Association of Low $PaCO_2$ with Central Sleep Apnea and Ventricular Arrhythmias in Ambulatory Patients with Stable Heart Failure

Shahrokh Javaheri, MD, and W.S. Corbett, BS

Background: Central sleep apnea frequently occurs in patients with heart failure. Because it is not practical to perform sleep studies on all patients, readily available laboratory tests that predict sleep apnea would be clinically useful. Arterial PCO_2 has a profound influence on breathing during sleep: When it decreases below a certain threshold, apnea occurs.

Objective: To study the value of a low $PaCO_2$ while patients are awake in predicting central sleep apnea in patients with stable, treated heart failure.

Design: Prospective study.

Setting: Referral sleep laboratory of a Department of Veterans Affairs Medical Center.

Participants: 59 patients with left ventricular ejection fractions of 45% or less.

Measurements: Arterial blood gases and hydrogen ion concentrations were measured, and cardiac radionuclide ventriculography, Holter monitoring, and polysomnography were done.

Results: Patients were classified as eucapnic ($PaCO_2 > 35$ and < 44 mm Hg [$n = 41$]) or hypocapnic ($PaCO_2 \leq 35$ mm Hg [$n = 18$]). The mean ($\pm$ SD) hourly episodes of apnea or hypopnea (36 ± 25 and 20 ± 27; $P = 0.015$), the prevalence of central sleep apnea (78% and 39%; $P = 0.01$), and the mean hourly occurrences of ventricular tachycardia (2 ± 3 and 0.1 ± 0.1; $P = 0.003$) were significantly greater in hypocapnic patients than in eucapnic patients.

Conclusion: Data on patients with heart failure in this study are consistent with the physiologic notion that a low $PaCO_2$ results in ventilatory instability and central apnea during sleep. The positive predictive value of a low $PaCO_2$ for central sleep apnea is 78%. The prevalence of ventricular tachycardia was 20 times greater in hypocapnic patients than in eucapnic patients.

Ann Intern Med. 1998;128:204-207.

From the Department of Veterans Affairs Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio. For current author addresses, see end of text.

A recent study (1) showed that about 45% of patients with stable, treated heart failure may have periodic breathing during sleep. These episodes of apnea and hypopnea are associated with severe arterial oxyhemoglobin desaturation and excessive arousals that disrupt sleep.

Because heart failure is highly prevalent, performance of sleep studies on all patients with heart failure is not practical. However, it is difficult to predict which patients may develop periodic breathing during sleep (1). Therefore, simple laboratory tests that could predict periodic breathing during sleep would be helpful screening tools.

Arterial PCO_2 has a dominant influence on breathing. A carefully performed study (2) done during sleep in normal humans showed that central apnea may be induced when the $PaCO_2$ is experimentally lowered by 1 to 3 mm Hg below the resting $PaCO_2$ while patients are awake. Therefore, a low $PaCO_2$ while awake may predispose to ventilatory instability and development of central sleep apnea.

To examine the predictive value of resting $PaCO_2$ while awake for central sleep apnea in heart failure, we studied patients with stable heart failure and no major comorbid conditions.

Methods

Ambulatory male patients with stable, medically treated left heart failure (left ventricular ejection fraction $\leq 45\%$) took part in this study. Details on these patients have been published elsewhere (1, 3). Patients were clinically stable (symptoms or signs of heart failure had not changed in the preceding 4 weeks) and received standard therapy; no change had been made in cardiac medications in the preceding 4 weeks. Exclusion criteria were major comorbid disorders or use of morphine derivatives, benzodiazepines, or respiratory stimulants, such as theophylline and acetazolamide (1–3). We studied only men because women are seldom referred to our center.

After patients spent an adaptation night in the sleep laboratory, polysomnography was performed by using standard techniques, as detailed elsewhere (1, 3, 4). Apnea was defined as cessation of inspiratory airflow for 10 seconds or more. Obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. Central apnea was defined as the absence of rib cage and abdominal excursions and absence of air-

flow (1, 3, 4). Hypopnea was defined as a reduction of airflow lasting 10 seconds or more associated with a decrease of 4% or more in arterial oxyhemoglobin saturation or an arousal (5).

In the absence of measurements of esophageal pressure, however, differentiation of central apnea and hypopnea from obstructive events can be difficult. We classified hypopnea as obstructive if paradoxical thoracoabdominal excursions occurred or if the airflow decreased out of proportion to the reduction in the thoracoabdominal excursion. The apnea–hypopnea index was the number of episodes of apnea and hypopnea per hour.

Polysomnograms were scored in a blinded manner. Central sleep apnea was defined polysomnographically by the presence of 10 or more hourly episodes of apnea and hypopnea and 5 or more hourly episodes of central apnea. The number of hourly episodes of central disordered breathing had to be more than 50% of the overall total number of episodes of apnea and hypopnea. We defined absence of sleep apnea as fewer than 10 hourly episodes of apnea and hypopnea.

Arterial blood samples were obtained with the patient in a sitting position after he had rested for 15 minutes. To minimize pain, we used 2% lidocaine to anesthetize the skin where the radial artery was punctured. Afterward, by touching the skin with a sterile needle, we assured the patient that the procedure was painless. Our intent was to minimize changes in $PaCO_2$ caused by pain and anxiety. We performed pulmonary function tests, measured left ventricular ejection fraction, and did Holter monitoring as detailed elsewhere (1, 3, 6). Patients were classified as eucapnic ($PaCO_2 > 35$ and < 44 mm Hg [$n = 41$]) or hypocapnic ($PaCO_2 \leq 35$ mm Hg [$n = 18$]).

We used the Wilcoxon rank-sum test to assess significant differences between the two groups and chi-square analysis for proportions. Stepwise least-squares multiple regression analysis was used to determine the independent effects of certain variables on log transformation of the hourly rate of apnea and hypopnea. A two-sided P value less than 0.05 was considered statistically significant. Mean values ± SDs and percentages are reported as needed. We calculated 95% CIs by using t statistics. All calculations were done by using SAS software (7).

Results

In eucapnic and hypocapnic patients, the mean $PaCO_2$ and plasma concentrations of hydrogen and bicarbonate ions differed significantly, but demographic characteristics, results of pulmonary function tests, and left ventricular ejection fraction did not (**Table 1**).

Table 1. Characteristics of Eucapnic and Hypocapnic Patients with Stable Heart Failure

Variable	Eucapnic Patients ($n = 41$)	Hypocapnic Patients ($n = 18$)
Mean age ± SD, *y*	63 ± 11	64 ± 9
Mean body mass index ± SD, kg/m^2	27 ± 5	26 ± 5
Habitual snoring, %*	41	33
Excessive daytime sleepiness, %†	17	28
New York Heart Association class, %		
I and II	80	44‡
III	20	56‡
Paroxysmal nocturnal dyspnea, %	12	28
Orthopnea, %	22	28
Crackles, %	15	17
Mean predicted FEV_1 ± SD, %	80 ± 16	90 ± 20
Mean predicted FVC ± SD, %	85 ± 14	91 ± 20
Mean predicted functional residual capacity ± SD, %	98 ± 20	91 ± 21
Mean predicted total lung capacity ± SD, %	94 ± 16	94 ± 13
Mean predicted single-breath diffusing capacity for carbon monoxide ± SD, %	64 ± 18	67 ± 24
Mean Po_2 ± SD, *mm Hg*	83 ± 10	86 ± 10
Mean Pco_2 ± SD, *mm Hg*	39 ± 2	32 ± 3§
Mean hydrogen ion concentration ± SD, *nmol/L*	37 ± 2	35 ± 3‖
Mean bicarbonate ion concentration ± SD, *mmol/L*	26 ± 2	23 ± 3§
Mean left ventricular ejection fraction ± SD, %	25 ± 8	21 ± 9

* Habitual snoring was defined as snoring that occurred almost every night or every night.

† Excessive daytime sleepiness was defined as the presence of at least one of the following: falling asleep unintentionally daily at least three times in a week, falling asleep while driving a car, or taking three naps in a week despite having had adequate sleep at night.

‡ $P < 0.01$ when means were compared.

§ $P < 0.005$ when means were compared.

‖ $P < 0.05$ when means were compared.

Arterial PCO_2 ranged from 35.2 to 43.6 mm Hg in eucapnic patients (mean, 39 mm Hg [95% CI, 38 to 40 mm Hg]) and 23.0 to 35.0 mm Hg in hypocapnic patients (mean, 32.5 mm Hg [CI, 30.8 to 34.2 mm Hg]). Of the 18 hypocapnic patients, 14 (78% [CI, 52% to 93%]) had central sleep apnea; this prevalence was significantly higher than that in eucapnic patients (16 of 41 [39%; CI, 25% to 55%]; $P = 0.01$). Although the prevalence of subjective habitual snoring was lower and the prevalence of excessive daytime sleepiness was higher in the hypocapnic patients than in the eucapnic patients, the differences were not significant (**Table 1**). In eucapnic patients and hypocapnic patients, the use of vasodilators (93% and 89%), digoxin (73% and 67%), isosorbide dinitrate (41% and 39%), and diuretics (80% and 89%) did not significantly differ. However, significantly more hypocapnic patients were New York Heart Association class III and fewer were class I and class II compared with eucapnic patients (**Table 1**).

Hypocapnic patients had significantly more arousals and decreased sleep efficiency due to excessive periodic breathing (**Table 2**). The number of hourly episodes of apnea and hypopnea and central apnea was significantly greater in hypocapnic patients than in eucapnic patients (**Table 2**). Consis-

Table 2. Sleep Characteristics of Eucapnic and Hypocapnic Patients with Stable Heart Failure*

Variable	Eucapnic Patients	Hypocapnic Patients
Total dark time, *min*	396 ± 23	393 ± 21
Total sleep time, *min*	287 ± 61	251 ± 52†
Sleep efficiency, %‡	72 ± 14	64 ± 12†
Total sleep time spent in sleep stages, %		
Stage 1	36 ± 26	34 ± 21
Stage 2	45 ± 25	46 ± 22
Stages 3 and 4	0.4 ± 1.9	0.5 ± 1.6
Rapid eye movement	18 ± 9	20 ± 15
Breathing events, *n/h*		
Apnea or hypopnea	20 ± 27	36 ± 25†
Central apnea	12 ± 19	26 ± 21†
Obstructive apnea	0.1 ± 0.6	1.0 ± 1.0
Central hypopnea	7 ± 12	8 ± 8
Oxyhemoglobin saturation		
Baseline, %	95 ± 2	95 ± 1
Lowest value, %	84 ± 9	81 ± 14
<90% (percentage of total sleeping time), %	3 ± 13	13 ± 19
Arousals due to disordered breathing, *events/h*	9 ± 4	16 ± 3†
Premature ventricular contractions per hour, *n*	68 ± 185	229 ± 262†
Couplets per hour, *n*	1 ± 2	13 ± 18§
Ventricular tachycardias per hour, *n*	0.1 ± 0.1	2 ± 3§

* Values are given as the mean ± SD.
† $P < 0.05$ when means were compared.
‡ The ratio of total sleep time to total dark time.
§ $P < 0.005$ when means were compared.

tent with the difference in the number of hourly episodes of apnea and hypopnea, arterial oxyhemoglobin desaturation was more severe in hypocapnic patients than in eucapnic patients, although the differences were not statistically significant (**Table 2**). Hypocapnic patients had a significantly higher prevalence of ventricular irritability (**Table 2**). Ventricular tachycardia (defined as three premature ventricular depolarizations in a row) was 20 times more prevalent in hypocapnic patients than in eucapnic patients. The mean serum potassium level and concentrations of sodium and digoxin did not significantly differ between the two groups.

In a stepwise least-squares multiple regression analysis, we assessed the independent contribution of $PaCO_2$, hydrogen ion concentration (≤35 or >35 nmol/L), and New York Heart Association functional classes (III or I and II) with the apnea–hypopnea index as the dependent variable. The *P* values for $PaCO_2$ and hydrogen ion concentration were 0.014 and 0.034, respectively. When New York Heart Association functional classes were added, only $PaCO_2$ remained significant ($P = 0.04$ [for hydrogen ion concentration, $P = 0.06$]).

Discussion

Among 59 patients with stable heart failure who did not have other comorbid disorders, 18 (31%) were hypocapnic while awake. Only 4 of the 18 patients did not have central sleep apnea. Therefore, given the prevalence of central sleep apnea in study patients, 78% of patients with heart failure and low $PaCO_2$ had central sleep apnea.

As shown by our results, most hypocapnic patients will develop relatively severe periodic breathing during sleep, with an average of 36 hourly episodes of apnea and hypopnea (**Table 2**). Furthermore, in stepwise multiple regression analysis, $PaCO_2$ was associated with hourly episodes of apnea and hypopnea (although this may have been confounded by hydrogen ion concentrations). These episodes of apnea and hypopnea resulted in a moderate degree of arterial oxyhemoglobin desaturation, excessive arousals, and disrupted sleep (**Table 2**).

However, our results also show that in patients with stable heart failure, a low $PaCO_2$ while awake is not a prerequisite for development of central sleep apnea. Of 41 eucapnic patients, 16 (39%) had central sleep apnea. Because only 14 of the 30 patients with central sleep apnea were hypocapnic, the sensitivity (8) of a low $PaCO_2$ was 47%.

In the absence of systematic, large, longitudinal studies, we speculate that the degree of periodic breathing with associated arterial oxyhemoglobin desaturation and arousals, if left untreated, may adversely affect cardiac function and result in excessive illness and death (1, 9). The results of our current study and two previous studies (10, 11) suggest that performing sleep studies on hypocapnic patients with heart failure may identify patients who require sleep apnea therapy.

Another important finding was the significantly greater number of hourly episodes of ventricular arrhythmias during sleep in hypocapnic patients with heart failure (**Table 2**). The prevalence of ventricular tachycardia was 20 times greater in the hypocapnic patients than in the eucapnic patients. A low $PaCO_2$ while awake may also indicate the need for Holter monitoring because detection and appropriate treatment of ventricular tachycardia may improve survival (12).

Although a previous report (13) suggested that hypocapnia may contribute to the development of arrhythmias in patients with coronary artery disease, our report describes the largest systematic study to date to show the relation between hypocapnia and ventricular tachycardia in patients with left heart failure. We could not determine whether hypocapnia was the cause of ventricular arrhythmias, but hypocapnia may be associated with changes in calcium binding and shifts of sodium, potassium, and hydrogen ions across cell membranes (14). We observed no significant differences between eucapnic and hypocapnic patients in serum concentrations of sodium, potassium, and digoxin; PaO_2; and left ventricular ejection fraction, but serum hydrogen ion concentrations differed significantly (**Table 1**).

Several factors may result in periodic breathing

during sleep (10, 11, 15, 16). The observation that a low $PaCO_2$ is commonly associated with central sleep apnea in patients with stable heart failure is consistent with the physiologic notion of the apneic threshold. Accordingly, a low $PaCO_2$ promotes ventilatory instability, and the data obtained from normal persons while they are asleep show that lowering the PCO_2 by passive hyperventilation induces central sleep apnea (2).

Our study had some limitations. First, it was not designed to determine the mechanisms of the hypocapnia that occurred in 30% of study patients. However, hypocapnic patients were in the higher categories of the New York Heart Association classification and had a higher (although not a statistically significantly higher) prevalence of paroxysmal nocturnal dyspnea (**Table 1**). These patients may have had chronic pulmonary congestion that caused hyperventilation and dyspnea. However, patients in both groups were clinically stable, and the incidence of orthopnea and crackles, mean values for pulmonary function tests (including diffusing capacity for carbon dioxide), and left ventricular ejection fraction were similar in both groups. Second, because we studied only male patients and patients without comorbid disorders, our data may not be generalizable to all patients with left heart failure.

In summary, we found a high prevalence of central sleep apnea and ventricular tachycardia in hypocapnic patients with stable heart failure. We suggest that such patients be considered for sleep study and Holter monitoring because testing may guide appropriate therapy (3, 9, 12, 16–18).

Acknowledgments: The authors thank Dr. P.S. Gartside for advice and statistical analysis and Ms. F. Jones for secretarial assistance.

Grant Support: By Merit Review from the Department of Veterans Affairs.

Requests for Reprints: Shahrokh Javaheri, MD, Pulmonary Section (111F), Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220.

Current Author Addresses: Dr. Javaheri: Pulmonary Section (111F), Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220.
Mr. Corbett: Phoenix International, 5642 Hamilton Avenue, Cincinnati, OH 45224.

References

1. **Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, et al.** Occult sleep-disordered breathing in stable congestive heart failure. Ann Intern Med. 1995;122:487-92.
2. **Skatrud JB, Dempsey JA.** Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol. 1983;55:813-22.
3. **Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA.** Effects of theophylline on sleep-disordered breathing in stable heart failure. N Engl J Med. 1996;335:562-7.
4. **Javaheri S, Colangelo G, Lacey W, Gartside PS.** Chronic hypercapnia in obstructive sleep apnea syndrome. Sleep. 1994;17:416-23.
5. EEG arousals: scoring rules and examples. ASDA Report. Sleep. 1992;15:174-84.
6. **Javaheri S, Bosken CH, Lim SP, Dohn MN, Greene NB, Baughman RP.** Effects of hypohydration on lung functions in humans. Am Rev Respir Dis. 1987;135:597-9.
7. **SAS Institute, Inc.** SAS/STAT Users Guide. Version 6.03. Cary, NC: SAS; 1998.
8. **Griner PF, Mayewski RJ, Mushlin AI, Greenland P.** Selection and interpretation of diagnostic tests and procedures. Principles and applications. Ann Intern Med. 1981;94(4 Pt 2):557-92.
9. **Javaheri S.** Central sleep apnea-hypopnea syndrome in heart failure: prevalence, impact, and treatment. Sleep. 1996;19(10 Suppl):S229-31.
10. **Naughton M, Benard D, Tam A, Rutherford R, Bradley TD.** Role of hyperventilation in the pathogenesis of central sleep apnea in patients with congestive heart failure. Am Rev Respir Dis. 1993;148:330-8.
11. **Hanly P, Zuberi N, Gray R.** Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial Pco_2. Chest. 1993;104:1079-84.
12. **Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al.** Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med. 1996;335:1933-40.
13. **Ayers SM, Grace WJ.** Inappropriate ventilation and hypoxemia as causes of cardiac arrhythmias. The control of arrhythmias without antiarrhythmic drugs. Am J Med. 1969;46:495-505.
14. **Gennari FJ, Kassirer JP.** Respiratory alkalosis. In: Cohen JJ, Kassirer JP, eds. Acid-Base. Boston: Little, Brown; 1982:349-76.
15. **Cherniack NS.** Sleep apnea and its causes. J Clin Invest. 1984;73:1501-6.
16. **Yamashiro Y, Kryger MH.** Review: sleep in heart failure. Sleep. 1993;16:513-23.
17. **Hanly PJ, Millar TW, Steljes DG, Baert R, Frais MA, Kryger MH.** The effect of oxygen on respiration and sleep in patients with congestive heart failure. Ann Intern Med. 1989;111:777-82.
18. **Takasaki Y, Orr D, Popkin J, Rutherford R, Liu P, Bradley TD.** Effect of nasal continuous positive airway pressure on sleep apnea in congestive heart failure. Am Rev Respir Dis. 1988;140:1578-84.