

## EFFECT OF THEOPHYLLINE ON SLEEP-DISORDERED BREATHING IN HEART FAILURE

S. JAVAHERI, M.D., T.J. PARKER, M.D., L. WEXLER, M.D., J.D. LIMING, M.D., P. LINDOWER, M.D.,  
AND G.A. ROSELLE, M.D.

### ABSTRACT

**Background** Theophylline has been used to treat central apnea associated with Cheyne–Stokes respiration (periodic breathing). We studied the effect of short-term oral theophylline therapy on periodic breathing associated with stable heart failure due to systolic dysfunction.

**Methods** Fifteen men with compensated heart failure (left ventricular ejection fraction, 45 percent or less) participated in the study. Their base-line polysomnograms showed periodic breathing, with more than 10 episodes of apnea and hypopnea per hour. In a double-blind crossover study, the patients received theophylline or placebo orally twice daily for five days, with one week of washout between the two periods.

**Results** After five days of treatment, the mean ( $\pm$ SD) plasma theophylline concentration was  $11 \pm 2$   $\mu$ g per milliliter. Theophylline therapy resulted in significant decreases in the number of episodes of apnea and hypopnea per hour ( $18 \pm 17$ , vs.  $37 \pm 23$  with placebo and  $47 \pm 21$  at base line;  $P < 0.001$ ), the number of episodes of central apnea per hour ( $6 \pm 14$ , vs.  $26 \pm 21$  and  $26 \pm 20$ , respectively;  $P < 0.001$ ), and the percentage of total sleep time during which the arterial oxyhemoglobin saturation was less than 90 percent ( $6 \pm 11$  percent, vs.  $23 \pm 37$  and  $14 \pm 14$  percent, respectively;  $P < 0.04$ ). There were no significant differences in the characteristics of sleep, the frequency of ventricular arrhythmias, daytime arterial-blood gas values, or the left ventricular ejection fraction during the base-line, placebo, and theophylline phases of the study.

**Conclusions** In patients with stable heart failure, oral theophylline therapy reduced the number of episodes of apnea and hypopnea and the duration of arterial oxyhemoglobin desaturation during sleep. (N Engl J Med 1996;335:562-7.)

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**I**N most patients with the sleep apnea syndrome, episodes of apnea are due to obstruction of the upper airways (obstructive apnea). Application of nasal continuous positive airway pressure eliminates the obstruction and thus prevents associated arterial oxyhemoglobin desaturation. Uvulopalatoplasty has also been performed in patients with obstructive sleep-disordered breathing.

In contrast to obstructive apnea, central apnea is characterized by the absence of airflow due to inactivation of the inspiratory pump muscles. Episodes

of central sleep apnea associated with Cheyne–Stokes respiration (periodic breathing) occur most commonly in association with severe heart failure and systolic dysfunction.<sup>1-4</sup> In our previous systematic study of patients with stable heart failure, periodic breathing occurred in 45 percent of the patients.<sup>5</sup> Periodic breathing can result in severe arterial oxyhemoglobin desaturation,<sup>1-5</sup> which may further impair cardiovascular function. Unlike obstructive sleep apnea, central apnea may not be readily treatable with continuous positive airway pressure, and uvulopalatoplasty is not indicated.

In a preliminary study,<sup>4</sup> we found that the administration of theophylline improved periodic breathing in three patients with heart failure and repeated episodes of central apnea. In the present, placebo-controlled study, we assessed the efficacy of theophylline in the treatment of periodic breathing and arterial oxyhemoglobin desaturation during sleep in patients with stable heart failure and left ventricular systolic dysfunction.

### METHODS

Fifteen men with stable, medically treated heart failure and systolic dysfunction (left ventricular ejection fraction, 45 percent or less) took part in the study. These patients were a subgroup of 42 patients with stable heart failure and left ventricular systolic dysfunction who had undergone polysomnographic studies to determine the prevalence of periodic breathing, as reported previously.<sup>5</sup> Nineteen consecutive patients whose initial polysomnograms showed periodic breathing, with more than 10 episodes of apnea and hypopnea per hour, were asked to take part in the present study. Two of the patients did not return for further studies, and two died before randomization.

We evaluated all the patients to confirm that they were clinically stable (defined as having no change in signs or symptoms of heart failure within the previous four weeks) and receiving optimal therapy, with no change in medications within the previous four weeks. Medications included angiotensin-converting-enzyme inhibitors (in 13 patients), hydralazine (in 2), digoxin (in 11), isosorbide dinitrate (in 7), and furosemide (in all 15). Doses were adjusted according to the clinical status of each patient. The average daily dose was 91 mg for captopril, 17 mg for lisinopril, 28 mg for enalapril, 175 mg for hydralazine, 62 mg for isosorbide dinitrate, 0.182 mg for digoxin, and 74 mg for furosemide.

Exclusion criteria were unstable angina; unstable congestive

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From the Pulmonary Section (S.J., T.J.P., J.D.L.), the Cardiology Section (L.W., P.L.), and the Medical Service (G.A.R.), Veterans Affairs Medical Center and the University of Cincinnati College of Medicine — both in Cincinnati. Address reprint requests to Dr. Javaheri at the Sleep Disorders Laboratory, Pulmonary Section (111F), VA Medical Center, 3200 Vine St., Cincinnati, OH 45220.

heart failure; acute pulmonary edema; congenital heart disease; intrinsic pulmonary diseases, including interstitial lung disease and obstructive lung defects (ratio of predicted forced expiratory volume to forced vital capacity, <80 percent); intrinsic renal and liver disorders; untreated hypothyroidism or kyphoscoliosis; and use of morphine derivatives, benzodiazepines, or theophylline.

### Study Protocol

After giving written informed consent, the patients received placebo or theophylline (Theo-Dur; average dose, 3.3 mg per kilogram of body weight; Key Pharmaceuticals, Kenilworth, N.J.) orally twice daily for five days, in a randomized, double-blind fashion. Crossover studies were performed after a one-week wash-out period. During the study, the patients were admitted to the hospital for cardiac monitoring. To maintain blinding, the patients were monitored during both the theophylline and the placebo phases of the study. The study cardiologists, who were not blinded, supervised the administration of theophylline and the cardiac monitoring. Since the initial polysomnographic studies had shown marked arterial oxyhemoglobin desaturation during sleep, the patients were given oxygen at night during the study to prevent desaturation. In the sleep laboratory, however, the studies were performed while the patients were breathing room air. No change in medication was allowed during hospitalization.

The following studies were performed initially and on day 5 after the initial administration of theophylline or placebo: polysomnography with nocturnal Holter monitoring, serum theophylline measurements, radionuclide ventriculography, arterial-blood gas and pH measurements, and pulmonary-function tests.

Polysomnography was performed with the use of standard techniques, as described previously.<sup>4,6</sup> All the patients had been adapted to the sleep laboratory at the time of the initial evaluation. To determine the stages of sleep, we obtained an electroencephalogram (with two channels), chin electromyogram (one channel), and electro-oculogram (with two channels). Thoraco-abdominal excursions were measured qualitatively by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, N.Y.) or with pneumatic respiration transducers (Grass Instrument, Quincy, Mass.) placed over the rib cage and abdomen. Airflow was monitored qualitatively with an oronasal thermocouple (Model TCTIR, Grass Instrument). Arterial-blood oxyhemoglobin saturation was recorded with the use of an ear oximeter (Biox IIA, Bioximetry Technology, Boulder, Colo.). These variables were recorded on a multichannel polygraph (Model 78D, Grass Instrument).

An episode of apnea was defined as the cessation of inspiratory airflow for 10 seconds or more. 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.<sup>4,6</sup> It should be noted, however, that without measurements of esophageal pressure, it is sometimes difficult to distinguish central from obstructive apnea. 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 or an electroencephalographic arousal, or both. An electroencephalographic arousal was defined as the appearance of alpha waves on the electroencephalogram for at least three seconds.<sup>7</sup> The number of episodes of apnea and hypopnea per hour is referred to as the apnea-hypopnea index. The polysomnograms were scored blindly.

To determine whether theophylline treatment was associated with the development of ventricular or supraventricular arrhythmias, Holter monitoring was performed during polysomnography. Three electrocardiographic channels (leads V<sub>1</sub>, V<sub>3</sub>, and V<sub>5</sub>) were recorded with the use of a Marquett Laser SxP Holter monitor system (Marquett Electronics, Milwaukee). The tapes were analyzed by computer and interpreted by a cardiologist.

Since theophylline is thought to improve cardiac function,<sup>8,9</sup> right and left ventricular ejection fractions were calculated from

gated first-pass and multigated radionuclide ventriculograms, respectively, with the use of standard techniques.

To determine the effect of theophylline on pulmonary function, we recorded lung volumes and flow rates,<sup>10</sup> maximal inspiratory and expiratory pressures,<sup>11</sup> and arterial-blood gas concentrations<sup>12</sup> using strict criteria, as described previously.<sup>10-12</sup> To minimize pain, 2 percent lidocaine was used to anesthetize the skin where the radial artery was punctured. By touching the skin with a needle, we assured the patients that the procedure was painless. Our intent was to minimize pain and anxiety and, thus, any attendant change in the arterial partial pressure of carbon dioxide.

Serum samples were obtained on days 2 and 5 during the theophylline and placebo phases of the study. Serum theophylline concentrations were measured by the colorimetric process, with the use of an Ekta-chem Analyzer 700 (Johnson and Johnson, Rochester, N.Y.).

### Statistical Analysis

We used a two-way analysis of variance for repeated measures to compare variables during the base-line, placebo, and theophylline phases of the study. For paired comparisons, a two-tailed paired t-test with the Bonferroni correction was used. A P value of less than 0.025 was considered to indicate statistical significance. Values are reported as means  $\pm$ SD. Calculations were made with the use of SAS software.<sup>13</sup>

## RESULTS

The 4 patients who were eligible but could not participate in the study had a mean apnea-hypopnea index of  $40 \pm 11$  and a mean left ventricular ejection fraction of  $24 \pm 7$  percent — values similar to those in the 15 patients who took part in the study.

Serum theophylline concentrations on day 5 ranged from 6.9 to 14.9  $\mu$ g per milliliter, with a mean value of  $11 \pm 2$   $\mu$ g per milliliter during the period when the patients were taking the drug. Theophylline was undetectable in serum during the placebo period and at base line.

The mean values for the study variables at base line and while the patients were receiving placebo or theophylline are shown in Tables 1, 2, and 3. There were no significant differences in the characteristics of sleep, the numbers of episodes of sleep apnea and hypopnea, the values for arterial oxyhemoglobin desaturation, the values for arterial-blood gases and pH while the patients were awake, or the results of pulmonary-function tests at base line and during the placebo phase of the study.

### Stages of Sleep and Periodic Breathing

Treatment with theophylline resulted in a considerable reduction in periodic breathing and episodes of central apnea (Table 1). This reduction was associated with a significant improvement in the arterial oxyhemoglobin saturation during sleep, as reflected by a decrease in the total sleep time during which the saturation was less than 90 percent, as well as by an increase in the lowest saturation value during sleep (Table 1). There was also a decrease in the number of electroencephalographic arousals due to periodic breathing (Table 1).

**TABLE 1. SLEEP-DISORDERED BREATHING EVENTS AND ARTERIAL-BLOOD VALUES AT BASE LINE, DURING THE ADMINISTRATION OF PLACEBO, AND DURING THE ADMINISTRATION OF THEOPHYLLINE IN 15 PATIENTS WITH HEART FAILURE.**

VARIABLE	BASE LINE	PLACEBO	THEOPHYLLINE	P VALUE*
	mean $\pm$ SD			
Breathing event (no. of episodes/hr)				
Apnea-hypopnea	47 $\pm$ 21	37 $\pm$ 23	18 $\pm$ 17	<0.001
Central apnea	26 $\pm$ 20	26 $\pm$ 21	6 $\pm$ 14	<0.001
Obstructive apnea	2 $\pm$ 6	2 $\pm$ 3	2 $\pm$ 5	0.7
Mixed apnea	2 $\pm$ 3	2 $\pm$ 4	1 $\pm$ 1	0.06
Hypopnea	17 $\pm$ 13	7 $\pm$ 6	9 $\pm$ 11	0.06
Arousal due to disordered breathing	24 $\pm$ 11	17 $\pm$ 15	8 $\pm$ 10	<0.001
Oxyhemoglobin saturation†				
Base line (%)	95 $\pm$ 2	94 $\pm$ 2	96 $\pm$ 2	0.7
Lowest value (%)	78 $\pm$ 10	79 $\pm$ 9	82 $\pm$ 11	0.038
<90% (% of total sleeping time)	14 $\pm$ 14	23 $\pm$ 37	6 $\pm$ 11	0.036
Partial pressure of oxygen (mm Hg)‡	83 $\pm$ 8	82 $\pm$ 12	84 $\pm$ 12	0.7
Partial pressure of carbon dioxide (mm Hg)‡	37 $\pm$ 4	39 $\pm$ 5	36 $\pm$ 4	0.1
Hydrogen ions (nmol/liter)‡	36 $\pm$ 2	36 $\pm$ 3	35 $\pm$ 4	0.3

\*P values are for comparisons among the three periods of the study (at base line, during the administration of placebo, and during the administration of theophylline). There were no significant differences between the base-line values and those during the placebo period.

†Oxyhemoglobin saturation was measured with the use of pulse oximetry.

‡Values were measured during the waking state.

Sleep stages, sleep efficiency (the ratio of the total sleep time to the total dark time), and the total number of arousals did not differ significantly among the three phases of the study (Table 2).

#### Pulmonary Function

Theophylline treatment significantly improved the forced vital capacity and forced expiratory volume in one second, although the ratio of forced expiratory volume in one second to forced vital capacity and the maximal respiratory pressures did not change significantly (Table 3). The mean values for arterial-blood gases and hydrogen ions while the patients were awake also did not change significantly (Table 1).

#### Cardiac Function and Rhythm

There were no significant differences in the right ventricular ejection fraction during the three study phases (50 $\pm$ 14 percent at base line, 49 $\pm$ 9 percent during the administration of placebo, and 48 $\pm$ 12 percent during the administration of theophylline), nor were there significant differences in the left ventricular ejection fraction (26 $\pm$ 10, 26 $\pm$ 11, and 28 $\pm$ 12 percent, respectively), the number of isolated premature ventricular depolarizations per hour of

sleep (159 $\pm$ 276, 189 $\pm$ 357, and 240 $\pm$ 307, respectively), the number of couplets per hour of sleep (6 $\pm$ 8, 7 $\pm$ 16, and 11 $\pm$ 17, respectively), or the number of episodes of ventricular tachycardia (defined as three or more premature ventricular beats in a row) per hour of sleep (1 $\pm$ 2, 1 $\pm$ 2, and 1 $\pm$ 3, respectively). Dizziness and supraventricular tachycardia developed in one patient on the third day of treatment with theophylline; the serum theophylline concentration was 8.6  $\mu$ g per milliliter. Although we were not certain whether the administration of theophylline caused the tachycardia, treatment was stopped on the evening of day 3, and polysomnography was performed.

The men's mean body weight did not differ significantly among the three phases of the study (88.8 $\pm$ 13.6 kg at base line, 88.1 $\pm$ 14.1 kg during the administration of placebo, and 87.7 $\pm$ 13.4 kg during the administration of theophylline). There was no significant correlation between changes in weight and the number of episodes of central apnea per hour.

#### DISCUSSION

In this study, the short-term administration of oral theophylline improved sleep-disordered breathing and reduced associated arterial-blood oxyhemoglobin desaturation in patients with stable heart failure. Treatment with theophylline also improved the results of pulmonary-function tests. These effects occurred at therapeutic serum theophylline concentrations.

#### Effect of Theophylline on Periodic Breathing

Our patients had relatively severe periodic breathing during sleep, with an average apnea-hypopnea index of 37 during the placebo phase of the study, resulting in arterial oxyhemoglobin desaturation during approximately one quarter of the sleep time.

Theophylline has long been known to alleviate Cheyne-Stokes respiration and central apnea in premature infants<sup>14</sup> and adults,<sup>15</sup> although to our knowledge, no controlled studies have been reported. In an earlier study,<sup>4</sup> using polysomnography, we reported that theophylline improved periodic breathing during sleep in three patients with heart failure and left ventricular systolic dysfunction. The present study shows that, as compared with placebo, theophylline resulted in a 51 percent reduction in the apnea-hypopnea index, mostly because of a reduction in the number of episodes of central apnea. The number of episodes of obstructive apnea was not significantly changed by theophylline therapy, confirming a previous finding<sup>16,17</sup> and suggesting that our identification and classification of episodes of sleep apnea were probably correct.

While receiving theophylline, the patients had an arterial oxyhemoglobin saturation below 90 percent

**TABLE 2.** CHARACTERISTICS OF SLEEP AT BASE LINE, DURING THE ADMINISTRATION OF PLACEBO, AND DURING THE ADMINISTRATION OF THEOPHYLLINE.\*

CHARACTERISTIC	BASE LINE	PLACEBO		THEOPHYLLINE
		mean $\pm$ SD		
Total dark time — min	389 $\pm$ 24	391 $\pm$ 18	388 $\pm$ 11	
Total sleep time — min	266 $\pm$ 38	295 $\pm$ 46	296 $\pm$ 75	
Sleep efficiency — %†	68 $\pm$ 10	75 $\pm$ 11	76 $\pm$ 19	
Time to onset of sleep — min	14 $\pm$ 16	15 $\pm$ 17	10 $\pm$ 12	
Wakefulness after onset of sleep — min	109 $\pm$ 48	81 $\pm$ 46	83 $\pm$ 76	
Sleep stage — min (% of total sleep time)				
1	86 $\pm$ 60 (33 $\pm$ 23)	93 $\pm$ 72 (32 $\pm$ 25)	92 $\pm$ 88 (33 $\pm$ 26)	
2	134 $\pm$ 61 (50 $\pm$ 21)	134 $\pm$ 72 (46 $\pm$ 24)	148 $\pm$ 69 (49 $\pm$ 20)	
3 or 4	4 $\pm$ 9 (1 $\pm$ 3)	12 $\pm$ 16 (4 $\pm$ 5)	12 $\pm$ 17 (4 $\pm$ 5)	
Rapid eye movement — min (% of total sleep time)	43 $\pm$ 21 (16 $\pm$ 7)	57 $\pm$ 34 (19 $\pm$ 10)	44 $\pm$ 26 (14 $\pm$ 7)	
Nonrapid eye movement — min (% of total sleep time)	223 $\pm$ 34 (84 $\pm$ 7)	238 $\pm$ 31 (81 $\pm$ 10)	252 $\pm$ 68 (86 $\pm$ 7)	
Arousal — no. of episodes/hr	41 $\pm$ 20	33 $\pm$ 21	29 $\pm$ 20	

\*There were no significant differences among the values during the three phases of the study.

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

for only 6 percent of their total sleep time (as compared with 23 percent while they were receiving placebo). Nocturnal arterial oxyhemoglobin desaturation reduces survival among patients with chronic obstructive pulmonary disease, and survival is improved considerably with the administration of oxygen.<sup>18</sup> It is therefore very likely that the treatment of marked arterial oxyhemoglobin desaturation in patients with heart failure also improves survival. Studies of long-term treatment involving large groups of patients are needed to establish the effect of theophylline therapy on survival.

The way in which theophylline improves central apnea remains unclear. Theophylline is a phosphodiesterase inhibitor, but its inhibitory action does not occur at the serum concentration (about 11  $\mu$ g per milliliter) reached in our patients.<sup>19</sup> At therapeutic serum concentrations, however, theophylline competes with adenosine at some of its receptor sites.<sup>19</sup> In the central nervous system, adenosine is a respiratory depressant, and theophylline stimulates respiration by competing with adenosine.<sup>20-22</sup> It is therefore conceivable that an increase in ventilation as a result of treatment with theophylline<sup>11,20-22</sup> results in a decreased number of episodes of central apnea during sleep.<sup>23</sup> Larger studies with appropriate measurements are needed to confirm this possibility.

#### Effect of Theophylline on the Characteristics of Sleep

The effects of theophylline on the stages of sleep, sleep efficiency, and the number of electroencephalographic arousals have been variable and controversial.<sup>17,24,25</sup> We found that in patients with heart

failure, in spite of the reduction in periodic breathing and associated arousals, the stages of sleep and the total number of arousals did not change significantly with theophylline therapy — findings that may have important implications for daytime functioning. However, the criteria for identifying an arousal vary among sleep laboratories, and a clinically relevant arousal has not yet been defined.

#### Effect of Theophylline on Pulmonary Function

Another interesting observation in our study was the improvement in the results of spirometric lung-function tests during treatment with theophylline. Our patients did not have obvious obstructive airway defects, and the ratio of the forced expiratory volume in one second to the forced vital capacity did not change significantly during the administration of theophylline. Furthermore, total lung capacity increased slightly during theophylline therapy. Theophylline thus improved the restrictive lung defect associated with heart failure.

The changes in the results of spirometric lung-function tests during treatment with theophylline were probably not related to changes in muscle strength, since the maximal inspiratory and expiratory pressures did not change significantly. This finding is consistent with our previous findings in normal persons.<sup>11</sup>

#### Effect of Theophylline on Cardiac Function

A limited number of controlled studies suggest that theophylline may improve the cardiac output<sup>8</sup> and ventricular ejection fraction<sup>9</sup> because of a posi-

**TABLE 3.** RESULTS OF SPIROMETRIC PULMONARY-FUNCTION TESTS AT BASE LINE, DURING THE ADMINISTRATION OF PLACEBO, AND DURING THE ADMINISTRATION OF THEOPHYLLINE.

TEST*	BASE LINE	PLACEBO	THEOPHYLLINE	P VALUE†
FEV <sub>1</sub> (liters/sec)	2.46±0.65	2.44±0.70	2.66±0.61	0.04
FVC (liters)	3.00±0.65	3.06±0.76	3.30±0.63	0.01
FEV <sub>1</sub> :FVC (%)	81±7	79±8	80±7	0.2
Functional residual capacity (liters)	2.80±0.84	2.74±0.80	2.80±0.66	0.6
DLCO (ml/min/mm Hg)	17.6±6.6	18.1±7.2	19.5±4.8	0.6
Total lung capacity (liters)	5.25±1.06	5.20±1.13	5.53±0.86	0.3
Maximal inspiratory pressure (cm of water)	83±27	80±29	83±33	0.7
Maximal expiratory pressure (cm of water)	164±65	168±57	171±68	0.9

\*FEV<sub>1</sub> denotes forced expiratory volume in one second, FVC forced vital capacity, and DLCO single-breath diffusing capacity for carbon monoxide.

†P values are for comparisons among the three phases of the study. There were no significant differences between the base-line values and those during the placebo period.

tive inotropic effect. An increase in the cardiac output may explain, at least in part, the reduction in the number of episodes of central sleep apnea.<sup>1</sup> The left and right ventricular ejection fractions, however, did not change significantly with theophylline therapy, although systematic hemodynamic studies are needed to address this question.

The prevalence of ventricular arrhythmias did not change significantly with the administration of theophylline. Only one patient had a supraventricular arrhythmia, which may or may not have been due to the drug. Theophylline thus appeared to be safe for the treatment of sleep apnea in our patients with heart failure.

#### Alternative Treatments

Several alternative treatments are available for periodic breathing in patients with heart failure.<sup>1</sup> Continuous positive airway pressure has had variable success<sup>3,4,26</sup> and should be used if there is obstructive apnea (e.g., in obese patients) or if the left ventricular end-diastolic pressure is increased.<sup>3,27</sup> This treatment may increase the number of episodes of central apnea<sup>28</sup> and may reduce the cardiac output, however, even in some patients with elevated left ventricular end-diastolic pressure.<sup>29</sup> In addition, compliance with the use of the appliance is variable. The administration of nasal oxygen is effective and is the safest therapeutic approach.<sup>30</sup> It is somewhat inconvenient, however, and patients may inadvertently re-

move the nasal cannula during sleep. On the basis of our findings, theophylline may be a reasonable alternative approach.

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