Influence of Pulmonary Capillary Wedge Pressure on Central Apnea in Heart Failure

Peter Solin, MBBS; Peter Bergin, MBBS; Meroula Richardson, MBBS; David M. Kaye, MBBS, PhD; E. Haydn Walters, DM; Matthew T. Naughton, MD

Background—Recent studies suggest that acute pulmonary congestion induces hyperventilation and that hyperventilation-related hypocapnia leads to ventilatory control instability and central sleep apnea. Whether chronic pulmonary congestion due to congestive heart failure (CHF) is associated with central apnea is unknown. We hypothesized that CHF patients with central apnea would have greater pulmonary capillary wedge pressure (PCWP) than patients without central apnea and that PCWP would correlate with central apnea severity.

Methods and Results—Seventy-five stable CHF patients underwent right heart catheterization and, on the basis of overnight sleep studies, were divided into central apnea (n=33), obstructive apnea (n=20), or nonapnea groups (apnea-hypopnea index [AHI] <5 events per hour). Mean PCWP was significantly greater in the central than in the obstructive and nonapnea groups (mean±SEM [range]: 22.8±1.2 [11 to 38] versus 12.3±1.2 [4 to 21] versus 11.5±1.5 [3 to 28] mm Hg, respectively; P<0.001). Within the central apnea group, PCWP correlated with the frequency and severity of central apnea (AHI: r=0.47, P=0.006) and degree of hypocapnia (PaCO₂: r=−0.42, P=0.017). Intensive medical therapy in 7 patients with initially high PCWP and central apneas reduced both PCWP (29.0±2.6 [20 to 38] to 22.0±1.8 [17 to 27] mm Hg; P<0.001) and central apnea frequency (AHI) (38.5±7.7 [7 to 62] to 18.5±5.3 [1 to 31] events per hour; P=0.005).

Conclusions—PCWP is elevated in CHF patients with central apneas compared with those with obstructive apnea or without apnea. Moreover, a highly significant relationship exists between PCWP, hypocapnia, and central apnea frequency and severity. (Circulation. 1999;99:1574-1579.)

Key Words: heart failure ■ sleep ■ apnea ■ hemodynamics ■ hypoxemia

Sleep apnea and congestive heart failure (CHF) are common disorders affecting 2% to 4% and 1% of the population, respectively.1,2 Moreover, ≈40% to 50% of patients with CHF are reported to have sleep apnea of either nonhypercapnic central or obstructive types.3,4 Evidence also exists that recognition and treatment of either form of sleep apnea in patients with CHF can augment cardiac function.3,5

Central apnea in CHF occurs as a result of ventilatory control instability, and patients typically complain of orthopnea, paroxysmal nocturnal dyspnea, witnessed apneas, fragmented sleep, and excessive daytime sleepiness.6 Recordings of ventilation during sleep reveal a characteristic cyclic pattern of central apnea and hypoxemia followed by crescendo/decrescendo ventilation, associated with an arousal at the peak of ventilation, known classically as Cheyne-Stokes respiration.6

Whereas ventilation is under the influence of several factors during wakefulness, ventilation during non-REM sleep is under a chemical-metabolic control, such that ventilation occurs while the level of metabolic signal (PaCO₂) is above the apnea threshold. Instability of this control occurs if (1) the ventilatory response to a given metabolic signal is increased and hyperventilation occurs, (2) oscillations in blood gases with each apnea cannot be buffered (as occurs when the body stores of oxygen or carbon dioxide are diminished or during ventilation/perfusion alterations when the individual is supine and asleep), or (3) the circulatory time between the lungs and chemoreceptors is prolonged.6 Although patients with CHF have circulatory delay, the major abnormality contributing to ventilatory control instability is thought to be hyperventilation and resultant hypocapnia.6 The supranormal ventilatory responses to increasing levels of carbon dioxide and marked hypocapnia observed in CHF patients with central apnea support this hypothesis.6,7

On the basis of animal experiments, it has been proposed that hyperventilation results from elevation of pulmonary interstitial pressure.8 Pulmonary edema and concomitant increase in interstitial pressure stimulates pulmonary J receptors, which lie within the interstitium in close proximity to the pulmonary capillaries.8 Neural impulses are transmitted via...
afferent pulmonary vagal C fibers to the ventilatory control center in the medulla.\textsuperscript{9} Stimulation of this afferent vagal system results in brief central apnea followed by tachypnea and hyperventilation.\textsuperscript{5–10}

In contrast to central apnea, the pathophysiological abnormality of obstructive apnea is intermittent upper-airway closure against which futile respiratory efforts are made.\textsuperscript{5} Large negative intrathoracic pressures are generated that increase left ventricular transmural pressure gradient and therefore afterload.\textsuperscript{11} Moreover, hypoxemia related to apnea and bursts of muscle sympathetic activity related to arousal cause rises in systemic blood pressure that further increase left ventricular afterload.\textsuperscript{11} However, the adverse effects of obstructive apnea on cardiac function are limited to periods of sleep and may not be apparent during wakefulness.

We hypothesized that the presence of elevated pulmonary vascular pressure in patients with stable CHF would be associated with hypoxemia and central sleep apnea. To test this hypothesis, we compared pressures on the right side of the heart within a group of patients with severe stable CHF, grouped by presence and type of apnea. Second, in the group of patients with central apnea, we assessed the relationship between pulmonary capillary wedge pressure (PCWP) and central apnea frequency and severity. Third, we assessed changes in central apnea frequency after intensive medical therapy in a subgroup of patients with high initial PCWP and central apnea.

Methods

Subjects

Patients being assessed by the Cardiac Transplant Service of the Department of Cardiology at the Alfred Hospital were invited to take part in this study. The Ethics Committee of the Alfred Hospital approved the study, and patients provided written informed consent. Consecutive patients aged 18 to 70 years with clinical evidence of significant chronic CHF and a left ventricular ejection fraction (LVEF) <40\% due to ischemic or idiopathic dilated cardiomyopathy were enrolled. All eligible patients participated in the study. All patients were taking medical therapy and were in a stable condition, defined as no hospital admission or medication changes within the preceding 2 weeks. No patient had previously undergone sleep monitoring or treatment for sleep apnea, nor were any patients selected on the basis of possible underlying sleep apnea.

Exclusion criteria included the following: pregnancy; unstable angina; primary valvular, congenital, or restrictive cardiomyopathy; significant renal, neurological, or respiratory disease; and obesity (weight >100 kg). Patients with CHF whose weight is >100 kg do not routinely undergo cardiac transplant assessment because of potential for therapeutic weight loss, donor-matching difficulties, and poor posttransplant outcome related to obesity.\textsuperscript{12}

Sleep Studies

Overnight sleep studies were performed in the usual manner with a computerized system (SomnoStar, SensorMedics Corp); 2 electroencephalogram channels, left and right electro-oculograms, and submental electromyogram (EMG) were used for the determination of sleep stages. Sleep stages were manually scored according to standard criteria by an experienced scorer blinded to the patients' details.\textsuperscript{13} Sleep efficiency was defined as total sleep time divided by time in bed and percent sleep stage as the total time spent in a particular sleep stage divided by the total sleep time. ECG and heart rate were recorded continuously from precordial lead II, arterial oxygen saturation was measured by an ear pulse oximeter (SpO\textsubscript{2}), and transcutaneous PCO\textsubscript{2} was measured by a capnograph placed on the anterior chest wall (Fastrac, SensorMedics Corp). Chest and abdominal movements were monitored with respiratory effort bands (Resp-ez, EPM Systems). Oronasal airflow was monitored by thermocouples (ProTech Services) and snoring was monitored with a piezo snore sensor (ProTech Services).

A central apnea was defined as an absence of oronasal airflow for ≥10 seconds associated with an absence of chest and abdominal movement. A central hypopnea was defined as a reduction in oronasal airflow associated with a ≥2\% fall in SpO\textsubscript{2} with in-phase chest and abdominal movement, no increase in submental EMG activity, and absence of snoring. An obstructive apnea was defined as an absence of oronasal airflow for ≥10 seconds despite continued out-of-phase chest and abdominal movements. An obstructive hypopnea was defined as a reduction in oronasal airflow for ≥10 seconds associated with a ≥2\% fall in SpO\textsubscript{2} despite continued out-of-phase chest and abdominal movements, increased submental EMG activity, or snoring. A mixed apnea was defined as absence of oronasal airflow associated with central followed by obstructive components. Because upper-airway closure occurs during mixed apneas, as a result of upper-airway instability, these events were defaulted into the obstructive sleep apnea group. The apnea-hypopnea index is the total number of apneas and hypopneas divided by the total sleep time and is expressed as the number of events per hour.

Awake Measurements

Catheterization of the right side of the heart was performed in the morning, while subjects were awake, and was followed by a sleep study that night. All procedures were performed by experienced cardiologists involved in the study but blinded to the sleep study results. Pressure measurements were recorded on the right side of the heart by use of a balloon-tipped flotation thermodilution catheter (7F Arrow, Arrow International) via the right internal jugular vein while subjects were in the supine position. Cardiac output was measured by the thermodilution technique at the pulmonary artery position, and an average was calculated from 3 values that varied by <10\%. Cardiac index was calculated as cardiac output divided by body surface area. Transpulmonary gradient was calculated as the difference between mean pulmonary artery pressure (PAP) and PCWP. Pulmonary vascular resistance was calculated as the transpulmonary gradient divided by cardiac output. Arterial blood gas samples were drawn 1 hour before sleep onset, while subjects were supine but awake, after ≥10 minutes of undisturbed rest. Awake LVEF was measured by 99m Tc radionuclide angiography by the equilibrium method and was also accomplished within the assessment period.

Protocol

Each patient underwent complete assessment over a 3-day period. On the basis of the results of the sleep study, patients were divided into 3 groups depending on the presence and type of sleep apnea, with a cutoff apnea-hypopnea index ≥5 events per hour. Patients were classified as having central apnea if ≥85\% of their events were purely central in origin. All others with an apnea-hypopnea index ≥5 were classified as having obstructive apnea, including those with mixed apneas. Patients with elevated PCWP and central apnea were invited to undergo repeat investigation after intensive medical therapy.

Statistical Analysis

Right-heart catheter data were compared between the 3 groups by 1-way ANOVA with Tukey post hoc analysis. PCWP was correlated with awake PaCO\textsubscript{2} and indexes of central apnea frequency (apnea-hypopnea index) and severity (minimum sleep SpO\textsubscript{2} and percent of total sleep time spent with SpO\textsubscript{2} <90\%) within the central apnea group by Pearson least squares method of analysis. Data are expressed as mean ± SEM. A P value of <0.05 was regarded as significant.
Results

Subject Characteristics

Seventy-five patients (61 men, 14 women) were studied, of whom 53 had sleep apnea (71%) (Table 1). Thirty-three patients (44% of the patient population) had central apnea, and 20 (27%) had obstructive apnea. The incidence of central and obstructive apnea, respectively, was 42% and 17% for an apnea-hypopnea threshold of 10 events per hour, 32% and 11% for an apnea-hypopnea threshold of 15 events per hour, and 24% and 9% for an apnea-hypopnea threshold of 20 events per hour.

Age, body mass index, LVEF, and lung function were not significantly different between the 3 groups (Table 1). The central apnea group had a significantly higher pH and lower PaCO\(_2\), with similar PaO\(_2\) and SaO\(_2\), compared with both the obstructive apnea and nonapnea groups.

Sleep Data

There were no significant differences in sleep architecture between groups except that the central apnea group had significantly less stage 3 and stage 4 sleep and more frequent arousals than the nonapnea group (Table 2). The central apnea group also had significantly lower minimum SpO\(_2\) and greater total sleep time spent with SpO\(_2\) <90% than did the nonapnea group. Although overnight transcutaneous PCO\(_2\) could be measured in only 42 of 75 subjects studied, there was a trend for lower transcutaneous PCO\(_2\) during sleep within the central apnea group compared with the obstructive apnea and nonapnea groups, but the difference failed to reach statistical significance (38.4±0.7 versus 42.2±1.4 versus 40.4±0.8 mm Hg, respectively; \(P=0.11\)).

Right-Heart Catheter Data

PCWP and mean PAP were markedly higher in the central apnea group than in the obstructive apnea and nonapnea groups (Table 3). PCWP (in mm Hg; mean±SEM [range]) in the central apnea group was significantly greater (22.8±1.2 [11 to 38]) than in the obstructive apnea group (12.3±1.2 [4 to 21]) or the nonapnea group (11.5±1.5 [3 to 28]) (\(P<0.001\)). There were no significant differences in PCWP or PAP between the obstructive apnea and nonapnea groups. Pulmonary vascular resistance, cardiac index, and transpulmonary gradient were not significantly different between the 3 groups.

Within the central apnea group, PCWP correlated significantly with PaCO\(_2\) (\(r=-0.42, P=0.017\)) and indexes of central apnea frequency and severity, namely, apnea-hypopnea index (\(r=0.47, P=0.006\)) (Figure 1), total sleep time with SpO\(_2\) <90% (\(r=0.51, P=0.002\)), and minimum sleep SpO\(_2\) (\(r=-0.36, P=0.049\)).

Seven patients with elevated PCWP and central apnea underwent repeat investigations after a period of intensive tailored medical therapy (3.6±0.8 months; range, 1 to 6 months) comprising increased diuretics (n=6) and/or ACE inhibition (n=4) or the introduction of nitrates (n=2), carvedilol (n=2), or continuous positive airway pressure (CPAP) (n=3). The patients undergoing CPAP therapy were restudied without CPAP. In all 7 subjects, there was a fall in both PCWP (29.0±2.6 [20 to 38] to 22.0±1.8 [17 to 27] mm Hg; \(P<0.001\)) and central apnea frequency (38.5±7.7 [7 to 62] to 18.5±5.3 [1 to 31] events per hour; \(P=0.005\)) (Figure 2).

Discussion

A number of novel findings emerge from this study, which was conducted within a group of patients with severe stable
CHF who were being assessed for cardiac transplant. We have shown that PCWP in patients with central apnea is approximately double that observed in nonapnea and obstructive apnea patients. A significant correlation existed between PCWP and central apnea frequency and severity in the central apnea group. After intensive medical therapy, a fall in PCWP was associated with a fall in central apnea frequency. Together, this provides strong evidence of a highly significant relationship between PCWP and the degree of central apnea.

Although the central apnea group had a significantly greater PCWP than either the nonapnea or the obstructive apnea group, cardiac index and LVEF were not significantly different between the 3 groups, which suggests a primary defect of central control of ventilation rather than of cardiac function in patients with central apnea. When an apnea-hypopnea threshold of 20 events per hour was used, which is generally regarded as a level of significant sleep apnea that requires treatment, central apnea occurred in 24% and obstructive apnea in 9% of patients being evaluated for cardiac transplant assessment, for an overall apnea prevalence of 33%.3

Central sleep apnea is precipitated by hyperventilation that results in the Pco2 level falling below the apneic threshold during non-REM sleep.4 During the apnea, the Pco2 level rises, and once above the apnea threshold, hyperventilation resumes. This further propagates hypocapnia, again causing central apnea, giving a classic Cheyne-Stokes pattern of respiration. Based on animal experimentation, it is likely that pulmonary venous congestion and elevation of interstitial pressure cause increased pulmonary vagal afferent nerve stimulation, which precipitates central apnea followed by rapid shallow ventilation with an increased minute ventilation.9–10 These mechanistic observations, however, are limited to surgically instrumented animal models, studied under anesthesia, with experimentally induced pulmonary edema over a few hours rather than over months to years, as experienced by humans with CHF. Moreover, the effect of elevated pulmonary vascular filling pressures on Pco2 levels

### TABLE 2. Sleep Data

<table>
<thead>
<tr>
<th></th>
<th>Nonapnea</th>
<th>OSA</th>
<th>CSA</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>315±13</td>
<td>317±13</td>
<td>302±12</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>76±3</td>
<td>77±3</td>
<td>74±2</td>
<td>NS</td>
</tr>
<tr>
<td>Stages 1 and 2, % total sleep time</td>
<td>56±2</td>
<td>60±3</td>
<td>59±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Stages 3 and 4, % total sleep time</td>
<td>13±2</td>
<td>11±2</td>
<td>8±1</td>
<td>0.028†</td>
</tr>
<tr>
<td>REM, % total sleep time</td>
<td>12±1</td>
<td>12±1</td>
<td>10±1</td>
<td>NS</td>
</tr>
<tr>
<td>Apnea-hypopnea index, n/h</td>
<td>2.3±0.3</td>
<td>18.6±3.2</td>
<td>29.0±3.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Arousal index, n/h</td>
<td>20.3±3.7</td>
<td>35.0±6.0</td>
<td>44.0±6.3</td>
<td>0.023†</td>
</tr>
<tr>
<td>Mean sleep SpO2, %</td>
<td>93.4±0.4</td>
<td>93.0±0.4</td>
<td>92.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum sleep SpO2, %</td>
<td>86.2±0.9</td>
<td>82.1±0.9</td>
<td>80.5±0.9</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Total sleep time with SpO2 &lt;90%, %</td>
<td>4.3±1.6</td>
<td>8.8±2.8</td>
<td>16.7±3.2</td>
<td>0.008†</td>
</tr>
<tr>
<td>Mean transcutaneous Pco2, mm Hg</td>
<td>40.4±0.8</td>
<td>42.2±1.3</td>
<td>38.4±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean sleep heart rate, bpm</td>
<td>66.2±2.4</td>
<td>69.9±2.6</td>
<td>70.5±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Rhythm, SR,AF,PM</td>
<td>21:0:1</td>
<td>17:2:1</td>
<td>22:7:4</td>
<td></td>
</tr>
</tbody>
</table>

OSA indicates obstructive sleep apnea; CSA, central sleep apnea; SR, sinus rhythm; AF, atrial fibrillation; and PM, paced rhythm.

*CSA different from both OSA and nonapnea groups; †CSA different from nonapnea group only; ‡CSA and OSA groups different from nonapnea group.

### TABLE 3. Right-Heart Catheter Data

<table>
<thead>
<tr>
<th></th>
<th>Nonapnea</th>
<th>OSA</th>
<th>CSA</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic BP, systolic, mm Hg</td>
<td>105±4</td>
<td>108±3</td>
<td>109±3</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic BP, diastolic, mm Hg</td>
<td>60±2</td>
<td>60±2</td>
<td>65±2</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic BP, mean, mm Hg</td>
<td>75±2</td>
<td>75±2</td>
<td>80±2</td>
<td>NS</td>
</tr>
<tr>
<td>PAP, systolic, mm Hg</td>
<td>31.2±2.4</td>
<td>32.0±2.0</td>
<td>48.7±2.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PAP, diastolic, mm Hg</td>
<td>12.6±1.5</td>
<td>12.5±1.3</td>
<td>21.2±1.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PAP, mean, mm Hg</td>
<td>19.6±1.7</td>
<td>20.4±1.3</td>
<td>32.5±1.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>11.5±1.3</td>
<td>12.3±1.2</td>
<td>22.8±1.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cardiac index, L· min⁻¹· m⁻²</td>
<td>2.20±0.12</td>
<td>2.32±0.13</td>
<td>2.02±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, mm Hg· L⁻¹· min⁻¹</td>
<td>2.12±0.23</td>
<td>1.88±0.15</td>
<td>2.83±0.33</td>
<td>NS</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>8.1±0.5</td>
<td>8.1±0.6</td>
<td>9.7±0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

OSA indicates obstructive sleep apnea; CSA, central sleep apnea; BP, blood pressure; PVR, pulmonary vascular resistance; and TPG, transpulmonary gradient.

*CSA different from both OSA and nonapnea groups.
or cyclical central apnea was not studied. Given the limitations of animal experiments, the current data support the hypothesis of increased vagal nerve activity with pulmonary edema related to CHF.

Considerable evidence supports the concept that the extent of central apnea is dependent on the degree of hyperventilation and hypocapnia. Central apneas induced by exposure of normal subjects to hypoxic gas mixtures were abolished by inhalation of CO₂.¹⁴ In patients with CHF, the evidence suggesting dependence of central apnea on hyperventilation and hypocapnia is 5-fold. First, patients with CHF and central apnea have significantly lower PcO₂ levels, awake and asleep, and hypocapnia is 5-fold. First, patients with CHF and central apnea have significantly lower PcO₂ levels, awake and asleep, than LVEF-matched nonapnea patients.⁵ Second, in CHF patients, periods of central apnea are associated with significantly greater minute ventilation and lower PcO₂ than during nonapnea periods.⁶ Third, cycles of central apneas during sleep are triggered by a large breath and a concomitant fall in PcO₂.⁶ Fourth, the severity of central apnea is inversely proportional to the overnight PcO₂.⁶ Finally, attenuation of central apnea with a 4-week course of nightly CPAP is associated with a fall in arousal frequency, a reduction in minute ventilation, and a rise in PcO₂ during sleep, an effect associated with improved cardiac function.¹⁵

The data from the current study, which suggest that PCWP is inversely proportional to PaCO₂ levels and directly proportional to the degree of central apnea, are therefore consistent with basic experimental data from animals and other observational data from humans. It also suggests that mechanisms relating pulmonary edema to hyperventilation observed in animals may well pertain to humans.

The obstructive apnea group had awake pulmonary vascular pressures similar to the nonapnea group and lower than those patients with central apnea. It must be emphasized that the obstructive apnea group did not have the “obesity-hypventilation syndrome” with secondary pulmonary hypertension. In a recent study, such patients were described as markedly obese (mean body mass index 34 kg/m²), relatively hypoxemic when awake (mean PaO₂ 64 mm Hg), severely hypoxemic when asleep (mean sleep Spo₂ 76%), and had a mean PAP of 26.0 mm Hg and resting PCWP of 8.3 mm Hg.¹⁶ In contrast, the patients with obstructive apnea and CHF in the present study were less obese (mean body mass index 27.9 kg/m²), and less hypoxemic awake (mean PaO₂ 82.8 mm Hg) and asleep (mean Spo₂ 93%) yet had similar mean PAP (20.4 mm Hg) and slightly greater PCWP values (mean 12.3 mm Hg). Pulmonary vascular pressures in the obstructive apnea group are likely to increase during sleep. In a study of moderately obese patients (mean weight 113 kg) with obstructive sleep apnea, both PAP and PCWP rose significantly from wakefulness to sleep (20 to 32 mm Hg and 12 to 20 mm Hg, respectively), which suggests adverse effects of hypoxia and negative intrathoracic pressures on pulmonary vascular pressures.¹⁷ The current study emphasizes that it is important to recognize that significant obstructive apnea may occur in CHF in the absence of marked awake hypoxemia or obesity.

This study highlights the relative frequency of sleep apnea in patients with stable CHF and extends the observation of sleep apnea in 45% of 42 patients with stable CHF reported by Javaheri et al.⁴ Several distinctions need to be made between our studies. First, Javaheri et al did not report the relative frequency of central or obstructive apnea in their patient population, nor were detailed concurrent measurements of cardiac function made. Second, Javaheri et al defined sleep apnea using an apnea-hypopnea index of ≥20 events per hour. If a similar apnea-hypopnea threshold were applied to the current study, then 33% of the sample (24% patients with central apnea and 9% with obstructive apnea) would be classified as having sleep apnea. This apparent difference in sleep apnea prevalence in patients with stable CHF could be explained by the fact that the patients reported by Javaheri et al were older, were all male, and were more obese.

Recognition of patients with elevated pulmonary vascular pressures may alert clinicians that such patients may have central sleep apnea. This is important because previous studies of CHF patients have suggested a greater mortality in those with elevated pulmonary vascular pressures and elevated levels of sympathetic activity.¹⁸ More recent studies¹⁹,²⁰ have shown that CHF patients with central apnea have elevated levels of awake plasma norepinephrine and overnight urinary catecholamines and possibly a greater mortality rate than nonapnea CHF patients matched for LVEF. The observations of the present study complement the above predictors of CHF mortality. Moreover, new therapies that

![Figure 1. Correlation between PCWP and apnea-hypopnea index (r=0.47, P=0.006) in central apnea group (n=33).](http://circ.ahajournals.org/)

![Figure 2. Seven patients with central sleep apnea and high PCWP in whom repeat investigations were performed after intensive medical therapy for 1 to 6 months. Note a significant reduction in PCWP (29.0±2.6 [20 to 38] to 22.0±1.8 [17 to 27] mm Hg; P<0.001) associated with a fall in frequency of central sleep apnea (apnea-hypopnea index) (38.5±7.7 [7 to 62] to 18.5±5.3 [1 to 31] events per hour; P=0.006). Arrows indicate direction of change with time and therapy.](http://circ.ahajournals.org/)
attenuate central apnea, namely, CPAP, oxygen, theophylline, or more intensive pharmacological therapy, have in recent times shown promise as adjunctive therapy for CHF. 321-23

In summary, elevated PCWP in patients with severe yet stable CHF is associated with hypocapnia and central apnea. This observation is consistent with experimental data from animals that indicate that increased pulmonary vagal afferent nerve traffic secondary to pulmonary edema stimulates hyperventilation and hypocapnia. Compared with CHF patients with obstructive apnea or no apnea, patients with central apnea have greater PCWP and PAP and are therefore likely to have more severe heart failure and possibly a worse prognosis. Finally, given the 33% prevalence of clinically significant sleep apnea in patients with stable CHF, recognition and specific treatment of such patients may improve their grave prognosis.

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