Raised Sympathetic Nerve Activity in Heart Failure and Central Sleep Apnea Is Due to Heart Failure Severity

Darren Mansfield, MBBS; David M. Kaye, MBBS, PhD; Hanspeter Brunner La Rocca, MD; Peter Solin, MBBS, PhD; Murray D. Esler, MBBS, PhD; Matthew T. Naughton, MD

Background—Congestive heart failure (CHF) patients with central sleep apnea (CHF-CSA) have elevated plasma norepinephrine (NE) compared with CHF patients without apnea (CHF-N). Patients with CHF-CSA also demonstrate higher mean pulmonary artery pressure (PAP), which is suggestive of worse cardiac function. Whether CSA contributes to chronic elevation of sympathetic nerve activity or is associated with more severe CHF remains unknown. We measured awake total body and cardiac NE spillover and related these to measurements of cardiac hemodynamics and apnea severity in CHF patients with CSA, with normal breathing, and with obstructive sleep apnea (CHF-OSA).

Methods and Results—A total of 55 CHF patients underwent right heart catheterization and measurements of total body and cardiac NE spillover using NE radioisotope dilution methodology. After polysomnography, patients were grouped by apnea type: 19 were CHF-N, 15 were CHF-OSA, and 21 were CHF-CSA. Compared with the CHF-N and CHF-OSA groups, the CHF-CSA group had significantly higher total body NE spillover (4.62 ± 0.56 versus 4.47 ± 0.54 versus 6.95 ± 0.89 nmol/min, respectively; P = 0.03), cardiac NE spillover (0.25 ± 0.05 versus 0.21 ± 0.05 versus 0.42 ± 0.06 nmol/min, respectively; P = 0.02) and mean PAP (23.5 ± 2.4 versus 21.2 ± 0.8 versus 30.4 ± 0.2 mm Hg, respectively; P < 0.02). However, controlling for severity of CHF resulted in no significant differences in NE kinetics among the 3 groups. In a stepwise regression, only mean PAP independently correlated with total body (r = 0.33, P = 0.03) and cardiac NE spillover (r = 0.44, P = 0.002). Sleep apnea severity bore no relationship to markers of sympathetic nerve activity.

Conclusion—Total body and cardiac sympathetic nerve activity are elevated in CHF-CSA compared with CHF-OSA and CHF-N patients and are related to heart failure not apnea severity. (Circulation. 2003;107:1396-1400.)

Key Words: heart failure ■ nervous system, sympathetic ■ sleep apnea syndromes

The importance of sympathetic nerve activity (SNA) in patients with congestive heart failure (CHF) is highlighted by the significant correlation between plasma norepinephrine (NE) and mortality.1 Sympathoexcitation has been proposed to play a major role in CHF progression and outcome through its influence on myocyte survival,2 arrhythmogenesis,3 and possible ventricular energetics.4

A subgroup of CHF patients exhibit central sleep apnea (CSA) associated with Cheyne-Stokes respiration. This condition is characterized by periods of crescendo-decrescendo hyperventilation with an arousal from sleep and interspersed by periods of central apnea with hypoxemia.5 CSA occurs in approximately one third of patients with CHF6–8 and may be associated with increased mortality compared with CHF patients without apnea.9,10 In patients with CHF and CSA (CHF-CSA), overnight urinary and awake plasma NE concentrations are elevated compared with patients without CSA, despite similar left ventricular ejection fractions.11

Another group of CHF patients suffer from obstructive sleep apnea (OSA), in which recurrent episodes of upper airway occlusion associated with vigorous inspiratory efforts and hypoxemia occur, terminated by an arousal from sleep. OSA is caused by upper airway instability, whereas CSA results from altered central respiratory control. Although SNA is known to be elevated in OSA patients without known CHF,12 the effect of OSA on NE levels in CHF is unknown.

Both organ-specific and total-body SNA can be measured using NE isotope dilution methodology. Determination of rates of spillover of NE from nerve terminals into plasma indicates sympathetic nerve firing rates and provides direct measures of SNA. Using this technique in CHF patients, cardiac-specific SNA has been shown to be upregulated13 and to correlate with pulmonary capillary wedge pressure (PCWP).14 Moreover, elevated cardiac-specific SNA is a more sensitive marker of mortality than plasma NE in patients with CHF.13

A contributory role of CSA to the elevated SNA during sleep has been postulated to be due to apnea-related arousals and hypoxemia during sleep, which correlate significantly with overnight NE excretion.15 However, CHF-CSA patients...
have persistently elevated plasma NE levels during wakefulness (in the absence of hypoxemia and arousals), suggesting that other factors, such as severity of cardiac function, are responsible for the persistent elevation of SNA. Because direct measurements of SNA have not been previously employed in a controlled study of CSA in CHF, the relative contributions of heart failure and sleep apnea severity toward raised SNA remain unknown.

To identify factors that contribute to the heightened mortality in CHF-CSA, we sought to determine whether cardi-specific SNA, using NE isotope dilution methodology, is elevated in patients with CHF-CSA compared with CHF patients without sleep-disordered breathing (CHF-N) and a second control group of CHF patients with OSA (CHF-OSA).

Methods

Patient Selection
Consecutive patients aged 18 to 70 years with clinical evidence of either ischemic or idiopathic dilated cardiomyopathy (NYHA II to IV) and left ventricular ejection fractions <40% were enrolled. All patients were on optimal medical therapy and were in a stable condition, as defined by no hospital admission or medication changes within the preceding 2 weeks. Exclusion criteria were unstable ischemic heart disease or known pulmonary, renal, or neurological disease. The protocol was approved by the Alfred Hospital Ethics Committee, and informed consent was obtained from all participants.

All patients underwent right heart catheterization, assessment of sympathetic nervous function with NE isotope dilution methodology, radionuclide assessment of ejection fraction, and overnight polysomnography.

Catheterization
Stimulants such as nicotine and caffeine were avoided on the morning of the procedure; however, medications were continued. Patients underwent standard right heart catheterization percutaneously through the right cubital fossa or right internal jugular approach with a balloon flotation catheter (7F, Arrow, Arrow International) during wakefulness. Central venous pressure, pulmonary artery pressure (PAP), and PCWP were obtained. Cardiac output was determined by the thermodilution technique. Coronary sinus cannulation (Webster CCS 7/8U 90A, Webster Laboratories) was performed under fluoroscopic guidance, and measurement of coronary sinus blood flow was obtained by a thermodilution algorithm. Blood pressure was monitored through a 3F radial arterial cannula.

NE isotope dilution methodology was used to determine rates of NE spillover into plasma from the heart and total body. Forty-five minutes before the right heart catheterization, an intravenous infusion of tritiated levo-NE (New England Nuclear) was commenced at a rate of 0.5 to 1.5 μCi/min. Samples were collected at steady-state from the radial artery and coronary sinus into chilled tubes containing an anticoagulant, ethyleneglycol-bis (β-aminoethyl ether) N,N'-tetracetic acid (EGTA) and an antioxidant, reduced glutathione. Specimens were centrifuged at 4°C, and the plasma was stored immediately at −70°C for later analysis. Total NE spillover into plasma, plasma NE clearance, and cardiac NE spillover were calculated as previously described.16

Assays
Catecholamines in plasma (1 mL) and samples of the infusion preparation (10 μL) were adsorbed onto alumina and quantified by liquid chromatography with electrochemical detection, as previously described.16 The concentration of HNE (tritiated levo-NE) was determined by collecting the appropriate fraction of the eluant leaving the detector cell and determining its radioactivity by liquid scintillation spectroscopy.

Sleep Studies
Full overnight polysomnography was performed using a computerized system (SomnOstar, SensorMedics Corp). Sleep staging was determined by monitoring with a 2-channel electroencephalogram, a 2-channel electro-oculogram, and submental electromyogram. A 30-minute period at the beginning of the night following instrumentation, while bed room lights remained on, was monitored and recorded as "pre-lights out" time to assess objectively for awake central apnea. Oronasal airflow was monitored by thermistor (ProTech Services). Thoracoabdominal movement was recorded using calibrated respiratory effort bands (Resp-ez, EPM systems). ECG recorded heart rate and rhythm from lead II. Oxygen saturation pulse (Spo2) was monitored using ear probe oximetry (Fastrac, SensorMedics Corp).

Sleep was manually staged according to standard criteria.27 A central apnea was defined as an absence of oronasal airflow during sleep for ≥10 s associated with absent respiratory effort. A central hypopnea was defined as any reduction in oronasal airflow for ≥10 s in the presence of out-of-phase thoracoabdominal effort. An obstructive hypopnea was defined as a fall in oronasal airflow for >10 s with ≥2% fall in Spo2. Obstructive apnea was defined as cessation of oronasal airflow for ≥10 s with ≥2% fall in Spo2. A mixed apnea was defined using the above criteria, when a central apnea included or terminated with obstructive components. Mixed apneas were classified as obstructive events.

Patients were then categorized according to the presence/absence of CSA. The CHF-CSA group was defined by an apnea-hypopnea index >5 events/h, whereby >75% of all events were central in origin. The CHF-N group was defined by an apnea-hypopnea index <5 events/h. Patients with an apnea-hypopnea index ≥5 events/h with ≥25% of noncentral events were classified as CHF-OSA.

Statistics
Data are presented as mean±SEM. Data were normally distributed and compared between the 3 groups by 1-way ANOVA with Tukey post hoc analysis. Analysis of covariates was performed matching for significantly different variables. Continuous variables were related using the least-squares method of linear regression. Multivariate analysis was used for significant correlations. Analysis was performed on the software package SPPS version 9. P<0.05 was considered significant.

Results
Fifty-six consecutive patients were enrolled; however, one patient with CHF-CSA was deleted from the analysis because the measured plasma NE concentration was >8 SDs outside the mean, producing an improbable result; thus, 55 patients were analyzed. Fifteen patients were classified as CHF-OSA group, 21 as CHF-CSA, and 19 as CHF-N. No patients were observed to have CSA during the catheterization and NE spillover assessment. The CHF-CSA and CHF-OSA groups had more severe symptoms of CHF than the CHF-N group, and the CSA group had higher right heart pressures (Table 1). Medications were not significantly different in each of the 3 groups (Table 2).

All markers of SNA were elevated in the CHF-CSA group compared with the CHF-N and CHF-OSA groups, as outlined in Table 3. Compared with the CHF-N and CHF-OSA groups, the arterial plasma NE was ~50% greater, the total...
There were significant differences in hemodynamic variables between the 3 groups (Table 1). When controlled for markers of cardiac dysfunction (mean PAP and cardiac index) using an analysis of covariates, the relationships between presence/absence of CSA and total and cardiac spillover were no longer significant ($R^2=0.23$, $P=0.18$; $R^2=0.17$, $P=0.19$, respectively) suggesting that the differences in SNA between patients with CSA, with OSA, and without sleep-disordered breathing were colinearly related to heart failure severity.

When a subgroup of patients from each group was matched for mean PAP ($\approx$27 mm Hg) and cardiac index ($\approx$2.2 L/min per m²), there were no differences in arterial, total, or cardiac NE spillover (Table 4).

Using least-squares regression, there were no significant correlations between measures of sleep apnea severity (ie, apnea-hypopnea index, SpO₂, or arousal index) and plasma NE, total body, or cardiac NE spillover in the CHF-CSA group (Table 5). The plasma NE and total NE spillover correlated significantly with right atrial, mean PAP, and PCWP (Table 5). Cardiac NE spillover correlated significantly with mean PAP and PCWP. In a stepwise multivariate analysis, mean PAP independently correlated with plasma NE concentration ($r=0.51$, $P=0.001$), total body NE spillover ($r=0.33$, $P=0.03$), and cardiac NE spillover ($r=0.44$, $P=0.002$).

**Discussion**

This study identified several novel, important findings that further our understanding of SNA in CHF with apnea. First, we demonstrated a significantly elevated awake cardiac and total body NE spillover in patients with CHF-CSA compared with CHF patients with OSA or normal ventilation during sleep. This confirms previous published data\(^{11}\) that CSA is associated with greater awake plasma and overnight urinary NE.

Second, and in contrast with previous findings,\(^{11}\) our results suggest that the elevated awake SNA in CSA relates to worse CHF rather than apnea for the following reasons. When the groups were matched for CHF severity, the differences in SNA between groups were no longer significant. In addition, the elevations in cardiac and total body SNA bore significant correlations with measures of cardiac dysfunction but not with markers of apnea severity. Finally, a multivariate analysis showed that mean PAP independently predicted cardiac and total body SNA.

Third, we identified that the elevated plasma NE in CHF-CSA, previously observed\(^{11}\) and now confirmed by more accurate measures, is due to elevated NE spillover rather than a reduction in plasma clearance. Finally, we identified that the NE spillover was no different between the CHF-N and the CHF-OSA groups.

CSA is a condition occurring in a third of patients with NYHA class II to IV CHF. It is associated with higher PCWP\(^7\) and probably greater mortality.\(^9\)–\(^10\) Pathophysiologically, hyperventilation and a prolonged circulation time underpin the development of CSA in CHF.\(^5\),\(^18\) Although the time taken for pulmonary venous blood to reach the peripheral chemoreceptor at the carotid body is prolonged in CHF due to reduced cardiac output,\(^19\),\(^20\) prolonged circulation time

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CHF-N (n=19)</th>
<th>CHF-CSA (n=21)</th>
<th>CHF-OSA (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female ratio</td>
<td>15:4</td>
<td>17:4</td>
<td>13:2</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.3±1.6</td>
<td>55.7±1.8</td>
<td>50.0±3.4</td>
<td>NS</td>
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<tr>
<td>BMI, kg/m²</td>
<td>26.7±0.8</td>
<td>26.1±1.0</td>
<td>28.4±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic:idiopathic ratio</td>
<td>7:12</td>
<td>8:13</td>
<td>7:8</td>
<td>...</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>24.6±2.3</td>
<td>22.0±2.3</td>
<td>24.1±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.3±0.2</td>
<td>3.0±0.2</td>
<td>2.9±0.2</td>
<td>0.008†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±3</td>
<td>69±3</td>
<td>68±5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>77±2</td>
<td>76±2</td>
<td>76±2</td>
<td>NS</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>6.2±1.0</td>
<td>7.8±0.8</td>
<td>6.1±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>23.5±2.4</td>
<td>30.4±2.2</td>
<td>21.2±1.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.4±0.1</td>
<td>2.0±0.1</td>
<td>2.4±0.2</td>
<td>0.05*</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>15.0±1.8</td>
<td>21.7±1.6</td>
<td>14.4±1.4</td>
<td>0.01*</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>77±2</td>
<td>84±3</td>
<td>85±3</td>
<td>0.07</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>42±1</td>
<td>38±1</td>
<td>42±1</td>
<td>0.007*</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>2±0</td>
<td>24±4</td>
<td>18±4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Mean SpO₂, %</td>
<td>94±1</td>
<td>93±0</td>
<td>93±1</td>
<td>NS</td>
</tr>
<tr>
<td>SpO₂ &lt;90%, %TST</td>
<td>1±0</td>
<td>12±4</td>
<td>10±4</td>
<td>NS</td>
</tr>
<tr>
<td>Arousal index, events/h</td>
<td>25±6</td>
<td>38±8</td>
<td>35±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. LV indicates left ventricular; AHI, apnea-hypopnea index; BMI, body mass index; and TST, total sleep time.

*CHF-CSA group different from CHF-N and CHF-OSA groups; †CHF-CSA and CHF-OSA groups different from CHF-N group.

Body NE spillover ≈50% greater, and the cardiac NE spillover ≈70% greater in the CHF-CSA group. The NE clearance rates were similar in all 3 groups, indicating that the higher plasma NE in CHF-CSA was due to increased NE spillover rather than a reduction in plasma clearance.

Of the group of 55 patients, no CHF-N or CHF-OSA patient and only 3 CHF-CSA patients demonstrated awake central apnea. The arterial plasma NE (3.52±0.29 versus 3.86±0.68 nmol/L), total body (6.93±0.96 versus 7.04±3.14 nmol/min), and cardiac NE spillover (0.41±0.06 versus 0.51±0.19 nmol/min) were not different between the CHF-CSA subgroups who demonstrated asleep (n=18) versus awake (n=3) central apneas.

**TABLE 2. Patient Medications**

<table>
<thead>
<tr>
<th></th>
<th>CHF-N (n=19)</th>
<th>CHF-CSA (n=21)</th>
<th>CHF-OSA (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>16</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other β-blockers</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>16</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>11</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Digoxin</td>
<td>16</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Antiaggregants</td>
<td>12</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
alone is insufficient to trigger CSA. Accordingly, there has been considerable interest in the factors likely to promote hyperventilation.

Two mechanisms responsible for hyperventilation in CHF-CSA patients have been proposed. The first is the stimulation of pulmonary vagal afferent nerves by elevation in pulmonary vascular pressures, which would be consistent with the observation of high PCWP in patients with CHF-CSA. However, we demonstrated CSA in a vagally denervated patient with CHF, indicating that other mechanisms must be operable.

The alternative theory for the development of CSA is the demonstration of upregulation of both central and peripheral chemoreceptors in humans, which is thought to be due, in part, to elevated circulating catecholamines. Heistad et al observed increases in ventilation with infusion of NE. Animal studies have confirmed that the peripheral chemoreceptors (carotid body) can be functionally altered by the presence of pacing-induced CHF over a 3- to 4-week period. This would imply that CSA is an acquired pattern secondary to CHF.

The data from the current study would support this latter theory: the primary event responsible for the development of CSA in CHF patients is cardiac failure per se and the associated elevated SNA and upregulated chemosensitivity is secondary to this. Elevated chemosensitivity and correspondingly reduced PaCO₂ values while awake support this reasoning.

Although we demonstrated a significant relationship between awake SNA and markers of cardiac dysfunction and not markers of sleep apnea severity, it is possible that the CSA is still partially contributory to elevated SNA. In support of this, Van De Borne et al demonstrated that SNA measured by microneurography increased during periods of CSA in sleeping subjects with CHF compared with the same patients when in stable respiration. However, our subset of patients matched for mean PAP had very similar cardiac NE spillover recordings and showed no significant differences in total body NE spillover and plasma NE. Nevertheless, it is possible that CSA does contribute to SNA at times of sleep, but less so into wakefulness.

In the current study, sleep and ventilation were not objectively monitored at the time of the right heart catheter procedure and, accordingly, central apneas during wakefulness may have occurred despite the careful observation of nursing staff and requests to patients to remain awake during the procedure as with our previous studies. Of the 55 patients, only 3 demonstrated central apneas while awake during 30 minutes of pre-lights out within the polysomnography set up, and each belonged to the CHF-CSA group. The SNA results of these 3 patients were no different than those of the CHF-CSA group without awake central apnea. This suggests that the acute changes in SNA that may occur during periods of CSA are not contributing substantially to our findings.

Further work from direct interventional studies which may abolish CSA without changing cardiac function (such as carbon dioxide inhalation) plus comparisons of SNA measures during sleep and wakefulness in CHF-CSA patients are required to assess the extent to which CSA impacts SNA in CHF.

The observation that SNA is similar between the CHF-N and CHF-CSA groups was novel and unexpected. OSA is known to be associated with elevated skeletal muscle microneurography, measured asleep and awake, compared with normal subjects and to fall with OSA treatment. Elevated SNA is thought to relate to arousals, hypoxemia during sleep, and resetting of homeostatic baroreceptor function. Given our results, we believe that the effects of CHF may simply overwhelm the effects OSA may have on awake SNA. Further work comparing SNA measures during wakefulness and sleep in CHF groups and after OSA treatment are required.

### TABLE 4. Subset of Patients Matched for Mean PAP

<table>
<thead>
<tr>
<th></th>
<th>CHF-N (n=11)</th>
<th>CHF-CSA (n=15)</th>
<th>CHF-OSA (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP, mm Hg</td>
<td>28±3</td>
<td>27±2</td>
<td>27±2</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.3±0.1</td>
<td>2.1±0.1</td>
<td>2.1±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial NE, nmol/L</td>
<td>2.82±0.23</td>
<td>3.06±0.26</td>
<td>2.55±0.72</td>
<td>NS</td>
</tr>
<tr>
<td>Total spillover, nmol/min</td>
<td>5.76±0.94</td>
<td>6.12±0.94</td>
<td>4.68±1.32</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac spillover, nmol/min</td>
<td>0.32±0.06</td>
<td>0.35±0.07</td>
<td>0.33±0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*Significant difference in CHF-CSA group from the CHF-N and CHF-OSA groups.
In summary, patients with CHF-CSA have significantly greater awake total body and cardiac NE spillover compared with CHF-N and CHF-OSA patients. This elevated awake SNA was related to heart failure severity rather than CSA severity. Because NE clearance rates were similar between the groups, the greater plasma NE concentration in CHF-CSA was explained by the greater total body NE spillover. These significant findings provide insight into the possible explanation for the higher mortality reported in CHF-CSA patients.

Acknowledgments

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References

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