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Impact of Sleep Apnea on Sympathetic Nervous System Activity in Heart Failure*

Peter Solin, MBBS, PhD; David M. Kaye, MBBS, PhD; Peter J. Little, PhD; Peter Bergin, MBBS; Meroula Richardson, MBBS; and Matthew T. Naughton, MD

Objectives: **To compare and establish the relevance of the relative degree of sympathetic nervous system activity (SNSA) in groups of patients with congestive heart failure (CHF) and obstructive sleep apnea (OSA), and in a control group.**

Background: **Elevated SNSA is a characteristic feature of CHF, as well as of OSA and nonhypercapnic central sleep apnea (CSA). OSA and CSA commonly occur with CHF; however, the relative contribution of apnea-related hypoxemia and sleep fragmentation to the SNSA of patients with CHF is not known.**

Methods: **This was a prospective, controlled, observational trial in which the overnight urinary norepinephrine (UNE) level, which is a measure of integrated overnight SNSA while asleep, was measured in 15 healthy male volunteers, 15 male OSA patients who did not have CHF, and 90 CHF patients (77 men). CHF patients also had right heart pressure measurements and then were grouped by the presence of sleep apnea.**

Results: **Compared with healthy individuals, the mean (± SD) UNE level was significantly elevated in the OSA group and was even further elevated in the CHF group (13.4 ± 5.6 vs 19.7 ± 12.3 vs 32.2 ± 20.2 nmol/mmol creatinine, respectively; $p < 0.001$ [by analysis of variance]). Within the CHF group, the mean UNE levels were greatest in the CHF-CSA group compared with the CHF-OSA group and the CHF nonapnea group (43.9 ± 24.1 vs 24.0 ± 10.8 vs 22.4 ± 8.9 nmol/mmol creatinine, respectively; $p < 0.001$). Using a multivariate regression model, the variance of the UNE level in the CHF group was predicted, in descending order, by pulmonary capillary wedge pressure (14% variance), rapid eye movement sleep (8%), and the mean sleep pulse oximetry level (7%).**

Conclusions: **Overnight SNSA is significantly greater in CHF patients than in OSA patients. Moreover, the hemodynamic severity of CHF contributes to the elevation of SNSA in CHF patients to a greater degree than apnea-related hypoxemia.**

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Key words: apnea; heart failure; sympathetic activity; urinary norepinephrine

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CAHI = central apnea-hypopnea index; CHF = congestive heart failure; CSA = central sleep apnea; EMG = electromyogram; LVEF = left ventricular ejection fraction; OSA = obstructive sleep apnea; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PNE = plasma norepinephrine; REM = rapid eye movement; SNSA = sympathetic nervous system activity; Spo_2 = pulse oximetric saturation; TST = total sleep time; UNE = overnight urinary norepinephrine

Elevated sympathetic nervous system activity (SNSA) is associated with a detrimental outcome in healthy individuals[1] and in patients with congestive heart failure (CHF).[2] In the early stages of CHF, an elevated SNSA compensates for a reduced cardiac output.[3] Thereafter, reduced sympathoinhibitory baroreceptor function, and increased sympathoexcit-

*From the Departments of Respiratory Medicine (Drs. Solin and Naughton) Cardiology (Drs. Bergin and Richardson), Alfred Hospital, Monash University, Melbourne, Australia; and the Baker Heart Research Institute (Drs. Kaye and Little), Melbourne, Australia.

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Correspondence to: Matthew T. Naughton, MD, Department of Respiratory Medicine, Alfred Hospital, Commercial Rd, Prahran, Melbourne, VIC, 3181 Australia; e-mail: m.naughton@alfred.org.au

atory input from arterial chemoreceptors and skeletal muscle metaboreceptors have been considered to be responsible for the increased levels of SNSA.[3] More recently, OSA and CSA have been observed to commonly coexist with CHF and, accordingly, are considered to be further contributors to the elevated SNSA in CHF patients,[4–15] however, these studies have not controlled for the severity of CHF.

Obstructive sleep apnea (OSA) is characterized by recurrent transient upper airway closure and asphyxia despite futile respiratory efforts. The rise in SNSA seen in OSA patients is thought to be due to hypoxemia and hypercapnia during apnea, and to arousals at apnea termination.[4,5] Moreover, SNSA levels fall with treatment.[4] OSA, which occurs in approximately 25% of CHF patients,[16–18] may worsen CHF via elevations in the left ventricular afterload, due either to negative intrathoracic pressures or elevated systemic BPs that coincide with the arousal from sleep.[19] Pulmonary capillary wedge pressures (PCWPs) and pulmonary artery pressures (PAPs) are known to rise in OSA patients who are free of heart disease during sleep compared with wakefulness.[20] During wakefulness, CHF-OSA patients have a significantly lower PCWP compared with CHF-central sleep apnea (CSA) patients.[17] Taken together, it is likely that the negative effects that OSA might have on CHF are largely confined to sleep rather than during wakefulness.

Nonhypercapnic CSA also occurs commonly (approximately 40%) in CHF.[16–18] Also known as Cheyne-Stokes respiration, it is characterized by a crescendo-decrescendo ventilatory pattern during non-rapid eye movement (REM) sleep followed by a central apnea associated with mild hypoxemia. An arousal from sleep may occur at the peak of ventilation. Characteristically, patients with CHF-CSA hyperventilate and are hypocapnic both awake and asleep, suggesting that the determining pathophysiologic process occurs during both sleep and wakefulness.[21] In contrast to OSA, elevations of PCWP,[17] plasma norepinephrine (PNE) levels,[18] and skeletal muscle microneurography[14] during wakefulness, in addition to elevated overnight urinary norepinephrine (UNE) levels,[6] suggest that CSA is associated with more severe CHF during both sleep and wakefulness.

In view of the above, we hypothesized the following: first, that there would be a stepwise increase in SNSA from healthy subjects to OSA subjects who were free of CHF, and to a greater degree still in a CHF population; and second, that the degree of SNSA elevation in CHF patients would be more related to the severity of CHF rather than to the severity of apnea. Our aims were to measure SNSA and hemodynamic parameters in a group of CHF subjects and to compare them with patients with OSA who did not have CHF, and healthy subjects.

Materials and Methods

Subjects

Patients being assessed by the Alfred Hospital Heart Failure Service and healthy volunteers were invited to take part in this study. Consecutive patients with CHF of either gender who were aged 18 to 75 years were enrolled if they met the following criteria: (1) clinical evidence of symptomatic CHF of at least 6 months duration and receiving medical therapy; (2) a left ventricular ejection fraction (LVEF) of $\leq 55\%$ and New York Heart Association class II to IV; and (3) stable condition, which was defined as no hospital admissions or medication changes within the preceding 2 weeks. The exclusion criteria were unstable angina, myocardial infarction within 3 months, significant neurologic, respiratory, or renal impairment (*ie*, creatinine clearance, < 0.5 mL/s; urea level, > 25 mmol/L; and creatinine level, > 0.20 mmol/L). Healthy male volunteers, who were receiving no regular medications, were enrolled from advertisements placed within the hospital. Male subjects with OSA who were attending the sleep clinic, were free of any significant medical disorder, and were receiving no regular medications were also recruited. Fifteen healthy volunteers, 15 patients with OSA, and 90 patients with CHF (77 men and 13 women) were studied. No subject had undergone investigation of a sleep disorder or had received treatment with continuous positive airway pressure. The Ethics Committee of the Alfred Hospital approved the study, and patients provided written informed consent.

Sleep Studies

Overnight sleep studies were performed in the usual manner with a computerized system (Somnostar; SensorMedics Corp; Yorba Linda, CA), using two EEG channels, left and right electrooculograms, and a submental electromyogram (EMG) for the determination of sleep stages. Sleep stages were manually scored according to standard criteria by an experienced scorer who was blinded to the patients' characteristics, as previously described.[17] *Sleep efficiency* was defined as the total sleep time (TST)/time in bed and the percentage of sleep stage as the total time spent in a particular sleep stage/sleep period time. ECG and heart rate were recorded continuously from precordial lead II, arterial oxygen saturation was measured by an ear pulse oximeter (*ie*, pulse oximetric saturation [Spo_2]) [Fastrac; SensorMedics Corp]. Chest and abdominal movements were monitored using respiratory effort bands that were calibrated for phase but not tidal volume (Resp-ez; EPM Systems; Midlothian, VA). Oronasal airflow was monitored by thermocouples (ProTech Services; Seattle, WA), and snoring was monitored using a piezo snore sensor (ProTech Services).

A *central apnea* was defined as an absence of oronasal airflow for at least 10 s that was associated with an absence of chest and abdominal movement. A central hypopnea was defined as a reduction in oronasal airflow for at least 10 s that was associated with a $\geq 2\%$ fall in Spo_2 with in-phase chest and abdominal movement, no increase in submental EMG activity, and the absence of snoring. An *obstructive apnea* was defined as an absence of oronasal airflow for at least 10 s despite continued out-of-phase chest and abdominal movements. An *obstructive*

Table 1—*Characteristics of Non-CHF and CHF Subjects

Characteristics	Groups: Normal (n = 15)	OSA (n = 15)	CHF (n = 90)	p Value
Age, yr	46.0 ± 13.4	52.5 ± 7.5	54.2 ± 10.2	0.020†
BMI	27.5 ± 4.4	29.4 ± 5.0	27.2 ± 3.3	NS
Sleep architecture				
TST, min	381 ± 53	357 ± 74	304 ± 71	<0.001‡
Sleep efficiency	84.0 ± 8.0	81.7 ± 10.9	74.0 ± 15.1	0.012†
Wake, % SPT	13.6 ± 7.2	13.2 ± 9.1	22.2 ± 14.5	0.008§
Stage 1 and 2, % SPT	55.4 ± 12.4	61.3 ± 8.6	56.9 ± 12.2	NS
Stage 3 and 4, % SPT	13.1 ± 7.2	10.8 ± 7.7	9.1 ± 7.5	NS
REM, % SPT	17.9 ± 5.7	14.8 ± 5.2	11.9 ± 6.6	0.002†
Sleep disturbance, events/h				
AHI	1.9 ± 1.6	16.3 ± 11.5	18.2 ± 17.7	0.002‖
MAI	15.7 ± 15.7	34.9 ± 27.7	31.7 ± 29.2	0.012‖
Pulse and oximetry				
Heart rate, beats/min	53.3 ± 7.0	55.6 ± 8.1	66.0 ± 11.4	<0.001‡
Mean Spo_2, %	95.4 ± 2.3	94.4 ± 2.2	93.8 ± 2.4	0.060
TST with Spo_2 < 90%, %	0.2 ± 0.5	4.9 ± 7.6	9.6 ± 17.0	0.065
Minimum Spo_2, %	90.3 ± 3.2	80.7 ± 9.3	82.4 ± 8.3	0.001‖
Urine				
Volume, mL	629 ± 274	670 ± 503	533 ± 302	NS
Norepinephrine, nmol/mL	0.13 ± 0.08	0.21 ± 0.18	0.24 ± 0.19	NS
Creatinine, mmol/L	9.9 ± 5.1	10.5 ± 5.4	7.8 ± 4.1	0.037
Urinary norepinephrine, nmol/mmol creatinine	13.4 ± 5.6	19.7 ± 12.3	32.2 ± 20.2	<0.001‡

*Values given as mean ± SD, unless otherwise indicated. NS = not significant; SPT = sleep period time; MAI = movement arousal index; HR = heart rate.
†CHF group different from non-CHF normal group.
‡CHF different from both non-CHF normal and non-CHF OSA groups.
§CHF group different from non-CHF OSA group.
‖CHF and non-CHF OSA groups different from non-CHF normal group.

hypopnea was defined as a reduction in oronasal airflow for at least 10 s that was associated with a ≥ 2% fall in Spo_2 despite continued out-of-phase chest and abdominal movements, increased submental EMG activity, or snoring. A *mixed apnea* was defined, using the above criteria, when a central event was followed by, or included, obstructive components. Because upper airway closure occurs during mixed apneas, which are related to upper airway instability, these events were classified as *obstructive events*. The *apnea-hypopnea index* (AHI) was defined as the total number of apneas and hypopneas divided by the TST and was expressed as the number of events per hour.

Catecholamine Measurements

UNE was measured from overnight urine that was produced during the period of the sleep study by a scientist (P.J.L.) who was blinded to any of the patients' clinical details. Urine collection began after patients had voided prior to retiring to bed (approximately 10 PM) and included all urine passed overnight, including the first morning void on arising (approximately 6 AM). Urine was collected in acidified containers with 20 mL 6 mol/L HCL and was stored at 4°C prior to analysis. Norepinephrine was measured by high-performance liquid chromatography with fluorescence detection[22] and was multiplied by 0.00591 to convert the values to nanomoles per milliliter. To take into account possible differences in urine volume and renal function, UNE was adjusted for urinary creatinine excretion and was expressed as the number of nanomoles per millimole creatinine, as previously described.[6]

Awake Measurements

Right heart pressures (*ie*, PCWP and PAP) and cardiac index were measured in 70 of 90 CHF patients, within 12 h of the sleep study, with the individual in the supine position, in the morning while awake, using a balloon-tipped flotation thermodilution catheter (7F Arrow; Arrow International; Reading, PA) via the right internal jugular vein. LVEF was measured by ^{99}Tc radionuclide angiography using the equilibrium method and was performed within 3 days of the overnight sleep study and urine collection. Arterial blood gas tensions were measured (model 865; Ciba Corning Diagnostics Corp; Medfield, MA) in the CHF group, in the supine position and awake, within 1 h prior to patients undergoing polysomnography.

Protocol

Patients with CHF were classified into three groups, dependent on the presence and type of sleep apnea. Sleep apnea was defined as being present when the AHI was > 5 events per hour. CSA (CHF-CSA) was defined as being present when at least 70% of all apneas and hypopneas were purely central in origin (ie, central AHI [CAHI]/AHI ratio, ≥ 70%) and central apneas and/or hypopneas occurred at a rate of > 5 events per hour (*ie*, CAHI, > 5). Patients with an AHI of > 5 due to obstructive or mixed apneas (CAHI/AHI ratio, < 70%) were classified as having OSA (*ie*, CHF-OSA patients).

Healthy volunteers who did not have CHF with normal overnight polysomnography findings (normal group) or OSA

were used for baseline comparison. Five patients with CHF-CSA had repeat polysomnography after undergoing a heart transplantation.

Statistical Analysis

One-way analysis of variance with Tukey *post hoc* analysis was used to compare characteristics between the CHF group and both non-CHF groups, and then assessed the effect of apnea type in subjects with CHF. The Pearson least squares product moment correlation coefficient test was used to determine the significance of the relationships between UNE and the variables of apnea and CHF severity. Stepwise linear regression determined the influence on UNE on the following markers: (1) severity of cardiac dysfunction (*ie*, PCWP and LVEF), (2) sleep disturbance (*ie*, AHI, REM deprivation, and movement arousal index), and (3) oxygen desaturation (*ie*, mean Spo_2, minimum Spo_2, and TST with $Spo_2 < 90\%$), adjusting for the effects of age, gender, and body mass index (BMI).

Variables with skewed distributions were natural log-transformed to ensure normal distribution. The data were expressed as the mean ± SD. A p value < 0.05 was regarded as significant.

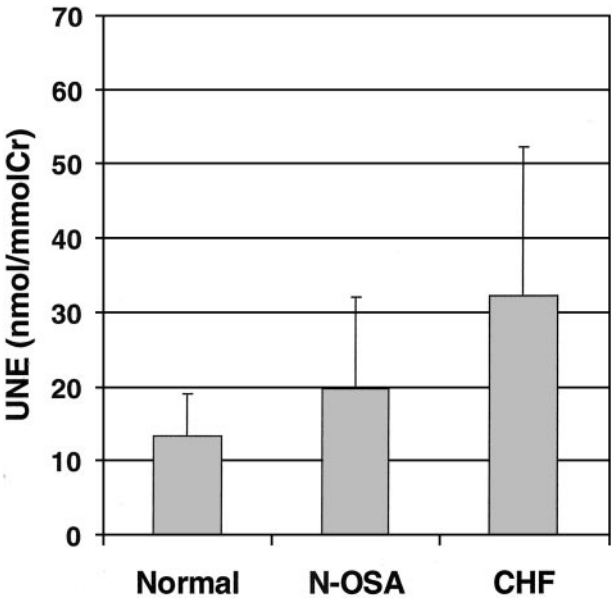

FIGURE 1. Comparison of UNE levels in 15 healthy volunteers without OSA (*ie*, normal group), 15 OSA patients without CHF (N-OSA group), and 90 CHF patients (CHF group) [$p < 0.001$]. Values are given as the mean ± SD.

RESULTS

Comparison Among the Normal, OSA, and CHF Groups

The demographic characteristics of the normal group (n = 15), the OSA group (n = 15), and the CHF group (n = 90; unselected for apnea) were similar, apart from the subjects in the normal group being 8 years younger than those in the CHF group (Table 1). The OSA and CHF groups had similar AHI values, movement arousal index values, and mean and minimum Spo_2 values. The CHF group had lower amounts of total and REM sleep than did the normal group. Furthermore, the CHF group had a greater mean sleep heart rate and greater UNE level compared with the normal and OSA groups. Compared with the normal group, the UNE level was 47% greater in the OSA group and 140% greater in the CHF group unselected for apnea (Fig 1).

Comparison Within Subgroups of CHF Patients

Of the 90 subjects with CHF, 27 had no sleep apnea (CHF-N group), 24 had OSA (CHF-OSA group), and 39 had CSA (CHF-CSA group) [Tables 2, 3]. The three groups were similar in age, LVEFs, medication use, mean systemic BP, and renal function. The CHF-CSA group was significantly more hypocapnic and alkalotic, and had greater right heart pressures and UNE levels compared with the CHF-N and CHF-OSA groups. Sleep architecture was similar across the three groups. The CHF-CSA group had a significantly greater AHI than did the CHF-OSA group. The movement arousal index and markers of overnight hypoxemia were significantly elevated in the CHF-CSA and CHF-OSA groups compared with the normal groups.

Urine volumes and renal function measurements were not significantly different among the CHF groups, but the CHF-OSA group produced 52% more urine than the CHF-N group (Table 3). The UNE levels were significantly greater in the CHF-CSA group compared with the CHF-N and CHF-OSA groups, which were not significantly different from each other (Fig 2).

There was no statistical difference in UNE levels between those of CHF-CSA patients who were receiving beta-blockers (n = 27) and those who were not (n = 12) [36.7 ± 38.1 vs 47.1 ± 15.0 nmol/mmol creatinine, respectively]. Five CHF-CSA patients underwent heart transplantation, which resulted in significant reductions in AHI (reduction, 31 ± 8 to 5 ± 2 events per hour, respectively) and UNE levels (reduction, 47.0 ± 23.8 vs 9.9 ± 3.8 nmol/mmol creatinine, respectively).

Within the CHF group, significant univariate correlates of UNE included markers of awake cardiac function (*ie*, PCWP, PAP, mean sleep heart rate, and LVEF), ventilatory variables (*ie*, arterial pH and $Paco_2$ inversely), and severity of apnea (*ie*, sleep efficiency, percentage of REM sleep, AHI, mean Spo_2, minimum Spo_2, and TST with Spo_2 at $< 90\%$) [Table 4].

Based on the significant univariate correlates cited above, a multivariate stepwise linear regression model was used to determine the influence on UNE

Table 2—*Characteristics in 90 Patients With CHF

Characteristics	Subgroups			p Value
	CHF-N	CHF-OSA	CHF-CSA	
Patients, No. (% women)	27 (5)	24 (1)	39 (7)	
Age, yr	52.4 ± 11.0	55.7 ± 10.0	54.6 ± 10.0	NS
BMI	26.3 ± 3.0	29.9 ± 5.0	26.8 ± 4.3	0.006†
Medications, % patients				
Beta-blockers	44	32	32	
ACE Inhibitor or AT receptor antagonist	96	100	100	
Digoxin	74	36	34	
Diuretics	89	95	84	
Arterial blood gas				
PH	7.44 ± 0.03	7.43 ± 0.03	7.46 ± 0.04	<0.001‡
$Paco_2$, mm Hg	42.2 ± 4.4	43.7 ± 5.5	38.1 ± 4.9	<0.001‡
Pao_2, mm Hg	81.8 ± 10.6	81.9 ± 10.0	84.6 ± 11.2	NS
Cardiopulmonary data				
Mean systemic BP, mm Hg	77.9 ± 13.5	78.0 ± 17.1	76.9 ± 12.5	NS
LVEF, %	22.5 ± 10.5	27.3 ± 10.4	20.9 ± 9.3	0.050‡
PAP, mm Hg	19.4 ± 11.6	21.2 ± 7.9	29.7 ± 10.3	0.001‡
PCWP, mm Hg	12.3 ± 10.6	13.0 ± 7.2	20.4 ± 8.2	0.002‡
Cardiac index, L/min/m^2	2.3 ± 0.5	2.4 ± 0.5	2.0 ± 0.4	0.021§
Renal function				
Serum urea, mmol/L	9.5 ± 3.6	10.2 ± 4.5	9.7 ± 4.5	NS
Serum creatinine, mmol/L	0.11 ± 0.02	0.13 ± 0.12	0.11 ± 0.02	NS
Creatinine clearance, mL/s	1.08 ± 0.36	1.32 ± 0.42	1.07 ± 0.44	NS

*Values given as mean ± SD, unless otherwise indicated. ACE = angiotensin-converting enzyme; AT = angiotensin II. See Table 1 for other abbreviations not used in the text.
†CHF-OSA different from both CHF-CSA and CHF-normal groups.
‡CHF-CSA different from both CHF-normal and CHF-OSA groups.
§CHF-CSA group different from CHF-OSA group.

of cardiac dysfunction (*ie*, PCWP, PAP, mean sleep heart rate, and LVEF), sleep disturbance (*ie*, AHI, REM sleep, and movement arousal index), and hypoxemia (*ie*, mean Spo_2, minimum Spo_2, and TST spent with Spo_2 at $< 90\%$). Forty-three percent of the UNE variance was explained by the combination of PCWP, LVEF, AHI, REM sleep, mean and minimum Spo_2, TST with Spo_2 at $< 90\%$, age, gender, and BMI. Using a second model, which was adjusted for age, gender, and BMI, PCWP emerged as the best predictor, accounting for 14% of the variance of UNE, followed by the percentage REM sleep (8% of variance) and mean Spo_2 (7% of variance). The AHI did not significantly contribute to UNE in this analysis.

Discussion

Although CHF, OSA, and CSA are known to be associated with elevated SNSA, their relative contributions have not been previously investigated. In this study, the overnight UNE level was used as an integrated marker of SNSA when patients were asleep, and awake invasive hemodynamic pressures were measured in a large population of, mainly male, CHF patients and then was compared with that of healthy male volunteers without sleep apnea and male OSA subjects who were free of heart disease. Two significant observations were made. First, compared with healthy subjects, the UNE level was 47% greater in the OSA group and 140% greater in the CHF group. Importantly, the SNSA of CHF patients who were unselected for apnea was significantly greater than that seen in the OSA group. Second, within the CHF group, although UNE levels correlated with markers of cardiac dysfunction (*ie*, PCWP, PAP, LVEF, and mean sleep heart rate) and markers of sleep apnea and hypoxemia, the most significant predictors of UNE, when adjusted for age, gender, and BMI, were PCWP, loss of REM sleep, and mean Spo_2. This would suggest that CHF, *per se*, is a more important contributor to the overall SNSA of CHF patients than is coexistent apnea.

OSA has been associated with elevated SNSA[7] via the mechanisms of arousals from sleep,[8] hypoxemia, and hypercapnia, which act synergistically to increase sympathetic activity, which is an effect more marked during an apnea when the sympathoinhibi-

Table 3—*Polysomnography and Overnight Urine Levels in 90 Patients With CHF

Variables	Subgroups			p Value
	CHF-N	CHF-OSA	CHF-CSA	
Sleep architecture				
TST, min	305 ± 72	312 ± 65	297 ± 76	NS
Sleep efficiency, %	75 ± 16	75 ± 15	73 ± 15	NS
Wake, % SPT	20.6 ± 14.5	21.2 ± 14.6	24.0 ± 14.6	NS
Stage 1 and 2, % SPT	56.1 ± 11.9	57.5 ± 11.7	56.9 ± 13.1	NS
Stage 3 and 4, % SPT	10.4 ± 6.3	8.5 ± 7.1	8.5 ± 8.6	NS
REM, % SPT	13.0 ± 6.1	13.0 ± 6.4	10.6 ± 6.9	NS
Sleep disturbance, events/h				
AHI	2.0 ± 1.6	17.8 ± 11.8	29.8 ± 18.1	< 0.001†
MAI	18.7 ± 18.9	28.4 ± 23.2	42.7 ± 34.3	< 0.001‡
Pulse and oximetry				
Heart rate, beats/min	65 ± 11	65 ± 11	67 ± 12	NS
Mean Spo_2, %	95.0 ± 1.9	93.2 ± 2.9	93.4 ± 2.1	0.009‡
Minimum Spo_2, %	86.5 ± 7.4	80.7 ± 8.5	80.7 ± 7.8	0.010‡
TST with Spo_2 < 90%, %	3.5 ± 11.9	13.1 ± 24.1	11.5 ± 13.8	0.087
$Ptcco_2$, mm Hg	40.4 ± 6.2	45.1 ± 4.8	37.8 ± 3.3	0.001§
Urine				
Volume, mL	438 ± 150	664 ± 423	519 ± 271	0.025‖
Norepinephrine, nmol/mL	0.18 ± 0.11	0.22 ± 0.23	0.29 ± 0.19	NS
Creatinine, mmol/L	7.9 ± 3.0	8.7 ± 6.0	7.2 ± 3.3	NS
Urinary norepinephrine, nmol/mmol creatinine	22.4 ± 8.9	24.0 ± 10.8	43.9 ± 24.1	< 0.001¶

*Values given as mean ± SD, unless otherwise indicated. $Ptcco_2$ = transcutaneous Pco_2. See Table 1 for abbreviations not used in the text.
†All groups different.
‡CHF-CSA and CHF-OSA group different from CHF-normal group.
§CHF-OSA different from both CHF-CSA and CHF-normal groups.
‖CHF-OSA different from CHF-normal group.
¶CHF-CSA different from both CHF-normal and CHF-OSA groups.

tory influence of the pulmonary afferents is eliminated.[9] The present study demonstrated that UNE level is a valid marker of the degree of sleep disturbance, as measured by AHI and mean overnight Spo_2, which is a finding that is similar to and consistent with those of previous studies.[10,12] The UNE level also correlated inversely with the amount of REM sleep, which is a less commonly used marker of the degree of sleep apnea, although it is commonly observed to increase once apnea is treated.

The observed 47% greater UNE level in those patients with OSA compared with healthy control subjects is consistent with the findings of previous studies,[11,13] which showed similar increases in levels of UNE and PNE of approximately 50% in OSA patients who were free of heart disease when compared with healthy subjects.

As the increased UNE level in the OSA group was significantly lower than that in the CHF group, the impact of CHF on SNSA was greater than the effect of OSA alone. Therefore, any effect of OSA on SNSA during sleep was overwhelmed by the impact of established CHF. The finding that UNE levels were similar in the CHF-OSA and CHF-N subgroups, despite a greater degree of arousal and hypoxemia during sleep in CHF-OSA patients, further supports this concept.

The UNE level in the CHF-CSA group was approximately double that of the CHF-OSA and CHF-N groups, which indicates that the CHF-CSA group was associated with a more severe degree of CHF and with greater impairment in cardiac function associated with higher filling pressures. These findings also support previous work[6] in which the overnight UNE level and the awake PNE level in patients with CHF-CSA were twice that of CHF patients without apnea. However, in that work, because no pulmonary-hemodynamic parameters were included, it was assumed that the severity of CHF in patients in the CHF-CSA and CHF-N groups was the same, based on similar LVEFs, and therefore that factors other than CHF severity (*eg*, apnea severity) were responsible for the elevated SNSA.[6] The present work extends these observations in that multiple control groups (*ie*, normal group, OSA group, and CHF-OSA group) are included for comparison, the sample size is four times greater, and detailed pulmonary hemodynamic parameters are included that demonstrate that the raised PCWP in the CHF-CSA group separates that group as a subpopulation of patients with more severe heart failure. Furthermore, the effects of heart transplantation and beta-blocker use on UNE level was assessed.

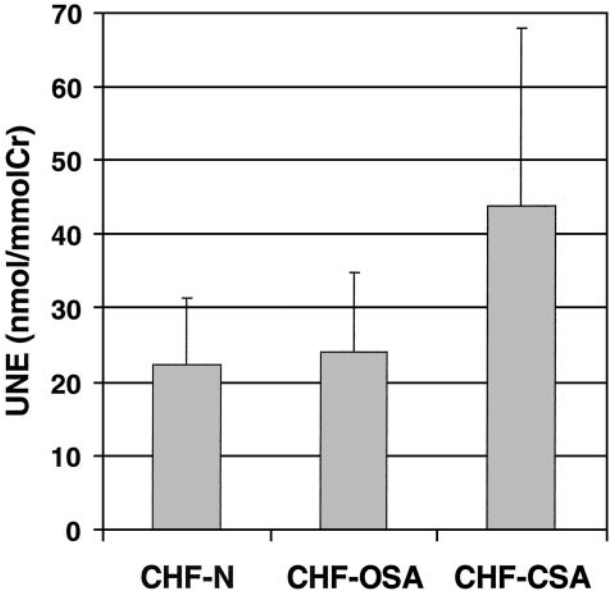

FIGURE 2. Comparison of UNE levels among CHF-N patients (n = 27), CHF-OSA patients (n = 24), and CHF-CSA patients (n = 39) [$p < 0.001$]. Values are given as the mean ± SD.

Table 4—*Correlation Coefficients of UNE in CHF Patients (n = 90)

Variables	*r* Value	p Value
Age, yr	−0.12	0.259
BMI	−0.17	0.117
pH	0.41	< 0.001
$Paco_2$, mm Hg	−0.29	0.008
Pao_2, mm Hg	−0.07	0.527
Cardiac parameters		
LVEF, %	−0.23	0.032
PCWP, mm Hg	0.37	0.044
Cardiac index, L/min/m^2	−0.07	0.565
Sleep architecture		
TST, min	−0.20	0.062
Sleep efficiency, %	−0.19	0.077
Wake	0.18	0.088
Stage 1 and 2, % SPT	−0.02	0.851
Stage 3 and 4, % SPT	−0.04	0.684
REM, % SPT	−0.32	0.002
Sleep disturbance		
AHI, events/h	0.33	0.002
Central AHI, events/h	0.28	0.035
Central AHI/AHI, %	0.28	0.036
MAI, events/h	0.26	0.015
Pulse and oximetry		
Mean HR, beats/min	0.23	0.027
Mean Spo_2, %	−0.29	0.007
Minimum Spo_2, %	−0.26	0.015
TST with $Spo_2 < 90\%$, %	0.22	0.039
Mean $Ptco_2$, mm Hg	−0.21	0.178

*See Tables 1 and 3 for abbreviations not used in the text.

The findings of the current study indicate that although PCWPs and UNE levels are elevated in patients with more severe CHF, the variance of the UNE level is predicted mostly by cardiac hemodynamics (*ie*, PCWP) and to a lesser extent by the loss of REM sleep and, thereafter, hypoxemia. In other words, UNE level is greater in the CHF-CSA group compared with the CHF-OSA group, even when adjusted for the effect of hypoxemia, the number of arousals, and AHI.

By extrapolation from the above data, CSA may simply be a compensatory mechanism for patients with severe CHF, albeit at the expense of arousals from sleep. Although this concept is controversial, there are five lines of evidence in support of this. First, CSA is considered by some researchers[23] to be simply a protective adaptation to counteract preexisting hypoxemia. Second, the crescendo ventilation period is associated with a gradual increase in end-expiratory lung volume, as measured by calibrated inductance plethysmography, thereby increasing pulmonary oxygen stores.[21] Third, under hypoxic conditions, cardiac muscle contractility increases with alkalosis,[24] which is a common finding in CHF patients with CSA. Fourth, the increased nonobstructed ventilatory effort during the CSA has been shown to augment stroke volume.[25] Finally, a pause in ventilation of 20 to 30 s during the central apnea may be sufficient to prevent fatigue in myopathic respiratory muscles.[26] Until it has been shown that reversal of CHF-CSA without raising intrathoracic pressure (such as that which can be achieved by theophylline[27] or carbon dioxide[28]) may augment cardiac function, we believe it to be premature to conclude that CSA itself is pathogenic in patients with CHF.

Although UNE measurement cannot differentiate organ-specific contributions to SNSA, it does provide an average measurement of total body SNSA over a medium term, such as during the sleep period when many patients with CHF complain of dyspnea. Norepinephrine turnover is complex and multicompartmental, involving synthesis, release, metabolism, and uptake, both locally and throughout organ systems. Locally, norepinephrine is continuously released from sympathetic nerve bodies at varying rates, 80% of which is metabolized or taken up by the surrounding tissue. The remaining 20% enters the bloodstream, and a portion is filtered by the kidney, with renal nerves contributing significantly to the final amount appearing in the urine.[29] Despite these limitations in the measurements of UNE, all subjects had no significant renal impairment, and all UNE values were corrected for creatinine excretion.

In conclusion, SNSA, as measured by overnight UNE excretion, is increased to a greater degree in CHF patients than in those with OSA, is greatest in

CHF patients displaying CSA overnight, and drops to levels similar to those of healthy control subjects after heart transplantation. The major contributor to the elevated SNSA in CHF patients is the severity of CHF, as measured by PCWP, and to a lesser degree by the severity of coexistent apnea and related hypoxemia.

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