into the neck and lungs.

OSA might be a cause rather than an effect of rostral LFV displacement because negative intrathoracic pressure during obstructive events might draw fluid from the legs. However, because overnight LFV displacement was not reduced through alleviation of OSA by CPAP, OSA could not be its cause but is more likely its effect. CPAP is thought to prevent pharyngeal collapse during sleep primarily through pneumatic splinting.¹⁹ In our obstructive-dominant group, the AHI correlated with overnight increase in neck circumference. Conversely, the reduction in AHI in response to CPAP correlated with the degree of attenuation of the overnight increase in neck circumference. This suggests that CPAP also alleviates OSA by preventing overnight fluid accumulation in the neck by increasing intrathoracic and extrathoracic airway pressure.

Our study is subject to some limitations. First, we were not able to analyze the time course of overnight fluid shift because knee flexion and contact between the 2 legs, which invariably occurred during sleep, interfere with the accuracy of the LFV measurements.⁴¹ However, others demonstrated that when subjects moved from standing to supine, most of the rostral fluid displacement occurred within 30 to 60 minutes.⁴² This suggests that rostral fluid displacement from the legs while recumbent occurs fairly rapidly. Second, in patients with OSA, CPAP was not applied randomly, and there was no untreated control group. However, the observation that a single night of CPAP practically eliminated the overnight increase in neck circumference in all subjects indicates that prevention of the overnight increase in neck

circumference was due to CPAP. Finally, because we studied only men, our results may not be applicable to women.

In conclusion, our findings suggest the novel concept that nocturnal rostral fluid shift contributes to the pathogenesis of both OSA and CSA in patients with HF. The magnitude of overnight rostral fluid movement contributed not only to the severity of sleep apnea but also to its predominant type. This fluid shift was directly related to the degree of leg edema and sitting time and inversely related to the degree of physical activity. Thus, sedentary living may contribute to the pathogenesis of sleep apnea in HF not only by facilitating weight gain but by promoting dependent fluid retention. Moreover, HF itself may contribute to the pathogenesis of OSA and CSA by predisposing to reduced physical activity and to both leg and pulmonary edema. The finding that, in patients with OSA, CPAP did not prevent fluid movement from the legs but prevented its accumulation in the neck favors a causal relationship between rostral fluid redistribution into the neck and OSA. Further studies will be needed to determine whether preventing leg fluid accumulation during the day or rostral fluid displacement during the night reduces severity of sleep apnea in patients with HF.

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Disclosures

None.

References

- Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*. 2009;373:82–93.
- Yumino D, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. *Proc Am Thorac Soc*. 2008;5:226–236.
- Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. *J Card Fail*. 2009;15:279–285.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.
- Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men, I: prevalence and severity. *Am J Respir Crit Care Med*. 1998;157:144–148.
- Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, Ruttanaumpawan P, Tomlinson G, Bradley TD. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol*. 2007;49:1625–1631.
- Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation*. 1999;99:1435–1440.
- Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of Pco₂ and circulatory delay. *Circulation*. 2001;103:238–243.
- Ryan C, Floras J, Logan A, Kimoff R, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Arzt M, Bradley TD; for the CANPAP Investigators. Conversion from central to obstructive sleep apnea in heart failure patients in the CANPAP Trial. *Eur Respir J*. 2010;35:592–597.
- Shiota S, Ryan CM, Chiu KL, Ruttanaumpawan P, Haight J, Arzt M, Floras JS, Chan C, Bradley TD. Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. *Thorax*. 2007;62:868–872.
- Chiu KL, Ryan CM, Shiota S, Ruttanaumpawan P, Arzt M, Haight JS, Chan CT, Floras JS, Bradley TD. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med*. 2006;174:1378–1383.
- Su MC, Chiu KL, Ruttanaumpawan P, Shiota S, Yumino D, Redolfi S, Haight JS, Bradley TD. Lower body positive pressure increases upper airway collapsibility in healthy subjects. *Respir Physiol Neurobiol*. 2008;161:306–312.
- Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su MC, Lam J, Bradley TD. Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. *Am J Respir Crit Care Med*. 2009;179:241–246.
- Yu J, Zhang JF, Fletcher EC. Stimulation of breathing by activation of pulmonary peripheral afferents in rabbits. *J Appl Physiol*. 1998;85:1485–1492.
- Lorenzi-Filho G, Azevedo ER, Parker JD, Bradley TD. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. *Eur Respir J*. 2002;19:37–40.
- Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. *Circulation*. 1999;99:1574–1579.
- Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis*. 1993;148:330–338.
- Xie A, Skatrud JB, Puleo DS, Rahko PS, Dempsey JA. Apnea-hypopnea threshold for CO₂ in patients with congestive heart failure. *Am J Respir Crit Care Med*. 2002;165:1245–1250.
- Schwab RJ, Pack AI, Gupta KB, Metzger LJ, Oh E, Getsy JE, Hoffman EA, Gefter WB. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med*. 1996;154:1106–1116.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540–545.
- Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol*. 1989;64:651–654.
- Heart and blood vessels. In: Seidel HM, Ball JW, Dains JE, Benedict GW, eds. *Mosby's Guide to Physical Examination*. 4th ed. St Louis, Mo: Mosby, Inc; 1999:458.
- EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. 1992;15:173–184.
- Rechtschaffen A, Kales AA. *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles, Calif: UCLA Brain Information Service/Brain Research Institute; 1968.
- Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353:2025–2033.
- Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Relationship between sleep apnoea and mortality in patients with ischaemic heart failure. *Heart*. 2009;95:819–824.
- Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003;348:1233–1241.
- Perkins NJ, Schisterman EF. The inconsistency of “optimal” cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol*. 2006;163:670–675.
- Gibbs JS, Cunningham D, Shapiro LM, Park A, Poole-Wilson PA, Fox KM. Diurnal variation of pulmonary artery pressure in chronic heart failure. *Br Heart J*. 1989;62:30–35.
- Widdicombe JG, Nadel JA. Airway volume, airway resistance, and work and force of breathing: theory. *J Appl Physiol*. 1963;18:863–868.
- Artzt M, Young T, Finn L, Skatrud JB, Ryan CM, Newton GE, Mak S, Parker JD, Floras JS, Bradley TD. Sleepiness and sleep in patients with

- both systolic heart failure and obstructive sleep apnea. *Arch Intern Med.* 2006;166:1716–1722.
32. Bucca CB, Brussino L, Battisti A, Mutani R, Rolla G, Mangiardi L, Cicolin A. Diuretics in obstructive sleep apnea with diastolic heart failure. *Chest.* 2007;132:440–446.
 33. Tang SC, Lam B, Lai AS, Pang CB, Tso WK, Khong PL, Ip MS, Lai KN. Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol.* 2009;4:410–418.
 34. Dong F, Langford WF. Models of Cheyne-Stokes respiration with cardiovascular pathologies. *J Math Biol.* 2008;57:497–519.
 35. Maw GJ, Mackenzie IL, Taylor NA. Redistribution of body fluids during postural manipulations. *Acta Physiol Scand.* 1995;155:157–163.
 36. Cho S, Atwood JE. Peripheral edema. *Am J Med.* 2002;113:580–586.
 37. Stick C, Jaeger H, Witzleb E. Measurements of volume changes and venous pressure in the human lower leg during walking and running. *J Appl Physiol.* 1992;72:2063–2068.
 38. Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. *Sleep.* 2004;27:480–484.
 39. Giebelhaus V, Strohl KP, Lormes W, Lehmann M, Netzer N. Physical exercise as an adjunct therapy in sleep apnea: an open trial. *Sleep Breath.* 2000;4:173–176.
 40. Yamamoto U, Mohri M, Shimada K, Origuchi H, Miyata K, Ito K, Abe K, Yamamoto H. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. *J Card Fail.* 2007;13:825–829.
 41. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, Lilienthal Heitmann B, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols AMWJ, Pichard C; ESPEN. Bioelectrical impedance analysis, part II: utilization in clinical practice. *Clin Nutr.* 2004;23:1430–1453.
 42. Berg HE, Tedner B, Tesch PA. Changes in lower limb muscle cross-sectional area and tissue fluid volume after transition from standing to supine. *Acta Physiol Scand.* 1993;148:379–385.

CLINICAL PERSPECTIVE

Obstructive and central sleep apnea (OSA and CSA, respectively) occur commonly in patients with heart failure (HF) and are associated with increased mortality. However, causes of these breathing disorders are not well established in the setting of HF but are thought to arise through different mechanisms: OSA through obesity and anatomic narrowing of the pharynx, and CSA through hypocapnia and increased chemoreceptor sensitivity. However, the observation that OSA and CSA can occur simultaneously in HF patients suggested a common pathophysiological mechanism linking these 2 disorders. Because HF is a fluid-retaining state, we hypothesized that overnight displacement of fluid from the legs into the neck might lead to OSA by narrowing the pharynx and to CSA if fluid shifted into the lungs and caused stimulation of vagal receptors that stimulate hyperventilation and lower PCO_2 . We confirmed these hypotheses in HF patients by demonstrating that the degree of overnight shift of fluid from the legs was related to the severity of sleep apnea as determined by the apnea-hypopnea index. In the case of OSA, this was through a concomitant increase in neck circumference. In the case of CSA, this was through an inverse relationship with PCO_2 , presumably because of fluid movement into the lungs. Thus, a common mechanism linking OSA and CSA in HF patients is fluid retention and overnight rostral fluid displacement. These novel findings suggest that manipulation of fluid status may be a novel means by which to treat OSA and CSA in HF patients.

Nocturnal Rostral Fluid Shift: A Unifying Concept for the Pathogenesis of Obstructive and Central Sleep Apnea in Men With Heart Failure

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