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Effect of Inhaled 3% CO_2 on Cheyne-Stokes Respiration in Congestive Heart Failure

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Summary: Cheyne-Stokes respiration (CSR) in severe stable congestive heart failure (CHF) may be associated with significant nocturnal arterial oxygen desaturation and sleep disruption. Previous investigations of inhaled CO_2 in CSR have been uncontrolled and of short duration, sleep has not been monitored electroencephalographically, and most patients studied have had neurological disease with or without cardiac disease. The purpose of our study was to document the effects of inhaled CO_2 on CSR in patients with severe stable CHF (left ventricular ejection fraction <35% and NYHA class 3 or 4 dyspnea) in controlled all-night polysomnographic studies. Six patients were studied for 3 nights and days: adaptation, control and inhalation of CO_2. These patients received a constant F_iCO_2 = 0.03 in air (with a 4–5 mm Hg increase in $PaCO_2$) on night 3. This caused virtual abolition of CSR as reflected by CSR duration/total sleep time (62–2.2%; p = 0.0012) and CSR duration/nonrapid eye movement (NREM) sleep time (73–2.4%; p = 0.00064), and NREM apnea index was reduced from 33.5 to zero (p = 0.026). The apparatus used to accurately control F_iCO_2, however, was intrusive and some features of sleep structure such as sleep latency were adversely affected. We conclude that inhalation of CO_2 with a constant F_iCO_2 = 0.03 virtually eradicates CSR in all-night polysomnographically monitored studies in patients with severe stable CHF. The clinical significance of these findings remains to be determined. **Key words:** Carbon dioxide—Cheyne-Stokes respiration—Congestive heart failure—Periodic breathing—Sleep.

Cheyne-Stokes respiration (CSR) in patients with severe congestive heart failure (CHF) is associated with significant nocturnal arterial oxygen desaturation even in patients who have normal awake resting arterial oxygen saturation (SaO_2) (1–4). It also disrupts sleep (1–6) and probably contributes to the daytime fatigue and sleepiness often seen in these patients (3,5).

Of the various interventions employed over the decades to eradicate CSR, inhalation of CO_2, in concentrations of 3–7%, has been most successful (7–10). The inhalation of increased concentrations of CO_2 is thought to abolish CSR by various mechanisms, including prevention of attaining the CO_2 apnea threshold and increased ventilation, resulting in increased O_2 stores with increased damping, increased SaO_2 with resultant reduction in controller gain and shift of respiratory control from the peripheral to the central chemoreceptors (8,11,12).

Previous studies of the effect of inhaled CO_2 on CSR have generally been uncontrolled and of short duration (minutes to a few hours) and have not monitored sleep electroencephalographically (7–10). They have usually included patients with both neurological and cardiac disease, even though the predominant mechanisms responsible for periodic breathing in these two disorders may differ. Other studies have reported the effects of inhaled CO_2 in experimental situations that are thought to have physiological mechanisms in common with those in CSR of neurological or cardiac origin. Such experimental models include passive positive-pressure hyperventilation apnea and simulated high altitude (13–16).

The purpose of our study was to determine the effects of CO_2 inhalation on CSR in patients with stable heart failure during controlled all-night studies in which sleep architecture was accurately monitored. In particular, we were interested to determine if CO_2 inhalation would eradicate CSR in CHF. A secondary aim was to determine if there was any obvious effect of such an intervention on sleep architecture and daytime performance.

METHODS

Study design

Six patients (five with ischemic heart disease and one with idiopathic dilated cardiomyopathy) underwent polysomnography on three consecutive nights, the first of which was an adaptation night during which no facial appliance was worn. The second was a control night, and the third was the active intervention night.

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A mask was not worn on the adaptation or control night. On night 3 the patients received a constant F_ICO_2 of 0.03. One hundred percent CO_2 and air were mixed via an oxygen blender to produce a P_ICO_2 of 22 mm Hg (F_ICO_2 0.03), which was monitored in-line by a capnograph. This gas mixture was delivered to an airflow generator and then was delivered to the patient via a mask covering both nose and mouth at a rate of approximately 20 l/minute via a flow-by system (a T-piece in association with a Cushion-Flex® face mask). A 10-l reservoir bag was placed between the patient and the airflow generator so that instantaneous inspiratory flow rates greater than 20 l/minute could be met by the system. This CO_2 delivery system resulted in a constant F_ICO_2 of 0.03. This protocol was not randomized and patients did not wear a mask on the control night because the mask, which was tight-fitting in order to prevent entrainment of room air and, in turn, a variable F_ICO_2, was known to be uncomfortable and patients would not have tolerated it for two consecutive nights.

A concentration of 3% CO_2 was chosen partly because of results of previous acute intervention studies in CSR (8), and partly because of results of studies of the CO_2 apnea threshold in passive positive-pressure hyperventilation apnea and simulated high-altitude studies, which suggested that the apnea threshold is 3–6 mm Hg below the usual NREM sleep $PaCO_2$ during normoxia and 1–2 mm Hg during hypoxia (13–16). We predicted from the alveolar gas equation that inhalation of a constant F_ICO_2 of 0.03 would result in an increase in $PaCO_2$ of 1.5 to 7 mm Hg for CO_2-ventilatory response slopes of 6 to 1 l/minute/mm Hg, respectively. In addition, in a pilot study of the effect of inhaled CO_2 on CSR, one of our patients with known marked CSR was studied with the above-mentioned apparatus and the F_ICO_2 was changed intermittently throughout the night. The patient exhibited marked CSR during stages 1 and 2 NREM sleep while breathing air but this was abolished each time the F_ICO_2 was increased to 3%. The CSR reproducibly recurred on reducing the F_ICO_2 to zero.

Patient selection

Males aged less than 70 years with stable significant (NYHA class 3 or 4 for dyspnea) CHF and some degree of subjective daytime sleepiness or reduction in mental function were recruited. A left ventricular ejection fraction (LVEF) on technicium-99m pertechnetate multiple gated cardiac acquisition (MUGA) scanning of less than 35% was required. Exclusion criteria comprised ingestion of drugs known to alter sleep (e.g. sedatives, antidepressants), presence of an intrinsic sleep disorder (such as obstructive sleep apnea and narcolepsy) and significant intrinsic lung or chest wall disease as determined clinically and by pulmonary function testing. Verbal consent was obtained from each patient's general practitioner and cardiologist, and patients gave written consent.

Daily protocol

Patients arrived at the sleep laboratory at 2100 hours and were instrumented for polysomnography. Lights out was at their usual bedtime or when they felt ready for sleep (whichever occurred first). They were awakened at 0600–0630 hours, underwent a battery of 10 questions relating to sleep parameters, and performed the following tests to assess attention and concentration, the speed of cognitive function, orientation and short-term memory: trailmaking tests A and B, symbol copying test and digit symbol substitution test. Patients subsequently underwent multiple sleep latency testing (MSLT) at 0900, 1100, 1300 and 1500 hours.

Monitoring and data collection

The variables monitored and recorded overnight (using the Grass Model 78E polysomnograph) were the electroencephalogram, electrooculogram, mental electromyogram, electrocardiogram, airflow at the nose and mouth (by CO_2 analyzer), arterial oxygen saturation (SaO_2) [using the Ohmeda Biox 3740 pulse oximeter (Ohmeda, Boulder, CO) attached to the ear], rib cage and abdominal respiratory motion (by respiratory inductance plethysmography) and heart rate. The latter five variables were recorded on a microcomputer. The microcomputer produced a binary time stamp on the polygraph recording chart such that data obtained directly from the latter could be synchronized with the data stored on computer. Sleep staging was performed using standard criteria (17), with an epoch length of 30 seconds. The manually derived sleep data and the computer data were then merged to provide integrated data of sleep architecture and respiratory variables (SaO_2 and heart rate).

Because the patients spent a substantial portion of the night not sleeping, and because for several variables the awake values could be quite different from the sleep variables, indices were calculated for sleep time and time in bed. The latter data are labeled "night".

The desaturation index (the number of desaturations per hour) was derived from desaturations in the oximetry data using an existing computer procedure (18).

Determination of periods of CSR

Cheyne-Stokes respiration was defined as breathing in which periods of reduced or absent respiratory effort alternate with periods of normal or increased effort;

TABLE 1. *Descriptive statistics and pulmonary function. Values are expressed as mean ± SD*

Age (years)	61.6 ± 5.4
BMI (kg/m²)	27.8 ± 2.6
LVEF (%)	21.0 ± 6.2
FEV_1 (l)	2.78 ± 0.19
FEV_1 % predicted	87.8 ± 9.0
FEV_1/FVC (%)	79.8 ± 5.8
FEV_1/FVC % predicted	113.2 ± 7.3
VC % predicted	87.8 ± 5.4
TLC % predicted	93.2 ± 5.6
RV % predicted	101.3 ± 15.6
RV/TLC % predicted	101.5 ± 11.3
FRC % predicted	87.2 ± 13.0
D_LCO % predicted	74.0 ± 26.0
pH	7.44 ± 0.04
$PaCO_2$ (mm Hg)	36.2 ± 4.4
PaO_2 (mm Hg)	82.2 ± 3.9
HCO_3^- (mmol/l)	24.5 ± 3.8
Base excess (mmol/l)	0.5 ± 3.9
SaO_2 (%)	96.3 ± 0.5

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; FEV_1, forced expiratory volume; FVC, forced vital capacity; VC, vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; D_LCO, diffusing capacity for CO; SaO_2, awake resting arterial oxygen saturation.

these cycles repeated with reasonable regularity and exhibited a crescendo–decrescendo pattern in the respiratory amplitude within a given cycle (11).

The rib cage and abdominal motion traces were printed onto paper with a scale of 3 minutes of data to approximately 21 cm, as previously described (19). These traces were then examined visually in conjunction with the polygraph recording chart; the number of cycles and the start and finish times of epochs of CSR were recorded. The proportion of sleep time with CSR [abbreviated as CSR as % of total sleep time (TST)] and cycle length were determined from this manually derived data.

A computer program was used to determine the degree of hypopnea for each cycle of CSR and to calculate the number of cycles attributed to two levels of hypopnea: apnea data with a greater than 90% reduction and apnea/hypopnea data with a greater than 50% reduction in nadir ventilation. Only those CSR epochs determined manually were used in the analysis; the nonperiodic episodes of apnea or hypopnea were omitted. The results from the computer analysis were verified manually and the few obvious errors were corrected by hand. Details of the computer program used to scan the respiratory motion data are described in the Appendix.

The apnea data were constrained to a period of at least twice the length of an average breath time. Values of twice an average breath time varied between 5.2 and 10.8 seconds, with average breath times being determined manually from the polygraph recording chart on the control night [during stage 2 nonrapid eye movement (NREM) sleep without CSR].

MSLT scoring

Multiple sleep latency testing was performed according to standard methods (20), but different criteria were used to determine sleep latency. Many patients with CSR do not achieve an epoch of sleep within 20 minutes, despite being obviously sleepy, because sleep is interrupted by arousals associated with the hyperpneic phase of the respiratory cycle. Therefore, we defined sleep latency as the time to the first episode of sleep (whether greater than or less than 50% of any 30-second epoch) that was interrupted by an arousal associated with a respiratory event.

Terminology (sleep parameters)

Total wake time. The sum of the duration of all epochs scored as awake; microarousals were not included in this measure.

Latency to stage 1. Time from the start of recording to the first epoch of stage 1.

Latency to REM. Time from the start of recording to the first epoch of rapid eye movement (REM) state.

Awakening. After onset of persistent sleep, a wake entry lasting more than 15 seconds that followed at least 10 seconds of continuous sleep.

Microarousal. After onset of persistent sleep, a wake entry lasting 3–15 seconds that followed at least 10 seconds of continuous sleep.

Arousals/total sleep time. The sum of the number of microarousals and the number of awakenings divided by the total sleep time in hours.

Wake time during sleep period. The time spent awake after the onset of persistent sleep and prior to the last epoch of any sleep stage.

Statistical analysis

Analysis was performed by comparing the results on nights 2 and 3 with the paired *t* test. Because we hypothesized improvement in respiration, the one-tailed paired *t* test was used to assess the respiratory variables (except cycle length), but the two-tailed paired *t* test was employed to assess sleep-related parameters. We chose the latter because the face mask was only worn on night 3 and proved to be very uncomfortable for most patients. Therefore, we could not predict the direction of change.

RESULTS

Patients (Table 1) were not obese, and all had a resting SaO_2 of greater than 90% despite having LVEFs of less than 35% and NYHA class 3 or 4 dyspnea. They tended to be mildly alkalotic and mildly hypocapnic.

TABLE 2. *Respiratory variables*

	Control	CO_2	p value[a]
SaO_2 baseline awake	93.7 (1.0)	96.5 (0.4)	0.0060
SaO_2 Δ to NREM	−2.2 (0.67)	−0.4 (0.3)	0.021
SaO_2 Δ to REM	−2.4 (1.0)	−1.6 (0.5)	0.19 b
SaO_2 by stage			
Stage 1	92.4 (1.3)	96.0 (0.4)	0.014
Stage 2	91.4 (1.4)	96.1 (0.4)	0.0072
Stage 3 and 4	91.6 (1.3)	96.1 (0.4)	0.0047 d
REM	91.4 (2.0)	94.8 (0.9)	0.041 b
Sleep	91.4 (1.4)	96.0 (0.4)	0.0090
Night	91.6 (1.2)	96.0 (0.4)	0.0065
Desaturation index[b]			
NREM	13.6 (5.3)	0.6 (0.2)	0.029
REM	7.8 (2.6)	0	0.015
Night	12.3 (4.2)	0.9 (0.2)	0.022
Proportion of night			
SaO_2 <90%	33.6 (16.3)	0.5 (0.3)	0.049
SaO_2 <85%	9.9 (8.6)	0	0.17 c
CSR parameters			
CSR/TST (%)[c]	61.9 (10.4)	2.2 (1.1)	0.0012
CSR/TRT (%)[d]	49.4 (8.7)	1.1 (0.5)	0.0011
CSR/NREM (%)[e]	73.1 (10.8)	2.4 (1.1)	0.0006
Cycle length (seconds)	60.1 (8.6)	66.1 (7.9)	0.37
Apnea-hypopnea index			
Night	28.9 (7.1)	0.4 (0.1)	0.0050
Sleep	41.1 (11.8)	1.0 (0.7)	0.0099
NREM	50.4 (14.0)	1.0 (0.7)	0.0086
Apnea index			
Night	18.4 (5.8)	0	0.012
Sleep	27.3 (11.2)	0	0.030
NREM	33.5 (13.2)	0	0.026

Values are expressed as mean (SE).
[a] n = 6; b, n = 5; c, n = 4; d, n = 3.
[b] Desaturation, apnea and apnea-hypopnea indices are expressed as events per hour; night refers to the time in bed.
[c] CSR/TST is total time spent with CSR divided by the total sleep time.
[d] CSR/TST is total time spent with CSR divided by the total recording time.
[e] CRS/NREM is total time spent with CSR divided by the total NREM time.

Two patients had clinical evidence of right heart failure, and one patient had experienced a stroke several years previously but showed no residual deficit.

Respiratory variables (Table 2)

Accurate measures of $PaCO_2$ were not available for the control night. On night 3 we had the opportunity to document accurate end-tidal CO_2s in stage 2 NREM sleep in two patients with an F_ICO_2 of 0.03 and an F_ICO_2 of zero (room air). This was possible because these two patients were still asleep at 0600–0630 hours with their masks in situ and the F_ICO_2 was reduced to zero. The end-tidal CO_2s were 4–5 mm Hg higher with the F_ICO_2 of 0.03.

Baseline awake SaO_2 was determined by averaging the SaO_2 over several minutes soon after lights out when there was little body movement with the patient awake with stable respiration. Baseline awake SaO_2 rose significantly (by almost 3%) on the CO_2 nights. There was a significant reduction in the fall in SaO_2 from baseline awake to that in NREM sleep. SaO_2 rose significantly in all sleep stages on the CO_2 night and the increase was most marked in the NREM sleep stages (Fig. 1). The desaturation index improved significantly in both NREM and REM sleep on the CO_2 night.

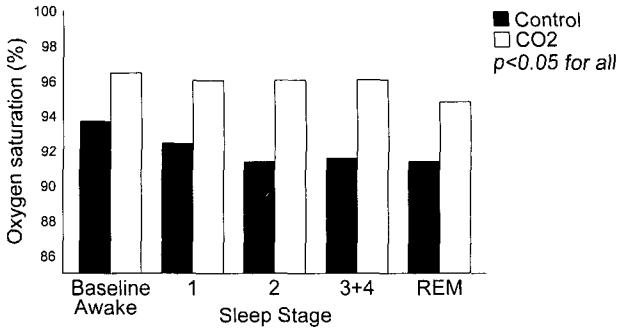

FIG. 1. Arterial oxygen saturation for baseline awake and in the various sleep stages. Refer to Table 2 for actual p values.

The apnea-hypopnea index (AHI) and the apnea index, expressed as a function of TST or NREM time (when most CSR occurred), were dramatically reduced on the CO_2 night, and the inhalation of gas with a constant F_ICO_2 of 0.03 reduced the apnea index to zero and the AHI almost to zero. The reduction in CSR/TST (Fig. 2) and CSR/NREM time was highly significant. Thus, inhalation of CO_2 at a constant F_ICO_2 of 0.03 virtually abolished CSR in all patients.

Assessment of sleep parameters (Tables 3 and 4)

All patients found the face mask very uncomfortable. In the last two patients entered into the trial, total

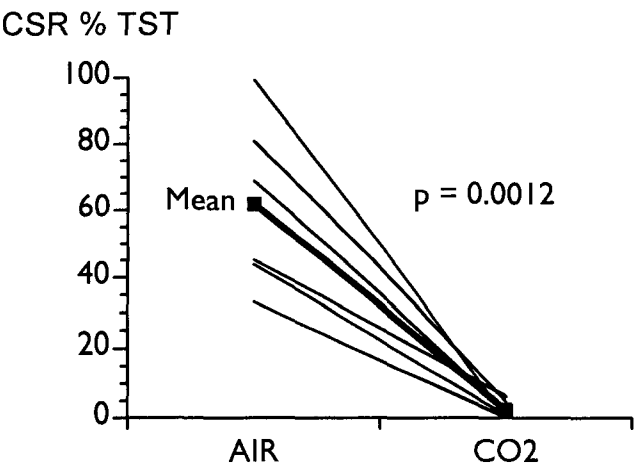

FIG. 2. Proportion of total sleep time spent with Cheyne-Stokes respiration. Individual and mean data.

TABLE 3. *Objective assessment of sleep*

	Control	CO_2	p value[a]
Overall measures			
Time in bed	452.9 (10.8)	332.0 (51.2)	0.062
Total sleep time	346.9 (41.2)	180.7 (50.0)	0.018
Total wake time	106.0 (35.6)	151.3 (36.3)	0.13
Sleep efficiency (%)	76.1 (8.4)	51.7 (9.4)	0.015
Latency measures			
Stage 1	22.0 (12.1)	42.5 (25.2)	0.22
REM	120.9 (13.3)	139.5 (31.2)	0.54 c
Staging (%)			
Stage 1	11.8 (5.9)	6.9 (1.9)	0.30
Stage 2	62.6 (5.4)	73.8 (4.9)	0.073
Stages 3 and 4	6.8 (3.4)	10.2 (4.1)	0.15
REM	18.8 (2.0)	9.1 (3.3)	0.038
Maintenance measures (events per hour of sleep)			
Awakenings	8.1 (5.1)	4.6 (1.1)	0.48
Microarousals	10.1 (2.3)	6.7 (1.7)	0.097
Arousals in Stage 1	38.3 (9.4)	20.3 (6.0)	0.026
Arousals in Stage 2	20.3 (7.4)	11.4 (1.7)	0.26
Arousals in REM	9.0 (2.1)	15.9 (3.1)	0.14 c
Arousals in sleep	19.9 (7.4)	12.1 (1.8)	0.27
MSLT	4.9 (1.2)	5.4 (2.1)	0.83 d
Morning performance tests			
Digit symbol substitution	59.3 (11.6)	66.2 (10.6)	0.035 d
Trailmaking test A (seconds)	56.0 (8.1)	40.3 (4.8)	0.13 d
Trailmaking test B (seconds)	170.5 (35.6)	126.3 (24.8)	0.051 d
Symbol copying test (number)	174.5 (42.2)	180.3 (28.5)	0.73 d

Values are expressed as mean (SE).
[a] n = 6; c, n = 5; d, n = 4.

sleep time was markedly reduced and the mask had to be removed and the trial terminated in the early hours of the morning. Thus, overall, TST and sleep efficiency were significantly reduced. Differences in latency measures and sleep stages were not significant, except that the proportion of REM sleep was reduced on the CO_2 night. There was a tendency for maintenance measures to improve on the CO_2 night, but the only variable for which this was statistically significant was the arousal index for stage 1 NREM sleep. There was no significant change in daytime drowsiness as assessed by MSLT and no convincing change in overall daytime performance (Table 3). The change in digit symbol substitution was significant (but the mean change small) and the trailmaking test B was almost significant. Subjective assessment of sleep revealed tendencies to increased difficulty falling asleep and poorer sleep quality, although there was no change in daytime function (Table 4).

DISCUSSION

Despite normal awake resting SaO_2, many patients with stable severe CHF and CSR during sleep demonstrate nocturnal hypoxemia of similar degree to that reported in chronic obstructive pulmonary disease, obstructive sleep apnea and interstitial lung disease (2). Many previous studies have demonstrated the nadir of SaO_2 to occur during the hyperpneic phase of the periodic breathing cycles (7,8,21,22), and several studies have noted significantly poorer nocturnal oxygenation in CHF patients with CSR than those without (1,4). Despite this, it remains uncertain as to whether CSR represents an independent poor prognostic factor in patients with left ventricular failure (23), although there is some suggestion that this may be the case (1). In patients with left ventricular failure, CSR disrupts sleep (1–6), and the amount of CSR correlates significantly with the number of arousals and sleep stage changes and is inversely related to the TST (2). As a

TABLE 4. *Subjective assessment of sleep*[a]

	Control	CO_2	p value
Sleep latency (minutes)	47.5 (17.5)	52.5 (4.3)	0.83
Ease to fall asleep[b]	27.8 (8.4)	75.2 (13.2)	0.09
Awakenings per night	2.5 (0.6)	5.5 (2.3)	0.18
Sleep time (minutes)	379.5 (30.3)	225.0 (69.8)	0.73
Sleep quality[c]	2.3 (0.5)	3.8 (0.2)	0.06
Morning sleepiness[d]	31.2 (12.7)	30.8 (19.5)	0.97
Ability to concentrate[c]	3.0 (0.4)	3.3 (0.5)	0.39

Values are expressed as mean (SE).
[a] n = 4.
[b] VAS (visual analog scale): 0 = very easy; 100 = not easy at all.
[c] Categories: 1 = excellent; 2 = good; 3 = fair; 4 = poor.
[d] VAS (visual analog scale): 0 = very sleepy; 100 = not sleepy at all.

result of sleep disruption, it is likely that CSR is a major contributing factor to the daytime fatigue and sleepiness often seen in these patients (3,5). It seems clear that CSR is at least a cause of morbidity in patients with CHF (23) and that further research into the mechanisms responsible for the initiation and perpetuation of this type of periodic breathing, as well as research into potential therapeutic modalities, are required.

Although inhalation of increased concentrations of CO_2 has been previously shown to eradicate CSR, these studies have been uncontrolled and of short duration, and sleep has not been monitored electroencephalographically (7–10). They have also included patients with both cardiac and neurological bases for their periodic breathing despite the likelihood that the mechanisms predominantly responsible for CSR in each situation are likely to be different. We have shown in controlled all-night polysomnographic studies that inhalation of CO_2 with a constant F_ICO_2 of 3% virtually abolishes CSR in patients with stable severe CHF.

Several aspects of the methodology of our protocols require consideration. First, our assessment of CSR varied from most previous studies in that a measure of ventilation (amplitude divided by time) with a two-breath moving average was used to determine the degree of hypopnea within a cycle and considered cycles with at least a 50% reduction, whereas most previous studies have defined hypopnea as amplitude falling for more than 10 seconds to less than 50%. We used a measure of ventilation, rather than amplitude, to define the degree of hypopnea, because at the nadir value it represents a time average of several small breaths and it compensates for the difference in breath duration between the waxing and waning parts of CSR. We also defined a fall in ventilation to less than 10% for a duration of twice the average NREM non-CSR breath length as apnea, whereas most studies have stipulated a period of 10 seconds to define apnea. The majority of apneas in our studies were, in fact, more than 10 seconds in duration. Second, transcutaneous CO_2 measurements were not made because we were uncertain as to whether they would accurately reflect changes in $PaCO_2$ given the poor peripheral perfusion often found in patients with severe heart failure. Third, the unrandomized design and the "unblindedness" of the protocol (the reasons for which were stated in the Methods section) have implications (discussed below) when interpreting sleep architecture and subjective quality of sleep, but we do not believe that they impact upon the validity of the results of respiratory variables, most of which were gated to specific sleep states or stages. In addition, in one test patient prior to the formal protocol being undertaken, intermittent inhaled F_ICO_2 = 0.03 eradicated CSR only during periods of CO_2 administration and not at other times with the face mask still *in situ* and F_ICO_2 of zero. In a previous preliminary study (24), 3% CO_2 was administered by the nasal route only, and a variable F_ICO_2 occurred because of associated mouth breathing and variability of minute ventilation. The increase in $PaCO_2$ was likely to be less than 1 mm Hg and variable. The uncontrolled administration of 3% CO_2 had only a modest effect on CSR, and the variable F_ICO_2 and any secondary increase in ventilation may have counteracted any beneficial effect. As a result, in this protocol we wished to ensure a constant F_ICO_2 with a tightly fitting face mask, which unfortunately was poorly tolerated.

Inhalation of CO_2 with a constant F_ICO_2 of 0.03 resulted in a 2.8% increase in baseline awake SaO_2. This is partly related to the fact that it virtually abolished CSR with its attendant effects on oxygenation. The unrandomized design and lack of similar conditions on the control and CO_2 nights made interpretation of sleep parameters difficult, but, once again, the reduction in arousal index in stage 1 NREM sleep was consistent with what occurs when CSR is improved by low-flow O_2 therapy (21).

Our study was not designed to determine the precise mechanism(s) by which inhalation of CO_2 ameliorates CSR in CHF. In fact, we cannot exclude the unlikely possibility that CO_2 inhalation might have improved circulation time, although the increase in cycle length (applying to the few cycles that were present) suggests that this was not the case. Previous studies have shown that cycle length is entrained by the circulation time (19,25) and, therefore, if CO_2 inhalation had improved CSR by reducing circulatory delay, then cycle length should have shortened.

Likely mechanisms by which CO_2 inhalation eradicated CSR are prevention of attainment of the CO_2 apnea threshold and the effects of increased ventilation. It has been shown in both passive positive-pressure hyperventilation apnea and simulated high-altitude studies that hypocapnia, not a change in PaO_2, induces apnea and, in the presence of hypoxia, subsequent periodic breathing (13–16). When the $PaCO_2$ crosses the apnea threshold, apnea occurs until the PaO_2 decreases and the $PaCO_2$ increases sufficiently to stimulate respiration once again. In normoxia or hyperoxia, the CO_2 apnea threshold appears to be 3–6 mm Hg below the usual NREM sleep $PaCO_2$ and 1–2 mm Hg below the awake $PaCO_2$. Hypoxia appears to lower the NREM $PaCO_2$ closer to the apnea threshold and, consequently, a reduction in $PaCO_2$ of only 1–2 mm Hg may induce apnea (13,14). The 4–5 mm Hg increase in $PaCO_2$ in this study likely prevented the $PaCO_2$ reaching the apnea threshold, thereby eliminating the factor most likely required for the initiation of periodic breathing.

Increases in ventilation associated with CO_2 inha-

lation will also make $PaCO_2$ more stable despite variations in ventilation, because there will be reduced CO_2 excretion per liter of ventilation and CO_2 production will be unchanged. The increased ventilation associated with CO_2 inhalation has several effects via oxygenation. Increased O_2 stores will result in increased damping, and the increase in PaO_2 will shift the PaO_2 further away from the hyperbolic section of the PaO_2-ventilation curve thereby reducing controller gain (11,12,26–28). Both of these will tend to shift respiratory control from the relatively volatile peripheral chemoreceptors to the more stable central chemoreceptors and, as a result, the ventilatory control system will be inherently more stable.

Because this study focused on whether controlled CO_2 would reduce CSR, a tight face mask was used to administer the CO_2. We expected the deterioration in sleep efficiency. An additional fourth night on the face mask with air would have answered the question of whether it was the CO_2 or the discomfort of the mask that caused this deterioration. The mask system was so uncomfortable, however, that the patients declined an additional fourth night with the face mask alone. Thus this study answered the question of whether CO_2 could reduce CSR while a patient slept, but did not answer the question of whether the CO_2 was responsible for the reduced sleep efficiency. Future studies, which will attempt to raise $PaCO_2$ to similar levels using less invasive methods, will answer the question of whether the elevation of $PaCO_2$ per se was responsible for the reduced sleep efficiency.

CONCLUSION

Elevation of PCO_2 by constant inhalation of F_I = 0.03 virtually abolished CSR during sleep. The improvement in breathing pattern was offset by the severely disruptive effects of the mask system used to control the F_ICO_2. Future studies with less disruptive systems are required to see whether CO_2 inhalation has any practical application to treat insomnia in CSR.

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APPENDIX

Computer analysis of respiratory abdominal motion

The steps involved in the computer analysis are listed below.

1. The data were collected by the acquisition program at a sampling rate of 40 per second, filtered online by a Gaussian reduction filter and stored to a disk file at a sampling rate of 10 per second.
2. A peak processor algorithm was used to detect the start, peak, end and respiratory pause section for each breath.
3. Respiratory pauses less than 0.5 second were removed from the data by adding the time to the preceding expiration. Apneic regions were divided into 0.5-second sections and each section was considered as a breath of zero amplitude.
4. An instantaneous ventilation was calculated by dividing the maximum amplitude of the breath by the length of the breath.
5. An equally spaced time series was derived from the breath-by-breath ventilations at a sample interval of 0.5 second.
6. A running average filter of a length equal to twice the average breath time was applied to the time series data.
7. The filtered time series was scanned for peaks and troughs using a procedure already developed for detection of desaturations in oximetry data.
8. A cycle length was determined as the time between successive peaks of ventilation. The minimum value of the ventilation between peaks was obtained. This minimum was normalized such that the value of the lowest of the two surrounding peaks was set at a value of 100.
9. Each cycle was assigned to the sleep stage prevailing 10 seconds before the peak.
10. The average value for the cycle length and the normalized nadir ventilation along with the minimum, maximum and standard deviations were computed for each sleep stage.
11. The number of cycles per hour for each sleep stage was calculated.
12. The cumulative proportions for the nadir ventilation data for values below 10 and 50% were calculated for each sleep stage.

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