Overnight Shift From Obstructive to Central Apneas in Patients With Heart Failure
Role of Pco2 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 PcO2 would be associated with an alteration in apnea type: a decrease in PcO2 should lead to CSA.

Methods and Results—To test this hypothesis, we evaluated minute ventilation (VI), transcutaneous PcO2 (PtcO2), circulation time, and periodic breathing cycle length during overnight polysomnography in 12 patients with CHF and coexisting OSA and CSA. VI was significantly greater (mean ± SEM, 9.4 ± 1.3 versus 8.0 ± 0.9 L/min; P < 0.05) and PtcO2 was lower (39.4 ± 1.0 versus 41.9 ± 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 ± 3.7 versus 21.1 ± 3.6 seconds, P < 0.01) and periodic breathing cycle length (53.7 ± 3.5 versus 49.6 ± 2.9 seconds, P < 0.01). In addition, the proportion of obstructive events decreased (from 68.5 ± 11.4% to 22.5 ± 7.2%, P < 0.001) and of CSA events increased (from 31.5 ± 11.4% to 77.5 ± 7.2%, P < 0.001) from the first to the last quarter of the night in association with a significant decrease in PtcO2 (from 42.6 ± 0.9 to 40.8 ± 0.9 mm Hg, P < 0.01).

Conclusions—In patients with CHF, the shift from OSA to CSA is associated with a reduction in Pco2. 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 • respiration • 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.1–3 A number of studies have reported that obstructive sleep apnea (OSA) and central sleep apnea (CSA) are very common and occur in ≈50% to 62% of patients with CHF.4,5 Both of these breathing disorders are associated with a Cheyne-Stokes pattern of periodic breathing with a waxing and waning of tidal volume (VT) 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.6 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.4,5 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 PcO2. In CHF patients, CSA is triggered by reductions in Pco2 below the apneic threshold.7,8 In contrast, OSA is not associated with a fall in Paco2.5 Therefore, one would expect that CSA events would be associated with a lower Paco2 than OSA events.

In patients with CHF, Paco2 is inversely proportional to pulmonary capillary wedge pressure.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.9,10 It has also been shown that while CHF patients are recumbent, cardiac output falls and left ventricular filling pressure rises overnight.11 These tendencies could be aggravated by OSA, which can elevate pulmonary capillary wedge pressure12 and reduce cardiac output.13,14
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\textsubscript{I}) would be higher and P\textsubscript{tCO\textsubscript{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\textsubscript{T} were recorded with a calibrated respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc.). Transcutaneous P\textsubscript{tCO\textsubscript{2}} was recorded with a transcutaneous capnograph (Kontron Medical). Oxyhemoglobin saturation (Sa\textsubscript{O\textsubscript{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\textsubscript{T} excursion for ≥10 seconds with no movements of the rib cage or abdomen. Central hypopneas were defined as a ≥50% reduction in V\textsubscript{T} from the baseline value, persisting for ≥10 seconds with proportional in-phase reductions in rib cage and abdominal movements.7,8 OSAs and hypopneas were similarly defined except that paradoxical thoracoabdominal motion had to be present throughout these events. Mixed apneas were defined as 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\textsubscript{I} was derived by multiplying mean V\textsubscript{T} by mean frequency for the ventilatory and apneic periods to give mean V\textsubscript{I} for the entire periodic breathing cycle. Mean P\textsubscript{tCO\textsubscript{2}} and mean Sa\textsubscript{O\textsubscript{2}} were calculated by averaging the high and low values for each 30-second epoch throughout the night. In addition, the lowest Sa\textsubscript{O\textsubscript{2}} and the percentage of OSA and CSA events in which Sa\textsubscript{O\textsubscript{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\textsubscript{T} signal, and as the time elapsed from one nadir in Sa\textsubscript{O\textsubscript{2}} to the subsequent nadir. As an approximation of lung-to-carotid body circulatory delay, we measured lung-to-ear circulation time (LECT) as the time elapsed from the end of an apnea to the subsequent nadir of Sa\textsubscript{O\textsubscript{2}}. Similarly, in individuals in whom a finger oximeter was used, we measured lung-to-finger circulation time. Mean values of V\textsubscript{I}, P\textsubscript{tCO\textsubscript{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\textsubscript{tCO\textsubscript{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/m\textsuperscript{2}, 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\textsubscript{2} desaturation.

**Minute Ventilation, P\textsubscript{tCO\textsubscript{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 \(V_t\) and lower \(P_{tc \text{CO}_2}\) than was the OSA. Analysis of grouped data for all 12 patients indicated that \(V_t\) was significantly higher \((P<0.05)\), \(P_{tc \text{CO}_2}\) 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 \((68.0\pm3.2\) versus \(67.1\pm3.4\) bpm, respectively). Periodic breathing cycle lengths measured with either the \(V_t\) signal (Figure 2) or the time elapsed between consecutive nadirs in \(\text{Sa}_O_2\) were essentially identical. Cycle lengths measured from the \(\text{Sa}_O_2\) signals were \(49.7\pm2.9\) versus \(54.0\pm3.4\) seconds for obstructive and central cycles, respectively \((P<0.001)\). In the 8 subjects who had ear oximetry, \(\text{LECT}\) was also significantly longer during CSAs compared with OSAs \((15.8\pm1.4\) versus \(13.4\pm1.3\) seconds, \(P<0.001)\). However, there was no significant difference in mean or lowest \(\text{Sa}_O_2\) or in the percentage of events in which \(\text{Sa}_O_2\) fell below 90% between OSAs and CSAs for the whole group \((93.7\pm0.3\) versus \(94.1\pm0.5\), \(P=\text{NS}\); \(89.5\pm0.7\) versus \(90.7\pm0.7\), \(P=\text{NS}\); and \(29.4\pm8.9\) versus \(27.8\pm9.1\), \(P=\text{NS}\), respectively). We also found a significant inverse correlation between the change in \(P_{tc \text{CO}_2}\) and the change in \(\text{LECT}\) 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 \(P_{tc \text{CO}_2}\) \((P<0.01;\) 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 \((29.9\pm3.7\) versus \(34.3\pm3.1\) events per hour, \(P=\text{NS}\)) nor the percentage of time spent in the supine position \((70.8\pm13.0\%\) versus \(51.3\pm14.7\%,\) \(P=\text{NS}\)) changed significantly from the first to the last quarter of the night.

**Figure 1.** Polysomnographic recording during stage 2 sleep from patient with CHF and OSA in first quarter and CSA during last quarter of night. Note that \(V_t\) preceding apnea was higher and \(P_{tc \text{CO}_2}\) was lower during CSA than OSA. Also note greater length of central periodic breathing cycle (68 seconds from beginning of one ventilatory period to beginning of next) than obstructive periodic breathing cycle (54 seconds).

**Figure 2.** From OSAs (OB) to CSAs (CN), \(V_t\) increased (from \(8.0\pm0.9\) to \(9.4\pm1.3\) L/min), \(P_{tc \text{CO}_2}\) decreased (from \(41.9\pm1.1\) to \(39.4\pm1.0\) mm Hg), circulatory delay increased (from \(21.1\pm3.6\) to \(23.6\pm3.7\) seconds), and periodic breathing cycle length increased (from \(49.6\pm2.9\) to \(53.7\pm3.5\) seconds). *\(P<0.05, **P<0.01.\)
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 PCO₂ resulting from increases in V̇̇ and by lengthening of circulation time. The close relationship between the overnight lengthening of circulation time and reductions in PCO₂ strongly suggests that the fall in PCO₂ and shift in apnea type are linked to an overnight deterioration in cardiac function.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 PCO₂ below the threshold for apnea. Inhalation of CO₂ abolishes them.8 In addition, CHF patients with CSA have lower Paco₂ during sleep than either those with OSA or those without sleep apnea.5 In patients with CSA, V̇̇ is higher and Ptc CO₂ is lower during periods of recurrent CSAs than during regular breathing.7 Therefore, the observation that the shift from OSA to CSA events was associated with an increase in V̇̇ and a decrease in PCO₂ is consistent with previous findings.

Three mechanisms could be involved in the overnight increase in V̇̇, the decrease in PCO₂, and the shift to more CSA: worsening hypoxia, increasing ventilatory responsiveness to CO₂, and worsening of pulmonary congestion.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.17–19

Javaheri20 reported a significantly greater ventilatory response to CO₂ in CHF patients with CSA than in those without it. However, neither V̇̇ nor PCO₂ was measured 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 CO₂.21 Thus, an overnight increase in ventilatory responsiveness to CO₂ probably does not account for the overnight decrease in PCO₂. A more likely explanation is development of pulmonary congestion.

Increases in pulmonary venous pressure induce hyperventilation in animals through stimulation of pulmonary vagal afferents.10 In addition, Solin et al19 demonstrated that Paco₂ is inversely related to pulmonary capillary wedge pressure in patients with CHF. Furthermore, CHF patients with CSA

![Figure 3](image3.png)

Figure 3. Inverse relationship between change in PtcCO₂ and LECT from OSA to CSA in 8 patients whose SaO₂ was measured by ear oximeter.

![Figure 4](image4.png)

Figure 4. PtcCO₂ decreased from 42.6±0.9 mm Hg during first quarter to 40.8±0.9 mm Hg during last quarter of night. *P<0.01.

![Figure 5](image5.png)

Figure 5. From first to last quarter of night, there was significant reduction in proportion of obstructive (OB; from 68.5±11.4% to 22.5±7.2%) and increase in proportion of central (CN; from 31.5±11.4% to 77.5±7.2%) respiratory events. *P<0.0001 vs first quarter.
have higher pulmonary capillary wedge pressure than those without it.9,22 The frequency of CSA is directly related to left ventricular filling pressure.9 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 hypocapnia 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.6,22 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,6 we can estimate that there was a reduction in cardiac output of $0.8$ L/min related to the 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.22

Overnight reductions in $P_{CO_2}$ were inversely proportional to overnight increases in LECT. These data suggest that an overnight reduction in cardiac output was accompanied by pulmonary congestion.9 This concept is consistent with the findings of Gibbs et al,11 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 OSA 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.12,13 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 OSA events.23,24 In a dog model of chronic OSA, Parker et al25 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 al16 also 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.26 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.14 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 time6; to pulmonary venous congestion, as reflected by increases in $V_1$ and reductions in $P_{CO_2}$; 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.24 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 entrap upper airway obstruction during the apneic portion of the Cheyne-Stokes respiratory cycle.27 Alternatively, CHF may give rise to increased neck vein distension and upper airway edema that could narrow the upper airway and increase its collapsibility.28 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 $P_{ACO_2}$. If $P_{ACO_2}$ 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 $P_{CO_2}$ caused by increases in $V_1$. Most important, the close relationship between overnight reductions in $P_{CO_2}$ 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 Somers29 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.24
Finally, longitudinal studies may be required to determine whether OSA can predispose to CSA over time in patients with CHF.

**Acknowledgments**

This work was supported by operating grant MT-11607 from the Canadian Institutes of Health Research. Dr Tkacova is the recipient of a research fellowship from Respironics Inc. Dr Niroumand was a research fellow of the Canadian Lung Association. Dr Lorenzi-Filho was supported by research fellowships from Fundacao de Amparo a Pesquisa do estado de Sao Paulo (FAPESP) Brazil and the Department of Medicine of the University of Toronto. Dr Bradley is a Senior Scientist of the Canadian Institutes of Health Research.

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Circulation. 2001;103:238-243
doi: 10.1161/01.CIR.103.2.238
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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