Muscle Sympathetic Nerve Activity During Wakefulness in Heart Failure Patients With and Without Sleep Apnea


Abstract—Sympathetic activation and sleep apnea are present in most patients with symptomatic systolic heart failure (HF). Acutely, obstructive and central apneas increase muscle sympathetic activity (MSNA) during sleep by eliciting recurrent hypoxia, hypercapnia, and arousal. In obstructive sleep apnea patients with normal systolic function, this increase persists after waking. Whether coexisting sleep apnea augments daytime MSNA in HF is unknown. We tested the hypothesis that its presence exerts additive effects on MSNA during wakefulness. Overnight sleep studies and morning MSNA recordings were performed on 60 subjects with ejection fraction <45%. Of these, 43 had an apnea-hypopnea index ≥15 per hour. Subjects with and subjects without sleep apnea were similar for age, ejection fraction, HF etiology, body mass index, blood pressure, and heart rate. Daytime MSNA was significantly higher in those with sleep apnea (76±2 versus 63±4 bursts per 100 heartbeats [mean±SEM], P=0.005; 58±2 versus 50±3 bursts/min, P=0.037), irrespective of its etiology (the mean difference for central sleep apnea was 17 bursts per 100 heartbeats; n=14; P=0.006; and for obstructive sleep apnea, 11 bursts per 100 heartbeats; n=29; P=0.032). In a subgroup (n=8), treatment of obstructive sleep apnea lowered MSNA by 12 bursts per 100 heartbeats (P=0.003). Convergence of independent excitatory influences of HF and sleep apnea on central sympathetic neurons results in higher MSNA during wakefulness in HF patients with coexisting sleep apnea. This additional stimulus to central sympathetic outflow may accelerate the progression of HF; its attenuation by treatment of sleep apnea represents a novel nonpharmacological opportunity. (Hypertension. 2005;46:1327-1332.)

Key Words: sleep apnea syndrome ■ heart failure ■ sympathetic nervous system

Depending on the degree of convergence of their afferent input on groups of central sympathetic neurons, the efferent response to simultaneous activation of 2 sympathoexcitatory stimuli may be equal to (simple additive summation), less than (mutual inhibition), or greater than the sum of their individual responses (mutual facilitation).1 The purpose of the present investigation was to determine whether the coexistence of heart failure (HF) caused by left ventricular systolic dysfunction and sleep apnea (SA) interact to increase muscle sympathetic nerve activity (MSNA) through a process of additive summation.

Muscle sympathetic burst incidence of untreated HF patients is, on average, 37 bursts per 100 heartbeats or 103% higher than in control subjects with normal ventricular systolic function.2-5 Mortality risk in HF relates to the magnitude of cardiac and peripheral sympathetic nervous system activation.6,7 SA is present in >50% of patients with chronic stable HF.8,9 One quarter to one half of such patients have obstructive SA (OSA), and one third to one half exhibit central apneas during sleep (CSA). Normally, MSNA, blood pressure (BP), and heart rate (HR) fall during nonrapid eye movement sleep.10 In contrast, 4 stimuli, common to OSA and CSA, increase MSNA acutely during sleep.10,11 Brief episodes of apnea increase MSNA by suspending the tonic inhibition of sympathetic outflow by pulmonary stretch receptors.12,13 The development of hypoxia and hypercapnia with more prolonged apneas augments sympathetic activity further by stimulating peripheral and central chemoreceptors.14,15 Arousal from sleep, which terminates apnea, evokes an additional surge in sympathetic traffic.10 Thus, HF patients with coexisting SA differ from those without SA in that their hearts, kidneys, and peripheral circulations are exposed to the adverse effects of catecholamine excess during asleep as well as while awake.

In subjects with normal left ventricular systolic function and OSA, these nocturnal sympathoexcitatory stimuli induce sustained increases in MSNA during wakefulness.16,17 Muscle sympathetic burst incidence of untreated OSA patients without HF is, on average, 22 bursts per 100 heartbeats or 48% higher than control subjects matched for age, sex, and body mass index (BMI).16,17 Not known is whether daytime MSNA of subjects with OSA or CSA and impaired left ventricular systolic function exceeds that of HF patients without SA. If excitatory path-
ways activated by HF and by SA converge on the same pool of central sympathetic neurons, daytime MSNA may not be increased above levels induced by HF, per se, either because of such redundancy or through a process of mutual inhibition. Conversely, if excitatory inputs activated by HF and SA impinge on distinct or separate groups of central sympathetic neurons, an output representing simple additive summation would be anticipated. Because these 4 nocturnal stimuli are common to all subjects with SA, whether obstructive, central, or mixed, the primary objective of the present investigation was to test the hypothesis that HF patients with coexisting SA exhibit significantly greater central sympathetic outflow to skeletal muscle measured while awake than those without SA. A secondary objective was to determine the independent influence of nocturnal OSA or CSA on daytime MSNA.

Methods

Subjects

Subjects eligible for inclusion were those with chronic symptomatic HF (left ventricular ejection fraction [EF] <45% as determined by isotopic ventriculography or echocardiography), in stable condition and without medication adjustment for >1 month, who, in addition, had overnight polysomnography and morning microneurographic measurements of MSNA in the course of ongoing clinical investigations approved by our institutional human subjects review committees. All subjects provided written informed consent before their participation. All patients were treated with optimal contemporary medical therapy, as determined by their attending HF clinic cardiologist, including β-adrenoceptor blockade (carvediolol or metoprolol), if tolerated, on a background of angiotensin-converting enzyme inhibition or substitute, and diuretics and additional therapy if required.

Polysomnography

The ECG was recorded from a single precordial lead. Oxyhemoglobin saturation was measured by pulse oximetry (Nellcor N200; Nellcor Puritan Bennett Inc.). Thoracoabdominal movements were measured by a calibrated respiratory inductance plethysmograph (Respiracare; Ambulatory Monitoring Inc.).13 Sleep stages were determined and apneas and hypopneas identified and defined as either obstructive or central according to our previously published criteria.21 Apnea was defined as the absence of tidal volume for >10 seconds. A ≥50% decrease in tidal volume from baseline lasting >10 seconds was scored as a hypopnea.21 Apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Subjects were classified as having SA if the AHI was ≥15 or no SA (NSA) if the AHI was <15. To test the secondary hypothesis, the SA group was subclassified as primarily OSA (when ≥50% of the total number of apneas and hypopneas were obstructive in character) or CSA (when the majority of events were central).8,9

Microneurography

MSNA was recorded from a muscle fascicle of the peroneal nerve.10,20 It was monitored with an automatic cuff recorder and HR using standard electrocardiographic limb leads. Respiratory excursions were recorded to ensure that all signals were obtained in the absence of apnea. Using a customized analysis program based on the LabView platform (National Instruments), MSNA was quantified by investigators unaware of the results of the polysomnographic studies as burst incidence (bursts per 100 heartbeats) and burst frequency (bursts/min).

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of HF Patients Without and With SA</th>
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<td>Characteristic</td>
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<tr>
<td>No. of subjects</td>
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<td>Male/female, No.</td>
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<tr>
<td>Age, years</td>
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<td>BMI, kg/m²</td>
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<td>EF, %</td>
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<tr>
<td>Etiology of HF, No. (%)</td>
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<tr>
<td>Ischemic</td>
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<tr>
<td>Idiopathic dilated</td>
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<tr>
<td>AHI</td>
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<td>Min SaO₂ while asleep (%)</td>
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<td>Arousals/hour of sleep</td>
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<td>Awake HR, min⁻¹</td>
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<td>Awake BP, mm Hg</td>
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<td>Mean</td>
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<tr>
<td>Awake MSNA</td>
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<tr>
<td>Bursts/min</td>
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<td>Burst/100 cardiac cycles</td>
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Values are expressed as mean±SE. Significantly different from no sleep apnea, *P<0.05 and †P<0.01. Min SaO₂ indicates minimum oxyhemoglobin saturation.

Statistics

Values are expressed as means±their SEs. For the primary analysis, normally distributed data were subjected to a t test. For OSA and CSA comparisons, normally distributed data were analyzed by repeated-measures 1-way ANOVA. Secondary analysis was performed post hoc using the Student-Newman–Keuls Method. Pearson product moments were determined for correlation between independent variables (STATISTICA 5.1; StatSoft Inc.). Statistical significance was accepted if P<0.05.

Results

MSNA During Wakefulness in HF Patients With and Without SA

Of the 60 subjects, the AHI was ≥15 events per hour in 43 patients and <15 events per hour in 17 (NSA). Minimum O₂ saturation during sleep was lower (P=0.005) and the frequency of arousals higher (P=0.011) in those with SA than those without (Table 1). Subjects with and without SA were otherwise similar with respect to clinical variables related to prognosis or to disease severity, such as age (P=0.83), left ventricular EF (P=0.74), BMI (P=0.20), HR (P=0.73), and systolic (P=0.08) or diastolic (P=0.20) BP (Table 1).

SA patients had significantly higher daytime MSNA burst incidence (P=0.005) and burst frequency (P=0.037; Table 1) than NSA patients. Of note, MSNA was similar in men and women in the NSA group (63 versus 62 bursts per 100 heartbeats) and tended to be higher in the 2 women with SA (74 versus 82 bursts per 100 heartbeats).

There were no significant correlations between either awake MSNA burst incidence and the AHI or arousal frequency in either the study population as a whole (r=0.19; P=0.15 and r=0.03; P=0.85, respectively) or in those with
Research Question

Hypothesis

Methodology

Results

Discussion

Similar Daytime MSNA in HF Patients With OSA or Central SA

In the OSA subgroup, 88.8±2.8% of the apneas or hypopneas were obstructive in origin, whereas the remainder were categorized as either central or mixed. Conversely, in the CSA subgroup, 86.0±4.0% of the recorded events were central in origin. Thus, there was wide separation in the 2 groups with respect to the proportion of obstructive and central apneas. The AHI, frequency of arousal from sleep, minimum O2 saturation, and BP were similar in patients with OSA (n=29) and CSA (n=14), as were MSNA burst incidence and burst frequency (Table 2). Compared with NSA subjects, on average, MSNA was 17 bursts per 100 heartbeats higher in those with coexisting CSA (P=0.006) and 11 bursts per 100 heartbeats higher in those with coexisting OSA (P=0.032; P=0.011 for between-group comparison). In contrast, there were no differences in left ventricular EF between subjects with central SA and those without SA (P=0.20) or between subjects with OSA and those without SA (P=0.29). Systolic BP was 18 mm Hg higher in those with OSA than in those without SA (P=0.02).

The key and novel finding in this study is that in patients with chronic stable HF, the presence of SA, whether predominantly central or obstructive, is associated with a significantly higher MSNA burst frequency and incidence during wakefulness. This finding therefore obliges reinterpretation of the prognostic implications of conventional markers of sympathetic tone in HF and reconsideration of the optimal approach to the management of patients with HF and coexisting SA.

Importantly, HF patients with and without SA were similar with respect to age, BMI, left ventricular EF, HR, BP, and HF etiology, indicating that these clinical factors with prognostic impact cannot account for the higher daytime MSNA in those with coexisting SA. Moreover, patients when referred were considered by their attending HF cardiologist to be receiving optimal contemporary medical therapy. This included a background of angiotensin-converting enzyme inhibition or β-adrenoceptor blockade with carvedilol or metoprolol if tolerated. It should be emphasized that neither carvedilol nor metoprolol alter MSNA when given chronically. Thus, the presence or absence of β-adrenoceptor blockade in the present subjects cannot account for the higher daytime MSNA in the group with coexisting SA.

Four stimuli (apnea, hypoxia, hypercapnia, and arousal), elicited by OSA and CSA, increase MSNA acutely during sleep. Exposure to brief episodes of intermittent hypoxia evokes long-lasting sympathetic activation and BP elevations that persist after the removal of the hypoxic stimulus. In rats, changes in the dopamine and norepinephrine content of carotid bodies after intermittent hypoxia permit greater in-
creases in sympathetic discharge and BP than those changes induced by sustained hypoxia.\textsuperscript{29} These observations suggest that the recurrent nocturnal apneas of OSA and CSA have the capacity to elicit sustained aftereffects on sympathetic vasoconstrictor outflow during wakefulness. Indeed, in subjects without HF, OSA itself has been associated with an \(\sim50\%\) increase in daytime MSNA.\textsuperscript{17–19} In nonrandomized studies, abolition of OSA by continuous positive airway pressure (CPAP) in subjects without HF has been reported to decrease MSNA burst incidence acutely during sleep\textsuperscript{17,30} and also after 6 months of nightly application by 14\% during wakefulness.\textsuperscript{17,30}

Coexisting obesity\textsuperscript{8} and persistent hypertension despite aggressive HF therapy\textsuperscript{31} are clues to the presence of OSA in patients with left ventricular systolic dysfunction. Grassi et al\textsuperscript{32} reported higher daytime MSNA in HF patients with these 2 conditions but did not investigate the prevalence of SA in their population or comment on the possibility that the mechanism responsible for both such increases might be unrecognized SA.

In a series of 301 patients with HF, we observed that daytime systolic BP was significantly higher in the 121 subjects with OSA than in those without OSA despite greater use of vasoactive medications\textsuperscript{31} and hypothesized that this higher BP reflected greater daytime sympathetic vasoconstrictor tone in those HF patients with OSA. In the present comparison, systolic BP was on average 18 mm Hg higher and MSNA 11 bursts per 100 heartbeats greater in HF patients with OSA than in those without SA. If the higher daytime MSNA in these patients with OSA represents the sum of the aftereffects of SA extending into wakefulness, plus the sympathoexcitatory effects of HF per se, then abolition of upper airway obstruction during sleep should suppress this neurogenic vasoconstrictor stimulus and lower awake BP. Conversely, if the higher daytime MSNA were a manifestation of pre-existing primary or essential hypertension in these subjects, then abolition of OSA with CPAP would have no effect on either awake BP or MSNA or might even increase the latter, reflexively, should BP fall. In a recent randomized controlled trial involving 24 patients with HF and OSA, 1 month of therapy with CPAP lowered systolic BP by 10±4 mm Hg.\textsuperscript{33} In an extension of that trial involving most of the OSA patients included in the present series, in CPAP-treated patients, MSNA burst incidence fell in all subjects, on average by 14\% (\(P=0.003\)) and systolic BP by 11\% (\(P=0.03\)).\textsuperscript{34} There were no changes in either systolic BP or MSNA in the control group.\textsuperscript{34} Thus, the higher MSNA in this cohort is a result of coexisting OSA rather than a manifestation of pre-existing primary hypertension. The parallel reduction in MSNA and systolic BP with treatment underscores the functional importance of this neurogenic stimulus to increased vasoconstrictor tone in this population.

Burst incidence tended to be highest in those with central SA. Importantly, this increase cannot be attributed to a lower EF in this subgroup for the following 3 reasons: (1) EF in this subgroup was not significantly different from that of patients without SA; (2) there was no correlation in the present series between EF and MSNA burst incidence; and (3) the present findings are consistent with previous published observations on MSNA in patients with left ventricular EF <40\%, in which no relationship with left ventricular EF could be detected in either untreated\textsuperscript{3} or treated subjects.\textsuperscript{35} The mean value for EF in the present series was 23\%.

Compared with HF patients without SA, those with CSA (AHI ≥15 events per hour) have higher daytime plasma norepinephrine concentrations\textsuperscript{20,36} that fall in response to chronic nocturnal CPAP.\textsuperscript{20} Whether patients with CSA exhibit increased MSNA while awake and breathing normally (versus during sleep\textsuperscript{11,37}) has not been reported. Mansfield et al\textsuperscript{38} detected higher rates of cardiac and total body norepinephrine spillover in subjects with CSA than in HF patients without CSA or with OSA and attributed these increases primarily to greater cardiac dysfunction in the CSA group. Importantly, Mansfield et al\textsuperscript{38} used a very low AHI (>5 events per hour) to define SA. In contrast, the present investigation focused on individuals with more severe SA (AHI ≥15 events per hour); those with milder SA (AHI <15 events per hour) were placed in the NSA group. Moreover, unlike MSNA, cardiac and total body norepinephrine spillover are subject to prejunctional inhibition by chronic \(\beta\)-adrenergic blockade.\textsuperscript{26} Because Mansfield et al\textsuperscript{38} did not record MSNA, a direct comparison with the present data is not possible.

Chemoreceptor-mediated sympathetic activation is a potential mechanism for higher daytime MSNA when SA coexists with HF. Augmented peripheral chemoreflex sensitivity to hypoxia is itself an adverse prognostic sign in HF.\textsuperscript{39} Although accentuated peripheral sensitivity to hypoxia\textsuperscript{40} and central chemosensitivities to CO\textsubscript{2} have been reported in HF patients, giving 100\% \(O_2\) during wakefulness did not suppress MSNA.\textsuperscript{41} Of note, because those patients were not characterized on the basis of their breathing patterns during sleep,\textsuperscript{42–43} the potential influence of coexisting SA on their MSNA is unknown.

An increase in the gain of peripheral and central chemoreceptors plays a role in the cyclic breathing oscillations characteristic of CSA.\textsuperscript{44} In the study in which peripheral and central chemoreceptor sensitivities in patients with HF were related to breathing patterns during sleep, ventilatory responses were 2- to 3-fold higher in those with CSA than in HF patients with OSA or NSA.\textsuperscript{45} Chemoreceptor responses in those with OSA were similar to those of HF patients without SA. Therefore, augmented chemosensitivit could contribute to the increase in MSNA in HF patients with CSA. On the other hand, the magnitude of intermittent hypoxemia is, in general, more pronounced in OSA than in CSA.\textsuperscript{4} Thus, in OSA, the aftereffects of intermittent nocturnal hypoxia could augment daytime MSNA in CSA,\textsuperscript{27–29} whereas in CSA, the summation of this carryover effect of nocturnal oxygen desaturation, plus enhanced peripheral and central chemosensitivity,\textsuperscript{7,9,46} would be anticipated to elevate daytime MSNA. Because many factors interact to elicit surges in sympathetic outflow at night, the absence of a specific individual correlation between 1 of these indices, such as AHI or arousal frequency, and daytime MSNA is not surprising.

Because repetitive apneas provoke arousals that disrupt sleep, the proportion of the night spent in restorative sleep is markedly diminished. A heightened state of arousal could
lead to sustained alterations in central neurotransmitter turnover in suprabulbar brain regions involved in adrenergic regulation.46

In summary, in patients with HF, the presence of SA, whether OSA or CSA, is associated with significantly higher daytime MSNA. In the present series, this increase was independent of age, left ventricular EF, and other clinical variables related to disease severity or prognosis. In the absence of HF, OSA has been shown to increase MSNA burst incidence, on average, by 22 bursts per 100 heartbeats (range 19 to 26) above that of control subjects without OSA,17–19 whereas HF, in the absence of drug treatment and OSA, increases MSNA burst incidence, on average, by 37 bursts per 100 heartbeats (range 29 to 42). In our study of patients with treated HF, the coexistence of OSA increased MSNA, on average, by an additional 11 bursts per 100 heartbeats. Thus, MSNA in patients with OSA and HF is greater than MSNA in either condition alone. The absence of simple additive summation may represent a threshold or saturation effect (in that burst incidence, as presented in the Figure, cannot exceed 100%) or reflect the potent influence of concurrent pharmacological therapy for HF and, in particular, angiotensin-converting enzyme inhibition on MSNA47 or indicate a degree of convergence of these 2 excitatory influences on central sympathetic neurons.1

In that HF is itself such a powerful stimulus to sympathoexcitation, some degree of overlap between MSNA burst incidence in the SA and NSA HF population (Figure) would be anticipated. In part, this also represents the recording condition (ie, MSNA was measured during wakefulness rather than during sleep, when the sympathoexcitatory influence of apneas would be greatest). However, this overlap also highlights a limitation of conventional microneurography, which integrates single fiber discharges within the cardiac cycle to generate envelopes of multifiber activity. Once patients with HF discharge 100 bursts per 100 cardiac cycles at rest, they cannot respond to further excitatory stimuli by increasing nerve firing rate. Instead, they are obliged to recruit additional, quiescent fibers and thereby increase burst amplitude.13 Using single fiber recordings during wakefulness in HF patients and OSA subjects lacking HF, Elam et al demonstrated a similar increase in the probability of nerve firing within a given cardiac cycle in both groups.48 Those with OSA were more likely to manifest an increase in the number of spikes a particular fiber generated per burst. Although not the purpose of the present investigations, future investigations of the effect of convergence of HF and SA on MSNA could apply single fiber recordings to overcome this ceiling, or saturation effect.

**Perspectives**

Despite advances in the pharmacological treatment of HF, its prognosis remains distressingly poor. Consequently, novel device-based approaches, such as CPAP for coexisting SA, have attracted considerable interest. In our randomized controlled trial, abolition of OSA by CPAP reduced MSNA burst incidence during wakefulness by 12 bursts per 100 heartbeats,34 a value almost identical to the increment in MSNA attributable to the presence of OSA in the present study.

In addition, concurrently measured systolic BP fell by 15 mm Hg34 (ie, a value similar to the 18 mm Hg difference between the OSA and the NSA groups, overall, in the present series). Furthermore, the 14% reduction in burst incidence after 1 month of CPAP in this randomized controlled trial34 is identical to the 14% reduction documented after 6 months of nonrandomized treatment in subjects with OSA but without HF.30 Although comparable data for the effects of CPAP on MSNA in HF patients with CSA have yet to be reported, these observations in HF patients with OSA are entirely consistent with the concept that sympathoexcitatory inputs activated by HF2–4,49 and SA1–19 impinge on separate and similar groups of central sympathetic neurons,1 resulting in higher efferent vasoconstrictor discharge than exhibited by each of these 2 conditions alone. This additive stimulus of nocturnal apnea to central sympathetic outflow during sleep and wakefulness may accelerate the progression of HF.50–52 If so, abolition or attenuation of SA would represent a novel nonpharmacological approach to the treatment of HF.

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**References**


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