Overnight Shift From Obstructive to Central Apneas in Patients With Heart Failure
Role of P\textsubscript{CO}\textsubscript{2} and Circulatory Delay

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Background—Obstructive (OSA) and central sleep apnea (CSA) can coexist in patients with congestive heart failure (CHF). However, the reason why OSA events occur at one time and CSA events at another has not been determined. We hypothesized that a change in P\textsubscript{CO}_2 would be associated with an alteration in apnea type: a decrease in P\textsubscript{CO}_2 should lead to CSA.

Methods and Results—To test this hypothesis, we evaluated minute ventilation (V\textsubscript{I}), transcutaneous P\textsubscript{CO}_2 (Ptc\textsubscript{CO}_2), circulation time, and periodic breathing cycle length during overnight polysomnography in 12 patients with CHF and coexisting OSA and CSA. V\textsubscript{I} was significantly greater (mean \pm SEM, 9.4 \pm 1.3 versus 8.0 \pm 0.9 L/min; P < 0.05) and Ptc\textsubscript{CO}_2 was lower (39.4 \pm 1.0 versus 41.9 \pm 1.1 mm Hg, P < 0.01) during episodes of CSA than of OSA. These changes were associated with significant lengthening of circulation time (23.6 \pm 3.7 versus 21.1 \pm 3.6 seconds, P < 0.01) and periodic breathing cycle length (53.7 \pm 3.5 versus 49.6 \pm 2.9 seconds, P < 0.01). In addition, the proportion of obstructive events decreased (from 68.5 \pm 11.4% to 22.5 \pm 7.2%, P < 0.001) and of CSA events increased (from 31.5 \pm 11.4% to 77.5 \pm 7.2%, P < 0.001) from the first to the last quarter of the night in association with a significant decrease in Ptc\textsubscript{CO}_2 (from 42.6 \pm 0.9 to 40.8 \pm 0.9 mm Hg, P < 0.01).

Conclusions—In patients with CHF, the shift from OSA to CSA is associated with a reduction in P\textsubscript{CO}_2. This appears to be related to an overnight deterioration in cardiac function as suggested by the concurrent lengthening of circulation time. Therefore, in CHF patients, alterations in cardiac function may influence apnea type. (Circulation. 2001;103:238-243.)

Key Words: sleep \hspace{1mm} respiration \hspace{1mm} heart failure

There is growing evidence that sleep-disordered breathing can play a role in the progression of congestive heart failure (CHF) and that treating these breathing disorders in such patients can lead to improvements in cardiovascular outcomes.\textsuperscript{1-3}\textsuperscript{1} A number of studies have reported that obstructive sleep apnea (OSA) and central sleep apnea (CSA) are very common and occur in \approx 50\% to 62\% of patients with CHF.\textsuperscript{4,5}\textsuperscript{4} Both of these breathing disorders are associated with a Cheyne-Stokes pattern of periodic breathing with a waxing and waning of tidal volume (V\textsubscript{T}) during hyperpnea. In addition, owing to low cardiac output, lung-to-chemoreceptor circulatory delay and cycle length of periodic breathing are longer in CHF patients with sleep apnea than in patients with sleep apnea but normal cardiac function.\textsuperscript{6}\textsuperscript{5} These observations suggest that in CHF patients, the periodic breathing cycle with or without upper airway obstruction is entrained by the prolonged circulation time.

Although there is usually a predominance of either OSA or CSA in CHF patients, both types may occur in the same individual.\textsuperscript{4,5}\textsuperscript{4} However, the reasons why OSA events occur at one time and CSA occur at another during the same night have not been examined. One factor that could be a determinant of apnea type is P\textsubscript{CO}_2. In CHF patients, CSA is triggered by reductions in P\textsubscript{CO}_2 below the apneic threshold.\textsuperscript{7,8}\textsuperscript{7} In contrast, OSA is not associated with a fall in P\textsubscript{ACO}_2.\textsuperscript{5}\textsuperscript{5} Therefore, one would expect that CSA events would be associated with a lower P\textsubscript{ACO}_2 than OSA events.

In patients with CHF, P\textsubscript{CO}_2 is inversely proportional to pulmonary capillary wedge pressure.\textsuperscript{9}\textsuperscript{9} Thus, hyperventilation in patients with CHF is probably due, in large measure, to stimulation of pulmonary vagal afferents by pulmonary congestion secondary to elevated left ventricular filling pressure.\textsuperscript{9,10}\textsuperscript{9} It has also been shown that while CHF patients are recumbent, cardiac output falls and left ventricular filling pressure rises overnight.\textsuperscript{11}\textsuperscript{11} These tendencies could be aggravated by OSA, which can elevate pulmonary capillary wedge pressure\textsuperscript{12}\textsuperscript{12} and reduce cardiac output.\textsuperscript{13,14}\textsuperscript{13}}
In view of these observations, we hypothesized that in patients with CHF in whom both OSA and CSA are present during the same night, minute ventilation ($V_I$) would be higher and $P_{CO_2}$ lower during Cheyne-Stokes respiration with CSA than with OSA events. We further hypothesized that if CSA events are associated with an overnight deterioration in cardiac function, they would be more frequent at the end than at the beginning of the night and would be accompanied by longer circulation time than OSA events.

**Methods**

**Subjects**

Patients with CHF referred to the sleep laboratory were included in the study if they met the following criteria: (1) chronic CHF (left ventricular ejection fraction <40%) secondary to ischemic or idiopathic dilated cardiomyopathy, (2) chronic exertional dyspnea, (3) appropriate pharmacological therapy for CHF, (4) stable clinical status as evidenced by an absence of acute exacerbations of dyspnea and edema or medication change for ≥1 month before entry, and (5) OSA coexisting with CSA on the same sleep study. The diagnosis of OSA coexisting with CSA was based on the presence of apneas and hypopneas occurring at a rate of ≥10 per hour of sleep, of which 15% to 85% had to be obstructive and the remainder central in nature. Exclusion criteria were a history of myocardial infarction, unstable angina, or cardiac surgery within 3 months of entry into the study. No patient was regularly taking alcohol or sedative medications. Alcohol, sedatives, and caffeinated beverages were not permitted during the 48 hours before the sleep studies. The protocol was approved by the Human Subjects Review Committee of the University of Toronto, and all patients gave written informed consent before participation.

**Sleep Studies**

Overnight sleep studies were performed in all subjects with the use of standard techniques. Respiratory efforts and $V_T$ were recorded with a calibrated respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc.). Transcutaneous $P_{CO_2}$ ($P_{tcCO_2}$) was recorded with a transcutaneous capnometer (Kontron Medical). Oxyhemoglobin saturation ($SaO_2$) was measured with an ear oximeter whenever a stable signal could be attained. When this was not possible, a finger oximeter was used.

CSAs and hypopneas were identified by the absence of a $V_T$ excursion for ≥10 seconds with no movements of the rib cage or abdomen. Central hypopneas were defined as a ≥50% reduction in $V_T$ from the baseline value, persisting for ≥10 seconds with proportional in-phase reductions in rib cage and abdominal movements. OSAs and hypopneas were similarly defined except that paradoxical thoracoabdominal motion had to be present throughout these events. Mixed apneas were defined as mixed apneas that began with a central component and ended with an obstructive component. Because mixed apneas were initiated by a central component lasting ≥10 seconds that made up >50% of the apnea and because <15% of all events with a central component in each patient were mixed, mixed apneas were included as CSA events for the purpose of this study. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep.

**Statistical Analysis**

$V_I$ was derived by multiplying mean $V_T$ by mean frequency for the ventilatory and apneic periods to give mean $V_I$ for the entire periodic breathing cycle. Mean $P_{tcCO_2}$ and mean $SaO_2$ were calculated by averaging the high and low values for each 30-second epoch throughout the night. In addition, the lowest $SaO_2$ and the percentage of OSA and CSA events in which $SaO_2$ fell below 90% were documented. Periodic breathing cycle length was measured 2 ways: from the beginning of inspiration of the first breath terminating one apnea to the onset of inspiration of the breath ending the next apnea from the $V_T$ signal, and as the time elapsed from one nadir in $SaO_2$ to the subsequent nadir. As an approximation of lung-to-carotid body circulatory delay, we measured lung-to-carotid circulation time (LECT) as the time elapsed from the end of an apnea to the subsequent nadir of $SaO_2$. Similarly, in individuals in whom a finger oximeter was used, we measured lung-to-finger circulation time. Mean values of $V_I$, $P_{tcCO_2}$, periodic breathing cycle length, circulation time, and, in those in whom an ear oximeter was used, LECT during periodic breathing with OSAs and CSAs were calculated by averaging data from 5 consecutive periodic breathing cycles with OSAs and 5 cycles with CSAs. These analyses were confined to stage 2 sleep to avoid any potential confounding influence of changes in sleep stage on breathing. In addition, the comparison of OSAs and CSAs was restricted to the same body position in each subject. Mean $P_{tcCO_2}$ and the proportion of obstructive and central respiratory events occurring in the first and last quarters of the night were also determined. Paired t tests were used to compare variables. Least-squares linear regression analysis was used to assess relationships between variables when appropriate. A value of $P<0.05$ was considered statistically significant. All results are expressed as mean±SEM.

**Results**

**Patient Characteristics**

Twelve (11 men, 1 woman) of 65 CHF patients who underwent sleep studies in our laboratory over a 1-year period met our inclusion criteria. Their mean age was 62.5±2.2 years, and their body mass index was 27.6±1.0 kg/m², indicating that they were generally not obese. The cause of CHF was coronary artery disease in 10 and idiopathic dilated cardiomyopathy in 2. Eight patients were in NYHA class II, and 4 were in class III. Severe left ventricular dysfunction was evidenced by a mean left ventricular ejection fraction of 28.4±3.2%. Medical therapy for CHF consisted of digoxin in 7, diuretics in 12, ACE inhibitors in 12, nitrates and/or hydralazine in 6, and β-blockers in 2 patients. Overnight polysomnographic data appear in the Table. The patients had a moderate frequency of respiratory events, as indicated by the AHI. There were relatively equal proportions of OSA and CSA events (range of OSA events was 27% to 84% and of CSA events was 16% to 73%). These events were accompanied by only mild $O_2$ desaturation.

**Minute Ventilation, $P_{tcCO_2}$, and Circulation Time**

Figure 1 shows a representative example of an OSA at the beginning of the night and CSA at the end of the night in 1
patient during stage 2 sleep. The CSA was associated with higher preceding Vt and lower PtcCO2 than was the OSA. Analysis of grouped data for all 12 patients indicated that Vt was significantly higher (P<0.05), PtcCO2 was significantly lower (P<0.01), and circulatory delay and periodic breathing cycle length were significantly longer (P<0.001 and P<0.01, respectively) during CSAs than OSAs (Figure 2). However, there was no significant difference in mean heart rate between OSA and CSA cycles (68.0±3.2 versus 67.1±3.4 bpm, respectively). Periodic breathing cycle lengths measured with either the Vt signal (Figure 2) or the time elapsed between consecutive nadirs in SaO2 were essentially identical. Cycle lengths measured from the SaO2 signals were 49.7±2.9 versus 54.0±3.4 seconds for obstructive and central cycles, respectively (P<0.001). In the 8 subjects who had ear oximetry, LECT was also significantly longer during CSAs compared with OSAs (15.8±1.4 versus 13.4±1.3 seconds, P<0.001). However, there was no significant difference in mean or lowest SaO2 or in the percentage of events in which SaO2 fell below 90% between OSAs and CSAs for the whole group (93.7±0.3% versus 94.1±0.5%, P=NS; 89.5±0.7% versus 90.7±0.7%, P=NS; and 29.4±8.9% versus 27.8±9.1%, P=NS; respectively). We also found a significant inverse correlation between the change in PtcCO2 and the change in LECT from OSAs to CSAs in the 8 subjects in whom an ear oximeter was used (r = -0.790, P<0.02; Figure 3).

Overnight Shift in Distribution of OSA and CSA Events
From the first to the last quarter of the night, there was a significant reduction in PtcCO2 (P<0.01; Figure 4) accompanied by a shift in the proportion of OSA and CSA events from predominantly obstructive to predominantly central (Figure 5). In none of these patients did we observe a shift from predominantly central to predominantly obstructive events over the night. Neither AHI (29.9±3.7 versus 34.3±3.1 events per hour, P=NS) nor the percentage of time spent in the supine position (70.8±13.0% versus 51.3±14.7%, P=NS) changed significantly from the first to the last quarter of the night.
Discussion

We have demonstrated in CHF patients having both OSAs and CSAs during the same night that OSA events predominate at the beginning and CSA events predominate at the end of the night. This overnight shift from OSA to CSA events was accompanied by reductions in PCO\textsubscript{2} resulting from increases in V\textsubscript{I} and by lengthening of circulation time. The close relationship between the overnight lengthening of circulation time and reductions in PCO\textsubscript{2} strongly suggests that the fall in P CO\textsubscript{2} and shift in apnea type are linked to an overnight deterioration in cardiac function.\textsuperscript{6,11,16} Taken together, these findings suggest that in patients with CHF, overnight alterations in cardiac function influence both the lengths of the Cheyne-Stokes respiratory cycles and the nature of the apneas that occur in association with them.

CSAs during sleep in patients with CHF are triggered by reductions in P CO\textsubscript{2} below the threshold for apnea. Inhalation of CO\textsubscript{2} abolishes them.\textsuperscript{8} In addition, CHF patients with CSA have lower Pco\textsubscript{2} during sleep than either those with OSA or those without sleep apnea.\textsuperscript{5} In patients with CSA, V\textsubscript{I} is higher and Ptc CO\textsubscript{2} is lower during periods of recurrent CSAs than during regular breathing.\textsuperscript{7} Therefore, the observation that the shift from OSA to CSA events was associated with an increase in V\textsubscript{I} and a decrease in P CO\textsubscript{2} is consistent with previous findings.

Three mechanisms could be involved in the overnight increase in V\textsubscript{I}, the decrease in P CO\textsubscript{2}, and the shift to more CSA: worsening hypoxia, increasing ventilatory responsiveness to CO\textsubscript{2}, and worsening of pulmonary congestion.\textsuperscript{9,16} Because there was no significant difference in the degree of hypoxia during OSA events at the beginning and CSA events at the end of the night, direct stimulation of ventilation by hypoxia is probably not the explanation for the overnight development of hypocapnia. Nevertheless, even mild degrees of intermittent hypoxia could increase sympathetic nervous activity and blood pressure and impair systolic and diastolic functions in the failing heart, thus contributing to overnight deterioration in cardiac function.\textsuperscript{17–19}

Javaheri\textsuperscript{20} reported a significantly greater ventilatory response to CO\textsubscript{2} in CHF patients with CSA than in those without it. However, neither V\textsubscript{I} nor Pco\textsubscript{2} was assessed at night. In addition, it is more likely that recurrent apneas and arousals would cause an overnight decrease rather than an increase in the ventilatory response to CO\textsubscript{2}.\textsuperscript{21} Thus, an overnight increase in ventilatory responsiveness to CO\textsubscript{2} probably does not account for the overnight decrease in P CO\textsubscript{2}. A more likely explanation is development of pulmonary congestion.

Increases in pulmonary venous pressure induce hyperventilation in animals through stimulation of pulmonary vagal afferents.\textsuperscript{10} In addition, Solin et al\textsuperscript{9} demonstrated that Paco\textsubscript{2} is inversely related to pulmonary capillary wedge pressure in patients with CHF. Furthermore, CHF patients with CSA
have higher pulmonary capillary wedge pressure than those without it.  

The frequency of CSA is directly related to left ventricular filling pressure.  

Reductions in pulmonary capillary wedge pressure by medical therapy and continuous positive airway pressure diminish the frequency of central respiratory events. These data imply that hypopnea and CSA are respiratory manifestations of elevated left ventricular filling pressures and pulmonary venous congestion.

Periodic breathing cycle length and LECT are inversely proportional to cardiac output. Accordingly, the most plausible explanation for the lengthening of the periodic breathing cycle and LECT from the beginning to the end of the night observed in the present study is an overnight fall in cardiac output. Although OSA events can be prolonged because of a delay in the onset of arousals that terminate them, such an effect cannot explain the longer cycle length of CSA than of OSA events. On the other hand, if we extrapolate from the data of Hall et al., we can estimate that there was a 2.5-second increase in circulatory delay from obstructive to central cycles. In CHF patients whose cardiac output is already low, such a further fall is liable to be clinically significant. Left ventricular volume could theoretically influence periodic breathing cycle length. However, we have no measures of left ventricular volume overnight. Moreover, we have previously shown that left ventricular end-diastolic volume influences periodic breathing cycle length only indirectly through its effect on cardiac output via Starling’s Law.

Overnight reductions in Pco2 were inversely proportional to overnight increases in LECT. These data suggest that an overnight reduction in cardiac output was accompanied by pulmonary congestion. This concept is consistent with the findings of Gibbs et al., who observed progressive overnight rises in pulmonary artery pressure in most patients with severe CHF. However, they provided no explanation for these overnight increases in pulmonary artery pressure. One possible explanation is an increase in venous return from the legs and abdomen while the patient is recumbent. Another possibility in patients such as ours is that OSAs at the beginning of the night contributed to overnight reductions in cardiac output and increases in left ventricular filling pressure.

In patients with OSA, cardiac output decreases and pulmonary artery wedge pressure increases during OSA events. These effects probably result from increases in left ventricular afterload caused by the effects of elevations in systemic blood pressures and exaggerated negative intrathoracic pressure during and immediately after OSAs. In a dog model of chronic OSA, Parker et al. made similar observations. They also found that over a 3-month period, these dogs developed increases in left ventricular mass and decreases in left ventricular ejection fraction. These data indicated that OSA can cause left ventricular hypertrophy and dysfunction. Fletcher et al. demonstrated that exposure of dogs to repetitive obstructive apneas for just 8 hours led to the development of interstitial pulmonary edema. These findings are compatible with case reports of acute nocturnal pulmonary edema in patients with OSA. Furthermore, in patients with CHF, generation of negative intrathoracic pressure during simulated OSAs causes profound reductions in cardiac output in patients with either ischemic or idiopathic dilated cardiomyopathy. In contrast, breath holds, which simulate the effects of CSAs, have no such effect. Taken together, these findings indicate that OSA can cause significant reductions in cardiac output and overnight development of pulmonary edema. CSAs appear less likely to do so.

The above findings suggest that in our patients with CHF, OSAs at the beginning of the night contributed to overnight reductions in cardiac output, as reflected by lengthening of circulation time; to pulmonary venous congestion, as reflected by increases in VI and reductions in PCO2; and to the development of CSAs at the end of the night. To test these hypotheses directly, it would be necessary to perform overnight hemodynamic monitoring in such patients. Our findings also raise an intriguing question: Can OSA predispose to the development of CSA as cardiac function deteriorates over time in patients with CHF?

As shown in Figure 1, both OSA and CSA events are associated with a Cheyne-Stokes ventilatory pattern. These observations raise the possibility that both OSA and CSA are part of a spectrum of periodic breathing, which under some circumstances presents mainly as OSA and under others mainly as CSA. They are also compatible with the concept that in patients with CHF, central controller instability may entrain upper airway obstruction during the apneic portion of the Cheyne-Stokes respiratory cycle. Alternatively, CHF may give rise to increased neck vein distension and upper airway edema that could narrow the upper airway and increase its collapsibility. However, because such an effect is most likely to occur later in the night after prolonged recumbency, it would not explain the shift from OSA to CSA at the end of the night. Finally, it is also possible that in some of our patients, OSA preceded the onset of CHF and that this predisposed to the development of Cheyne-Stokes respiration and CSA. Our study was not designed to determine which of these proposed mechanisms was involved in the development of OSA events in our patients. It is likely that the degree to which each of these factors contributed to the development of OSA varied from individual to individual. Nevertheless, apnea type is dependent on Paco2. If Paco2 remains above the apneic threshold, OSA events prevail; if it decreases below the threshold, CSA events prevail.

In conclusion, in some patients with CHF, both obstructive and central respiratory events occur during a single night and appear to represent extremes of a continuum of periodic breathing. Our findings further indicate that the overnight shift from OSA to CSA is related to reductions in PCO2 caused by increases in Vt. Most important, the close relationship between overnight reductions in Pco2 and increases in circulatory delay suggests that the overnight shift in apnea type is linked to deterioration in cardiac function. This concept is consistent with the suggestion of Somers that hemodynamic instability in patients with CHF may be related to instability in apnea type as well. Future acute studies with direct cardiac monitoring are needed to assess the potential role of OSAs in overnight worsening of heart function in patients with CHF. Our findings also imply that abolition of OSA would improve nocturnal hemodynamic function in patients with CHF.
Finally, longitudinal studies may be required to determine whether OSA can predispose to CSA over time in patients with CHF.

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