

A MECHANISM OF CENTRAL SLEEP APNEA IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Background Breathing is controlled by a negative-feedback system in which an increase in the partial pressure of arterial carbon dioxide stimulates breathing and a decrease inhibits it. Although enhanced sensitivity to carbon dioxide helps maintain the partial pressure of arterial carbon dioxide within a narrow range during waking hours, in some persons a large hyperventilatory response during sleep may lower the value below the apneic threshold, thereby resulting in central apnea. I tested the hypothesis that enhanced sensitivity to carbon dioxide contributes to the development of central sleep apnea in some patients with heart failure.

Methods This prospective study included 20 men who had treated, stable heart failure with left ventricular systolic dysfunction. Ten had central sleep apnea, and 10 did not. The patients underwent polysomnography and studies of their ventilatory response to carbon dioxide.

Results Patients who met the criteria for central sleep apnea had significantly more episodes of central apnea per hour than those without central sleep apnea (mean [\pm SD], 35 ± 24 vs. 0.5 ± 1.0 episodes per hour). Those with sleep apnea also had a significantly larger ventilatory response to carbon dioxide than those without central sleep apnea (5.1 ± 3.1 vs. 2.1 ± 1.0 liters per minute per millimeter of mercury, $P=0.007$), and there was a significant positive correlation between ventilatory response and the number of episodes of apnea and hypopnea per hour during sleep ($r=0.6$, $P=0.01$).

Conclusions Enhanced sensitivity to carbon dioxide may predispose some patients with heart failure to the development of central sleep apnea. (N Engl J Med 1999;341:949-54.)

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NORMALLY, the rate and depth of breathing are regulated by a negative-feedback system that maintains the partial pressure of arterial carbon dioxide within a narrow range throughout life. Changes in the partial pressure of carbon dioxide lead to changes in ventilation, so that the greater the sensitivity to carbon dioxide, the greater the ventilatory response.

Among normal persons there is considerable variation in sensitivity to carbon dioxide, which may in part be related to familial (genetic) influences.¹⁻⁴ In a study of patients with chronic obstructive pulmonary disease, Mountain and associates¹ found that diminished sensitivity to carbon dioxide, which presumably preceded the onset of pulmonary disease, increased the risk of chronic hypercapnia in patients with established pulmonary disease. Similarly, Moore et al.⁵

described a patient with a familial diminution in sensitivity who had respiratory failure.

The results of these studies,^{1,5} given our understanding of the operation of the negative-feedback system that controls ventilation, suggest that in persons with cardiopulmonary disorders, an increase in carbon dioxide sensitivity minimizes perturbations in the partial pressure of arterial carbon dioxide, thus protecting them against the long-term pathologic consequences of hypercapnia. Although this protective mechanism is advantageous during waking hours, the increased sensitivity can potentially destabilize breathing during sleep.⁶⁻⁹

During sleep, ventilation decreases and the partial pressure of carbon dioxide rises by 3 to 6 mm Hg. If during sleep the partial pressure of carbon dioxide decreases below a certain level, referred to as the apneic threshold, which is close to the waking level, ventilation ceases (a condition called central sleep apnea), and the partial pressure of carbon dioxide is restored to its previous level.

The partial pressure of carbon dioxide may fluctuate during sleep. In persons with increased sensitivity to carbon dioxide, the negative-feedback system that controls breathing elicits a large ventilatory response when the partial pressure of carbon dioxide rises; the consequent hyperventilation, by driving the partial pressure of carbon dioxide below the apneic threshold, results in central apnea. As a result of the apnea, the partial pressure of carbon dioxide rises again, which leads to an increase in ventilation. In this way, cycles of central apnea and hyperventilation recur during sleep.

Although central sleep apnea is a relatively rare condition,¹⁰ it is common in patients with heart failure.¹¹⁻¹⁴ In a prospective study of 81 ambulatory patients with treated, stable heart failure due to systolic dysfunction, my colleagues and I found that about 40 percent of the patients had central sleep apnea.¹⁴

On the basis of the correlation in normal persons between sensitivity to arterial carbon dioxide during waking hours and ventilatory oscillation during sleep⁸ and considering the increased sensitivity to carbon dioxide of patients with idiopathic central sleep apnea,¹⁵ I tested the hypothesis that enhanced sensitivity to carbon dioxide may contribute to the development of central sleep apnea in patients with heart failure.

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METHODS

Patients

Twenty patients with heart failure were studied, 10 of whom had central sleep apnea and 10 of whom did not.¹⁴ The patients were part of a prospective study designed to determine the prevalence and mechanisms of sleep apnea in heart failure. The details of that study have been published previously.^{14,16,17} The protocol was approved by the institutional review board of the University of Cincinnati, and written informed consent was obtained from all patients.

All 20 patients underwent polysomnographic studies after a night of adaptation in the sleep laboratory. Within 24 hours before or after the polysomnographic studies, radionuclide ventriculography, pulmonary-function tests, and tests to measure the ventilatory response to carbon dioxide were performed. Samples of venous blood and arterial blood for measurement of electrolytes and arterial-blood gases were obtained in the morning, before the ventilatory response was measured.

Polysomnography

Polysomnography was performed with the use of standard techniques, as described previously.^{18,19} To determine the stages of sleep, an electroencephalogram (with two channels), chin electromyogram (with one channel), and electro-oculogram (with two channels) were obtained. Thoracoabdominal excursions were measured qualitatively by respiratory inductance plethysmography (Respirace, Ambulatory Monitoring, Ardsley, N.Y.) or with pneumatic respiration transducers (Grass Instruments, Quincy, Mass.) placed over the rib cage and abdomen. Airflow was monitored qualitatively with an oronasal thermocouple (model TCTIR, Grass Instruments). Arterial-blood oxyhemoglobin saturation was recorded with the use of a pulse oximeter. These variables were recorded on a multichannel polygraph (model 78D, Grass Instruments).

An episode of apnea was defined as the cessation of inspiratory airflow for at least 10 seconds. An episode of obstructive apnea was defined as the absence of airflow in the presence of rib-cage and abdominal excursions. An episode of central apnea was defined as the absence of rib-cage and abdominal excursions and the absence of airflow. Hypopnea was defined as a reduction in airflow lasting 10 seconds or more and associated with at least a 4 percent decrease in arterial oxyhemoglobin saturation, an electroencephalographic arousal,²⁰ or both. The number of episodes of apnea and hypopnea per hour is referred to as the apnea-hypopnea index. The number of episodes of obstructive apnea and hypopnea per hour is referred to as the obstructive apnea-hypopnea index, and the number of episodes of central apnea per hour is referred to as the central-apnea index. The apnea-hypopnea index was used to define the presence or absence of clinically important sleep apnea, as previously described¹⁴ (≥ 15 episodes per hour indicated the presence of apnea, and < 15 episodes per hour indicated its absence). In addition, patients with central sleep apnea had to have a central-apnea index of at least five episodes per hour.

The number of episodes of arousal per hour is referred to as the arousal index. The results of all the polysomnographic studies were pooled and scored without knowledge of any laboratory data, including the carbon dioxide ventilatory response.

Studies of Pulmonary Function and Ventilation

Pulmonary-function tests, measurements of maximal inspiratory and expiratory pressures, and arterial-blood gas and pH measurements were performed as described previously.^{21,22} Measurements of ventilation, oxygen consumption, carbon dioxide production, and the ventilatory response to carbon dioxide (the hypercapnic ventilatory response) were performed in our laboratory as described previously.²²⁻²⁴ In brief, the tests were performed while the patients were sitting, wearing a nose clip, and breathing through a mouthpiece connected to a low-resistance, two-way valve. Measurements

were started several minutes after a steady state had been achieved, as evidenced by the finding of a stable end-tidal partial pressure of carbon dioxide. First, minute ventilation, oxygen consumption, and carbon dioxide production were measured.²² The hyperoxic hypercapnic ventilatory response²²⁻²⁴ was determined by Read's rebreathing method.²⁵ Linear regression was used to determine the slope according to the following equation: ventilation = $S \times (\text{the partial pressure of carbon dioxide} - B)$, where S is the slope of the hypercapnic ventilatory response and B is the intercept (on the x axis, which represents the partial pressure of carbon dioxide) of the line that relates ventilation to the partial pressure of carbon dioxide. The mean (\pm SD) value for the slope of the ventilatory response to carbon dioxide in 10 normal men in our laboratory was 2.92 ± 0.92 liters per minute per millimeter of mercury (range, 1.02 to 4.1).²²

In conducting the tests of ventilatory response, extreme caution was exercised to ensure uniformity in technique. All the tests were performed by one investigator. The patients were not allowed to drink caffeinated products on the morning of the tests. Tests were performed at least two hours after a meal, and the patients were asked to empty their bladders before the tests. The patients were familiarized with the equipment and breathed through the mouthpiece for several minutes before measurement began. An assistant monitored the patients continuously to ensure that they remained awake.

To compare the hypercapnic ventilatory response between patients with and those without central sleep apnea, the slope of the response was adjusted for the patients' body-surface area, oxygen consumption, carbon dioxide production, maximal voluntary ventilation, and forced vital capacity, since these factors affect the ventilatory response.

Characteristics of the Patients

Ten of the patients with heart failure did not meet the criteria for sleep apnea (i.e., they had scores on the apnea-hypopnea index of < 15 episodes per hour¹⁴). In these patients, the apnea-hypopnea index ranged from 0 to 6.8 episodes per hour, the obstructive apnea-hypopnea index was 0, and the central apnea index ranged from 0 to 3.2 episodes per hour. In the 10 patients with heart failure who did meet the criteria for central sleep apnea, the apnea-hypopnea index ranged from 19.5 to 107.2 episodes per hour, the obstructive apnea-hypopnea index ranged from 0 to 0.8 episode per hour, and the central-apnea index ranged from 6.1 to 79.1 episodes per hour. None of the patients had apneic episodes during waking hours.

The patients in the two groups were matched with respect to the results of their pulmonary-function tests, although some differences did exist. The patients in the two groups were also similar with respect to their medications. Medications included an angiotensin-converting-enzyme inhibitor (in 10 patients without central sleep apnea and 8 patients with central sleep apnea), furosemide (in 8 and 9 patients, respectively), digoxin (in 10 and 9 patients, respectively), and hydralazine (in 1 patient in each group). None of the patients were receiving beta-blockers, morphine derivatives, benzodiazepines, theophylline, or acetazolamide.

Statistical Analysis

The Mann-Whitney test was used to assess differences between patients with and those without central sleep apnea, and chi-square analysis was used to analyze proportions. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Values are reported as means. Spearman rank correlation was used to analyze the apnea-hypopnea index in relation to the unadjusted slope of the ventilatory response to carbon dioxide and the slope adjusted for body-surface area, oxygen consumption, carbon dioxide production, maximal voluntary ventilation, and forced vital capacity. All the calculations were done with InStat software, version 2.03 (GraphPad, San Diego, Calif.).

TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH AND THOSE WITHOUT CENTRAL SLEEP APNEA.*

VARIABLE	CENTRAL SLEEP APNEA (N=10)	NO CENTRAL SLEEP APNEA (N=10)
Age (yr)	68±7	63±12
Height (cm)	173±6	174±9
Body-mass index†	26.1±4.7	28.3±4.9
Body-surface area (m ²)	1.92±0.17	2.01±0.20
Systolic blood pressure (mm Hg)	115±18	121±15
Diastolic blood pressure (mm Hg)	67±6	68±10
Heart rate (beats/min)	78±15	79±21
Left ventricular ejection fraction (%)	21±6	25±7
Crackles (% of patients)	10	20
Leg edema (% of patients)	10	40
Hemoglobin (g/dl)	13.8±1.3	13.8±1.4
Hematocrit (%)	41±4	41±4
Serum creatinine (mg/dl)‡	1.3±0.3	1.3±0.3
Sodium (mmol/liter)	138±4	140±2
Potassium (mmol/liter)	4.2±0.2	4.5±0.4
Chloride (mmol/liter)	99±7	102±2
Total carbon dioxide (mmol/liter)	26±4	27±2

*Plus-minus values are means ±SD. There were no significant differences between the two groups.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.

RESULTS

There were no significant differences between the patients who met the criteria for central sleep apnea and those who did not with respect to demographic characteristics or various laboratory measurements (Table 1), the results of pulmonary-function tests (except for the percentage of predicted forced expiratory volume in one second) (Table 2), or measurements of ventilation (Table 3). Table 4 lists the characteristics of sleep and disordered breathing events and oxyhemoglobin saturation during sleep in the patients. Among patients with central sleep apnea, the mean central-apnea index was 35±24 episodes per hour. As a result, these patients had arterial oxyhemoglobin desaturation and an excessive number of arousals from sleep (Table 4). However, total sleeping time and the proportion of time spent in each stage of sleep did not differ significantly between these patients and those without central sleep apnea.

The unadjusted slope of the ventilatory response to carbon dioxide was significantly greater among patients with heart failure who had central sleep apnea than among those who did not have apnea (Table 3), although there was some overlap in values (Fig. 1). This difference remained significant when the ventilatory response was adjusted for body-surface area, forced vital capacity, maximal voluntary venti-

TABLE 2. RESULTS OF PULMONARY-FUNCTION TESTS.*

VARIABLE	CENTRAL SLEEP APNEA (N=10)	NO CENTRAL SLEEP APNEA (N=10)
Forced vital capacity		
Mean (liters)	3.4±0.5	3.5±1
% of predicted value	93±9	89±17
Forced expiratory volume in 1 second		
Mean (liters)	2.6±0.3	2.4±0.6
% of predicted value	91±15†	77±9
Ratio of forced expiratory volume in 1 second to forced vital capacity		
Mean (%)	77±9	70±8
% of predicted value	97±12	87±10
Total lung capacity		
Mean (liters)	5.8±1.1	6.1±1.4
% of predicted value	99±9	102±18
Functional residual capacity		
Mean (liters)	3.4±1.0	3.5±0.7
% of predicted value	101±22	109±19
Single-breath carbon monoxide diffusing capacity		
Mean (ml/min/mm Hg)‡	16±5	18±7
% of predicted value	64±17	69±23
Maximal voluntary ventilation (liters/min)	86±16	100±33
Maximal inspiratory pressure (cm of water)	105±4	108±7
Maximal expiratory pressure (cm of water)	198±7	203±12

*Plus-minus values are means ±SD.

†P=0.02 for the comparison with the patients without central sleep apnea.

‡The carbon monoxide diffusing capacity is expressed in units for the dry gas at standard temperature and pressure.

TABLE 3. ASSESSMENT OF VENTILATION.*

VARIABLE	CENTRAL SLEEP APNEA (N=10)	NO CENTRAL SLEEP APNEA (N=10)	P VALUE
Partial pressure of arterial oxygen (mm Hg)	87±9	79±9	0.05
Partial pressure of arterial carbon dioxide (mm Hg)	37.0±2.9	38.5±2.4	0.2
Respiratory rate (breaths/min)	15±4	18±6	0.3
Tidal volume (ml)	860±166	863±230	0.9
Minute ventilation (liters/min)†	6.7±1.5	7.3±1.7	0.5
Oxygen consumption (ml/min)†	157±26	171±37	0.6
Carbon dioxide production (ml/min)†	127±20	149±33	0.2
Slope of the ventilatory response to carbon dioxide (liters/min/mm Hg)			
Unadjusted	5.1±3.1	2.1±1.0	0.007
Adjusted for body-surface area	2.7±1.6	1.0±0.5	0.004
Adjusted for forced vital capacity	1.5±0.8	0.5±0.3	0.005
Adjusted for maximal voluntary ventilation‡	7±5	2±1	0.003
Adjusted for oxygen consumption‡	1.6±0.8	0.7±0.4	0.003
Adjusted for carbon dioxide production‡	2.1±1.2	0.8±0.5	0.002

*Plus-minus values are means ±SD.

†The values have been adjusted for body-surface area.

‡The values have been multiplied by 100.

TABLE 4. CHARACTERISTICS OF THE PATIENTS DURING SLEEP.*

VARIABLE	CENTRAL SLEEP APNEA (N=10)	NO CENTRAL SLEEP APNEA (N=10)	P VALUE
Total dark time (min)	391±11	389±40	0.4
Total sleeping time (min)	257±58	255±74	0.7
Sleep efficiency (%)†	66±14	65±15	0.7
Wakefulness after onset of sleep (min)	119±56	114±50	1.0
Sleep stage (% of total sleeping time)‡			
1	56±22	45±27	0.4
2	32±22	36±20	0.9
3 or 4	0.0±0.0	0.0±0.0	1.0
Rapid eye movement	13±9	19±12	0.3
Arousal index (no. of episodes/hr)	36±22	14±9	0.005
Breathing events (no. of episodes/hr)			
Apnea-hypopnea index§	57±25	3±2	<0.001
Central-apnea index	35±24	0.5±1.0	<0.001
Obstructive apnea-hypopnea index	0.1±0.3	0.0±0.0	1.0
Arterial oxyhemoglobin saturation			
Base-line value (%)	96±2	95±1	0.2
Lowest value (%)	76±13	92±2	<0.001
<90% (min)	64±47	0.4±1.2	<0.001

*Plus-minus values are means ±SD.

†Sleep efficiency was calculated as the ratio of total sleeping time to total dark time.

‡For an explanation of sleep stages, see Carskadon and Dement.²⁶

§A score of ≥15 episodes per hour indicated the presence of sleep apnea, and a score of <15 indicated its absence.¹⁴

lation, oxygen consumption, and carbon dioxide production. The ventilatory response to carbon dioxide before and after adjustment for these variables was 2.3 to 3.5 times as great in patients with central sleep apnea as in those without it (Table 3). Furthermore, there were significant correlations between the apnea-hypopnea index and the slope of the ventilatory response before adjustment ($r=0.6$, $P=0.01$) and after adjustment for forced vital capacity ($r=0.6$, $P=0.008$), maximal voluntary ventilation ratio ($r=0.6$, $P=0.005$), carbon dioxide production ($r=0.6$, $P=0.003$), and oxygen consumption ($r=0.6$, $P=0.005$).

DISCUSSION

The principal finding of this study is that patients with heart failure who had central sleep apnea had a significantly greater sensitivity to carbon dioxide (by a factor of 2.3 to 3.5) than patients with heart failure who did not have central sleep apnea, as assessed by the ventilatory response to carbon dioxide. There was also a significant, positive correlation between sensitivity to carbon dioxide and the number of episodes of apnea and hypopnea per hour during sleep.

An enhanced sensitivity to carbon dioxide could destabilize breathing during sleep. During sleep, the partial pressure of carbon dioxide rises and becomes

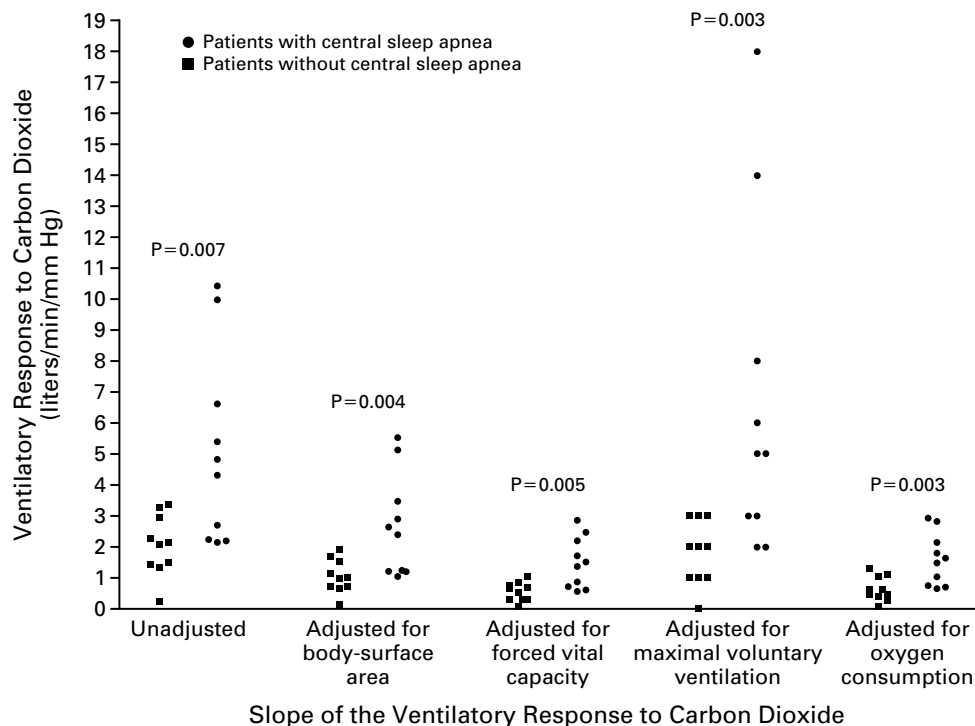


Figure 1. The Slopes of the Ventilatory Response to Carbon Dioxide in Patients with and Those without Central Sleep Apnea. Individual values are shown for the unadjusted slope of the ventilatory response to carbon dioxide and for the slope as adjusted for body-surface area, forced vital capacity, maximal voluntary ventilation, and oxygen consumption. Values adjusted for maximal voluntary ventilation and oxygen consumption were multiplied by 100. P values are for the comparisons between the two groups of patients. Mean values are given in Table 3.

the most potent stimulus of rhythmic breathing.²⁷ If the partial pressure of carbon dioxide decreases below the apneic threshold, breathing ceases. This state of central apnea results in an increase in the partial pressure of carbon dioxide, which in the presence of enhanced sensitivity to carbon dioxide elicits a large hyperventilatory response. This response may in turn lower the partial pressure of carbon dioxide below the apneic threshold. The result is periodic breathing with recurring cycles of apnea and hyperventilation.

In this study, in addition to differences in sensitivity to carbon dioxide between patients with and those without central sleep apnea, there was a significant and positive correlation between sensitivity and the number of episodes of apnea and hypopnea per hour. This finding further emphasizes the potential destabilizing effect of enhanced sensitivity to carbon dioxide on breathing during sleep in patients with heart failure.

The administration of oxygen decreases the number of episodes of central sleep apnea in patients with heart failure.¹¹⁻¹³ In a study of patients with heart failure and systolic dysfunction, periodic breathing improved and sensitivity to carbon dioxide decreased significantly after one week of nocturnal administration of supplemental nasal oxygen.²⁸ Although the exact cause-and-effect relation cannot be determined, the results of that study suggest that the decreased sensitivity to carbon dioxide may have contributed to the improvement in periodic breathing during sleep.

Mechanisms underlying the initiation and maintenance of central sleep apnea are complex.^{29,30} In addition to sensitivity, other factors have been implicated. The finding of a low partial pressure of arterial carbon dioxide during waking hours is highly predictive of central sleep apnea, since the level may drop below the apneic threshold during sleep.³¹⁻³³ Likewise, a low metabolic rate³⁴ and low functional residual capacity^{6,7,9} may contribute to periodic breathing during sleep. In the current study, there were no significant differences between groups in the partial pressure of carbon dioxide, oxygen consumption and carbon dioxide production (measures of metabolic rate), or functional residual capacity. Circulation time was not measured; however, a prolonged circulation time may not be a key factor in the genesis of central sleep apnea, but it may be important in determining the length of ventilatory cycles^{35,36} and in maintaining periodic breathing.³⁶ In experiments in dogs,³⁶ circulation time had to be increased severalfold before spontaneous periodic breathing could occur, and even then, it occurred in a minority of the animals.

In this study there was some overlap in the ventilatory response to carbon dioxide between patients with and those without central sleep apnea (Fig. 1), a finding that emphasizes the importance of other mechanisms in the development of central sleep apnea. One critical factor is the apneic threshold dur-

ing sleep, and whether this threshold differs between patients with heart failure who have central sleep apnea and those who do not have sleep apnea.

It is well known that increased sensitivity of the respiratory system to carbon dioxide or hypoxia may destabilize breathing during sleep. The relative contributions of the peripheral arterial chemoreceptors (the carotid bodies) and of the central chemoreceptors (those within the medulla of the brain stem) to the enhanced sensitivity and the consequent periodic breathing and central sleep apnea remain unclear, although it is generally believed that the central chemoreceptors have the larger role in sensitivity to carbon dioxide. In one study, during periods of natural sleep in unanesthetized dogs, hypocapnia that was confined to the carotid body did not result in central apnea.³⁷ This finding supports the role of the central chemoreceptors in the genesis of central sleep apnea.^{30,37} However, the sensitivity of the chemoreceptors may further change under conditions of heart failure. The increased sensitivity to carbon dioxide in heart failure appears to be specific to central but not obstructive sleep apnea.³⁸

Both acquired and genetic factors may affect the ventilatory response to carbon dioxide.^{1-5,37} In the current study, the two groups of patients with heart failure were well matched: differences in sex, age, body-mass index, base-line ventilation, partial pressures of arterial carbon dioxide and oxygen, metabolic rate, respiratory-muscle strength, and pulmonary function, all of which can affect the ventilatory response,³⁹ did not account for the large and significant differences in sensitivity to carbon dioxide between the two groups. In addition, the mean values for arterial blood pressure, heart rate, and left ventricular ejection fraction, as well as the cardiovascular medications, were similar in the two groups. Of the medications they used, only hydralazine is a known respiratory stimulant.⁴⁰ One patient in each group was receiving hydralazine.

Loss of sleep has been shown to decrease sensitivity to carbon dioxide,⁴¹ but in the current study, the mean total sleeping time was similar in the two groups. Sleep was more often interrupted (fragmented) in the patients who had central sleep apnea, but sleep fragmentation in the absence of sleep loss has not been shown to affect sensitivity to carbon dioxide.⁴²

The variation in ventilatory drive that has been noted among randomly selected normal persons is considerably smaller within families, and strong correlations in ventilatory drive among family members have been reported.^{2,3} The clustering and correlation of ventilatory drive among family members suggest that there are familial (presumably genetic) influences on the chemical control of ventilation. It is therefore conceivable that in my patients, familial enhancement of the ventilatory response to carbon dioxide predis-

posed them to the development of central sleep apnea after the onset of heart failure. This supposition is consistent with observations in patients with chronic obstructive pulmonary disease, a disorder in which diminished sensitivity to carbon dioxide (of a familial nature) predisposes patients to hypercapnia.¹ However, among normal persons, the range of the ventilatory response to carbon dioxide is broad.² Alternatively, patients with heart failure who have central sleep apnea could have spontaneously increased sensitivity to carbon dioxide, independent of familial or genetic influences.

In summary, in this study, patients with heart failure who had central sleep apnea had enhanced sensitivity to carbon dioxide. In addition, the degree of sensitivity was correlated with the severity of central sleep apnea, a finding that supports the possibility that increased sensitivity has a destabilizing effect on breathing during sleep.

Supported by Merit Review grants from the Department of Veterans Affairs.

I am indebted to Candice R. Brown for technical assistance and to Faye A. Jones for secretarial assistance.

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