Effects of inhaled CO₂ and added dead space on idiopathic central sleep apnea

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Xie, Ailiang, Fiona Rankin, Ruth Rutherford, and T. Douglas Bradley. Effects of inhaled CO₂ and added dead space on idiopathic central sleep apnea. J. Appl. Physiol. 82(3): 918–926, 1997.—We hypothesized that reductions in arterial Pco₂ (Paco₂) below the apnea threshold play a key role in the pathogenesis of idiopathic central sleep apnea syndrome (ICSAS). If so, we reasoned that raising Paco₂ would abolish apneas in these patients. Accordingly, patients with ICSAS were studied overnight on four occasions during which the fraction of end-tidal CO₂ and transcutaneous Pco₂ were measured: during room air breathing (N1), alternating room air and CO₂ breathing (N2), CO₂ breathing all night (N3), and addition of dead space via a face mask all night (N4). Central apneas were invariably preceded by reductions in fraction of end-tidal CO₂. Both administration of a CO₂-enriched gas mixture and addition of dead space induced 1- to 3-Torr increases in transcutaneous Pco₂, which virtually eliminated apneas and hypopneas; they decreased from 43.7 ± 7.3 apneas and hypopneas/h on N1 to 5.8 ± 0.9 apneas and hypopneas/h during N3 (P < 0.005), from 43.8 ± 6.9 apneas and hypopneas/h during room air breathing to 5.9 ± 2.5 apneas and hypopneas/h of sleep during CO₂ inhalation during N2 (P < 0.01), and to 11.6% of the room air level while the patients were breathing through added dead space during N4 (P < 0.005). Because raising Paco₂ through two different means virtually eliminated central sleep apneas, we conclude that central apneas during sleep in ICSA are due to reductions in Paco₂ below the apnea threshold.

Methods

Patients

Six patients with ICSAS (all men, aged 54–71 yr) were recruited for the study. ICSAS was defined as apneas and hypopneas occurring at a rate of ≧10 apneas and hypopneas/h of sleep, of which at least 75% had to be central in nature, without associated CO₂ retention (a daytime PaCO₂ < 45 Torr), hypoxia (arterial PO₂ > 70 Torr), lung disease, heart failure, neurological disease, or renal dysfunction in association with two or more of the following symptoms: habitual snoring, nocturnal choking, restless sleep, insomnia, or excessive daytime sleepiness. Patients were not permitted to take any stimulants, including caffeinated beverages, for at least 24 h and sedatives for at least 48 h before experiments. Written informed consent was obtained from all the patients, and the experimental protocols were approved by the Human Subjects Review Committee of the University of Toronto.

Experimental Setup

Sleep and ventilatory monitoring. Routine overnight sleep studies were performed on each patient as previously described (30). Sleep stages were identified by electroencephalogram (C3/A2; C4/A1), electrooculogram, and submental electromyogram recordings obtained from surface electrodes and were scored according to standard criteria (23). Movement arousals were defined by standard criteria as an increase in submental electromyographic activity accompanied by an increase in alpha activity or by paroxysmal bursts of high-voltage electroencephalographic activity (23). The electrocardiogram was monitored from a precordial lead. Thoracoabdom-
EFFECT OF CO₂ ON CENTRAL SLEEP APNEA

Apneas were defined by the absence of VT excursion for at least 10 s in the absence of esophageal pressure swings and thoracoabdominal movement. Central hypopneas were defined as a 50% or greater reduction in VT from the baseline value persisting for at least 10 s in the absence of phase shift or paradoxical motion of the rib cage and abdomen and in which esophageal pressure excursions paralleled reductions in VT (16, 29, 30). Apneas and hypopneas that were associated with phase shift or outright paradoxical motion of the rib cage and abdomen and/or progressive increases in esophageal pressure excursions were defined as obstructive. Periodic breathing was defined as at least three consecutive cycles of hyperpnea alternating with central apnea or hypopnea (30). Oxyhemoglobin saturation (SaO₂) was continuously measured by a transcutaneous oximeter (Oxyshuttle, Sensormedics, Anaheim, CA). Transcutaneous Pcco₂ (Ptcco₂) was continuously measured with a transcutaneous monitor (Kontron Medical, Hoffman-La Roche, Basel, Switzerland) with the CO₂ electrode on the anterior chest wall. The instrument was calibrated as previously described in our laboratory (21) and was recalibrated at the end of the study to Pcco₂ of 23 and 55 Torr. The Ptcco₂ during recalcibration at the end of the overnight study was always within 2 Torr of the test-gas value.Expired air was sampled from nasal prongs inside the nares, from which the fraction of end-tidal CO₂ (FETCO₂) was measured by an infrared CO₂ analyzer (model LB-2, Beckman, Schiller Park, IL). The instrument was calibrated at the beginning of each study and recalibrated at the end of the study by using dry gas samples of 3, 5, and 8.4% CO₂. The offset was within 0.1%. Data were recorded on a 16-channel polygraph (model 78D, Grass Instruments, Quincy, MA) at a speed of 1 cm/s. Ptcco₂ and SaO₂ were also recorded on a separate strip-chart recorder (type W-7025A, Linseis, Princeton, NJ) at a speed of 1 cm/min. CO₂ delivery system. The FETCO₂ was determined by mixing a CO₂-enriched gas mixture from the Douglas bag by turning the three-way stopcock, which was, in turn, connected to the inspiratory port of the face mask by vinyl tubing 2 min in length and 17 mm in internal diameter. Therefore, the circuit allowed the subjects to breathe either room air or the CO₂-enriched gas mixture from the Douglas bag by turning the three-way stopcock. Patients expired through the expiratory port of the face mask, which minimized dead space. The concentration of CO₂ in the Douglas bag and the switching of the inspired gas between room air and the CO₂ mixture were controlled by the experimenter in a separate room from the patient to minimize sleep disruption.

Protocol

The studies were conducted on four consecutive nights in the sleep laboratory. The first night (N1) served as a control night, during which patients breathed room air and no face mask was worn. During the second night (N2), patients went to sleep wearing a face mask, initially breathing room air. Once stage 2 (S2) non-rapid-eye-movement (NREM) sleep with recurrent central apneas became established for 5 min, the CO₂-enriched gas mixture was administered for 1 h, after which room air and the CO₂ mixture were alternated at 1-h intervals for the rest of the night. The initial FETCO₂ was 1.3% and was then gradually increased if apneas persisted. Because during the N2 study we found that an FETCO₂ of 1.0–2.0% was sufficient to abolish central apneas in all patients, on the third night (N3), the patients were administered an FETCO₂, slightly higher than during N2 (1.5–2.3%) to ensure that Ptcco₂ was increased at least as much as it was on N2. Four of the six patients agreed to undergo a 4th study night during which they breathed through a face mask with added dead space (N4). After room air breathing for 1 h, the face mask was applied and dead space was added in increments of 100 ml.

Data Analysis

Sleep stages and respiratory events were scored by a single technician. Stable breathing was defined as periods of rhythmic breathing lasting at least 3 min during which there were no apneas or hypopneas. The number of apneas per hour of sleep was defined as the apnea index (AI) and the number of apneas and hypopneas per hour of sleep as the apnea-hypopnea index (AHI). FETCO₂ was taken from the end of the expiratory plateau (11). Baseline FETCO₂ and VT were determined by averaging the FETCO₂ and VT of breaths during stable room air breathing in S2 sleep for 15 min. A 15-min period was chosen because this was the maximum amount of stable breathing in some of the patients. Preapneic FETCO₂ was determined by averaging the FETCO₂ of the last three breaths of the hyperpnea preceding every central apnea in S2 sleep for the N2 study. The mean preapneic FETCO₂ was calculated and the maximum preapneic FETCO₂ was measured for each subject during S2 sleep of the N2 study. The coefficients of variation of FETCO₂, VT and total respiratory cycle length (Ttot) were calculated. For N2, the analysis of breathing parameters was restricted to S2 sleep to control for effects of sleep state on breathing and because central apneas occur predominantly in this sleep stage in patients with ICSA (29, 30). For N1 and N3 studies, however, all sleep and respiratory data were scored and compared. For N4, the effect of adding dead space was analyzed by comparing the respiratory parameters with and without addition of dead space during S2 sleep. Comparisons were made by paired t-tests between conditions of CO₂ inhalation and room air breathing both for N2 and for N1 vs. N3. Because of the low sample size and high variance of baseline parameters among the four patients participating in the dead-space protocol, comparisons between dead-space and room air breathing on N4 were by analysis of variance controlling for differences in baseline values. In addition, during N2, the FETCO₂ for preapneic breaths, during stable breathing during room air breathing
and during stable breathing during CO2 inhalation were compared by analysis of variance for repeated measures with post hoc analysis by Newman-Keuls test to determine where significant differences lay. A P value of < 0.05 was considered to be statistically significant. Data are expressed as means ± SE.

RESULTS

Characteristics of Patients

Table 1 shows the characteristics of patients and their respiratory data from the N1 study. All six patients were men who were slightly overweight. They were normoxic and mildly hypocapnic while awake and had frequent apneas and hypopneas associated with mild O2 desaturation and a low mean PtcCO2 while asleep, as our laboratory has previously described (29, 30). Moreover, apneas and hypopneas occurred predominantly in S2 sleep (80.2% of total apneas and hypopneas) in association with periodic breathing.

CO2 Inhalation Vs. Room Air Breathing During N2

All patients had episodes of stable breathing and periodic breathing while breathing room air. As shown in Fig. 1, compared with stable breathing during room air breathing, the ventilatory pattern during periodic breathing was characterized by higher VT and consequently lower FETCO2 just before the onset of apnea. In fact, reductions in FETCO2 invariably preceded central apneas during S2 sleep. The maximum preapneic FETCO2 in the patients, which should be close to the apneic threshold, was on average 0.29% (2 Torr) lower than baseline FETCO2 during stable breathing in S2 sleep. FETCO2 during stable breathing during room air breathing did not fall lower than this without precipitating a central apnea. In addition, inhalation of the CO2-enriched gas caused an increase in FETCO2 and reduced its variability compared with stable breathing during room air breathing. Similarly, the group data in

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**Table 1. Characteristics of the patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>AH1 (no./h sleep)</th>
<th>MA (no./h sleep)</th>
<th>Awake Blood Gases</th>
<th>CO2 Inhalation Vs. Room Air Breathing During N2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pao2 (Torr)</td>
<td>Paco2 (Torr)</td>
<td>Mean Sleep, SaO2, %</td>
<td>Minimum Sleep, SaO2, %</td>
</tr>
<tr>
<td>1</td>
<td>57</td>
<td>37</td>
<td>37.9</td>
<td>26.8</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>26</td>
<td>27.6</td>
<td>16.6</td>
<td>84</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>35</td>
<td>44.9</td>
<td>25.8</td>
<td>71</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>23</td>
<td>46.8</td>
<td>101</td>
<td>101</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>28</td>
<td>79.1</td>
<td>82</td>
<td>86</td>
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<td>6</td>
<td>71</td>
<td>27</td>
<td>28.8</td>
<td>28.8</td>
<td>25.0</td>
<td>86</td>
</tr>
<tr>
<td>Mean</td>
<td>60</td>
<td>29</td>
<td>44.2</td>
<td>23.4</td>
<td>84</td>
<td>36</td>
</tr>
</tbody>
</table>

All patients were men. BMI, body mass index; AH1, apnea-hypopnea index; MA, movement arousals; Pao2, arterial Po2; Paco2, arterial Po2; SaO2, oxyhemoglobin saturation; PtcCO2, transcutaneous Po2.

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**Fig. 1.** Polysomnographic recordings from 1 patient in stage 2 sleep during alternating room air and CO2 breathing (N2) study. A: stable breathing during room air breathing. B: periodic breathing with central apneas during room air breathing. C: stable breathing while inhaling CO2-enriched gas (fraction of inspired CO2 is 2.2%). Note that fraction of end-tidal CO2 (FETCO2) is lower during preapneic breaths (B) than during stable breathing during either room air or CO2 breathing. In addition, FETCO2 and tidal volume (VT) are higher and variability in VT and FETCO2 among breaths is lower during CO2 breathing than during stable breathing during room air breathing. EOG, electrooculogram; EMGsm, submental electromyogram; EMGat, anterior tibial EMG; SaO2, oxyhemoglobin saturation.
Fig. 2 show that the preapneic FETCO2 was significantly lower than during stable breathing and that FETCO2 was higher during stable breathing during CO2 breathing than during room air breathing. ***P < 0.005 compared with stable breathing during room air breathing. *P < 0.05 compared with stable breathing during room air breathing.

Fig. 3. Comparison of coefficients of variation of VT, total respiratory cycle time (Ttot), and FETCO2 between conditions of stable breathing during room air breathing (solid bars) and during CO2 inhalation (open bars) during stage 2 sleep of N2 study. CO2 inhalation significantly reduced coefficients of variation of VT (from 34.4 ± 6.6 to 13.8 ± 3.8%) and FETCO2 (from 4.7 ± 0.9 to 2.4 ± 0.3%) but not of Ttot (from 11.2 ± 1.3 to 9.2 ± 1.4%). *P < 0.025 compared with stable breathing during room air breathing.

Overnight CO2 Inhalation (N3) Vs. Overnight Room Air Breathing (N1)

Table 3 illustrates that at baseline, sleep was fragmented by frequent movement arousals with reductions in the amounts of slow-wave and rapid-eye-movement (REM) sleep, as one would expect in a sleep apnea disorder (29, 30). However, neither sleep stage distribution nor frequency of movement arousals changed from N1 to N3, but inhalation of CO2 during N3 caused significant increases during sleep in mean PtcCO2 and mean SaO2 of 2.4 Torr and 2.1%, respectively. Furthermore, Table 4 and Fig. 5 demonstrate a reduction in AI and AHI in every patient for all sleep stages except REM sleep. These reductions in AI and AHI were due entirely to significant reductions in central apneas and hypopneas but not to obstructive apneas or hypopneas, which occurred predominantly in REM sleep (Fig. 6).

Dead-Space Night (N4)

Patients spent an average of 0.88 ± 0.40 h of S2 sleep without dead space and 2.44 ± 0.65 h breathing through added dead space. Figure 7 shows a polysomnographic recording from the same patient as shown in Fig. 1 during S2 sleep. It demonstrates that addition of 500 ml of dead space caused an increase in FETCO2 and stabilization of breathing similar to that induced by CO2 inhalation. As shown in Fig. 8, addition of 400–700 ml of dead space to the face mask caused a significant increase in PtcCO2 during S2 sleep, averaging 1.4 Torr, but no significant increase in mean SaO2. The increase in PtcCO2 was accompanied by significant reductions in AI and AHI similar to those seen during CO2 inhalation.

DISCUSSION

The present study provides important insights into the pathophysiology of central apneas during sleep in patients with ICSAS. First, we found that just before the onset of central apneas, FETCO2 fell below the baseline level during stable breathing. This observation indicates that central apneas in ICSAS are critically dependent on reductions in PaCO2 below the apneic threshold because of hyperventilation. Second, confirmation of this mechanism was provided by the observation that raising PaCO2 above the apneic threshold, either by administering a CO2-enriched gas mixture or by adding dead space to a face mask, virtually abolished central apneas and hypopneas in these patients.
Preapneic FETCO₂

Our laboratory previously demonstrated that central sleep apneas in patients with ICSAS were triggered by abrupt increases in ventilation (30) and that patients with ICSAS had significantly lower PaCO₂ during sleep than did normal control subjects (29). These observations strongly suggested that the PaCO₂ of patients with ICSAS during NREM sleep was close to their apneic threshold, such that abrupt increases in V̇I were sufficient to drive PaCO₂ below the apneic threshold. However, in these previous studies, breath-by-breath FETCO₂ was not measured, and, therefore, it was not possible to determine how far PaCO₂ fell before the onset of central apneas. In the present study we have clearly demonstrated that FETCO₂ abruptly decreased below the baseline level just before the onset of central apneas. In the present study we have clearly demonstrated that FETCO₂ abruptly decreased below the baseline level just before the onset of central apneas. This decrease in FETCO₂ averaged 0.70% (~5 Torr), but the maximum FETCO₂ preceding central apneas was only 0.29% (~2 Torr) below the baseline level during stable breathing. These data indicate that the reduction in PaCO₂ required to trigger a central apnea was ~2–3 Torr, which is less than the 3- to 6-Torr reduction below baseline reported to precipitate central apnea in normal subjects during NREM sleep (9, 25). Our findings suggest that PaCO₂ in patients with ICSAS is probably closer to the apneic threshold than it is in normal subjects without ICSAS. In addition, because apneas followed within a few seconds of the reduction in FETCO₂ during the last three breaths of hyperpneas, it is likely that inhibition of the peripheral chemoreceptors played a critical role in the initiation of central apneas because the time course would have been too short for inhibition of the central chemoreceptors. On the other hand, the central chemoreceptors probably played a role in determining the set point for a CO₂ response and the threshold for apnea (5, 9, 25).

If periodic reductions in PaCO₂ were responsible for triggering central apneas in patients with ICSAS, raising PaCO₂ above apneic threshold should eliminate central apneas. Our data confirmed this hypothesis. Although CO₂ has been administered to alleviate central apneas associated with neurological or cardiac diseases (10, 18, 26), after tracheostomy for obstructive sleep apnea (1), and for hypoxia-induced or hyperventilation-induced central apneas in experimental situations (5, 25), in these studies, CO₂ was administered for

Table 2. Night 2 study: CO₂ vs. air during S2 sleep

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Total S2 Time, h</th>
<th>SBT, % of S2</th>
<th>Al, no/h</th>
<th>AH1, no/h</th>
<th>SaO₂, %</th>
<th>PtcCO₂, Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
<td>CO₂</td>
<td>Air</td>
<td>CO₂</td>
<td>Air</td>
<td>CO₂</td>
</tr>
<tr>
<td>1</td>
<td>1.6</td>
<td>2.3</td>
<td>12.5</td>
<td>69.6</td>
<td>7.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>1.7</td>
<td>31.8</td>
<td>94.1</td>
<td>36.5</td>
<td>1.1</td>
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<td>3</td>
<td>2.6</td>
<td>1.7</td>
<td>50.0</td>
<td>94.1</td>
<td>2.4</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>0.8</td>
<td>22.7</td>
<td>100.0</td>
<td>3.2</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>2.7</td>
<td>33.3</td>
<td>55.6</td>
<td>23.9</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>0.6</td>
<td>50.0</td>
<td>100.0</td>
<td>12.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean</td>
<td>2.0</td>
<td>1.6</td>
<td>33.4</td>
<td>85.6</td>
<td>14.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

S2, stage 2; SBT, stable breathing time in S2 sleep (% of total S2 sleep time); Al, apnea index.
only a few minutes, $F_{ETCO_2}$ was not recorded, or sleep stages were not monitored. Moreover, ours is the first study to demonstrate that inhaled CO$_2$ and added dead space virtually eliminate central apneas in patients with ICSAS.

Effects of Alternating Room Air and CO$_2$ Inhalation (N2)

Compared with room air breathing, CO$_2$ inhalation resulted in virtual abolition of central apneas and hypopneas. This improvement was associated with an increase in $P_{TCO_2}$ of only 1.3 Torr and $SaO_2$ by 2.1% during S2 sleep. The concurrent increase in $F_{ETCO_2}$ during CO$_2$ inhalation above that observed during preapneic and stable breathing during room air breathing (Fig. 2) confirmed that CO$_2$ inhalation increased $PaCO_2$. The stabilization of breathing by a small increase in $PaCO_2$ is in agreement with Bersenbrugge and colleagues’ observation (5) that increasing the $FICO_2$ just enough to augment $PaCO_2$ 1–2 Torr could immediately abolish hypoxia-induced central apneas. Therefore, it is reasonable to attribute the abolition of central apneas and hypopneas during CO$_2$ inhalation to an increase in $PaCO_2$.

Another important effect of CO$_2$ inhalation observed during the N$_2$ study was the diminution of the breath-to-breath variability of $VT$ and $F_{ETCO_2}$ (Figs. 1 and 3). This finding is in accord with the previous observation that CO$_2$ inhalation consistently lowers the breath-to-breath amplitudes of the oscillations in arterial pH (2). During breathing of room air, $PaCO_2$ fluctuates from breath to breath in association with fluctuations in $VT$ (3, 27). However, during the breathing of CO$_2$, $PaCO_2$ is more stable and its breath-to-breath oscillations are less affected by $VT$ because alveolar $Pco_2$ is not diluted by inhalation of the CO$_2$-enriched gas as much as it would be by inhalation of room air. The reductions in the breath-to-breath oscillations of $PaCO_2$ and pH stabilize the signals detected by the peripheral chemoreceptors, which leads to stabilization of breathing (20). Because peripheral chemoreceptors respond to breath-to-breath fluctuations of $PaCO_2$ and pH (4, 6, 12), reduced breath-to-breath fluctuations in $PaCO_2$ would stabilize their activity. This effect would be particularly important in patients with ICSAS because they have an increased peripheral ventilatory responsiveness to CO$_2$ compared with healthy control subjects, which tends to destabilize their breathing (29).

Table 3. Data for nights 1 and 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Air Night</th>
<th>CO$_2$ Night</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time asleep, h</td>
<td>5.0 ± 0.4</td>
<td>4.9 ± 0.5</td>
<td>0.85</td>
</tr>
<tr>
<td>SPT, h</td>
<td>6.2 ± 0.4</td>
<td>6.7 ± 0.5</td>
<td>0.27</td>
</tr>
<tr>
<td>W time, %SPT</td>
<td>19.7 ± 5.6</td>
<td>19.7 ± 4.3</td>
<td>0.99</td>
</tr>
<tr>
<td>S1 sleep time, %SPT</td>
<td>5.8 ± 1.2</td>
<td>7.1 ± 2.0</td>
<td>0.64</td>
</tr>
<tr>
<td>S2 sleep time, %SPT</td>
<td>54.2 ± 5.7</td>
<td>54.6 ± 5.4</td>
<td>0.96</td>
</tr>
<tr>
<td>SW time, %SPT</td>
<td>9.1 ± 2.5</td>
<td>9.4 ± 2.1</td>
<td>0.87</td>
</tr>
<tr>
<td>REM time, %SPT</td>
<td>10.6 ± 2.8</td>
<td>8.1 ± 1.6</td>
<td>0.38</td>
</tr>
<tr>
<td>MAI, no./h</td>
<td>23.4 ± 2.1</td>
<td>17.0 ± 2.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Time supine, %SPT</td>
<td>63.7 ± 14.0</td>
<td>67.6 ± 15.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean $SaO_2$ %</td>
<td>93.2 ± 0.5</td>
<td>95.3 ± 0.5</td>
<td>0.045</td>
</tr>
<tr>
<td>Mean $P_{TCO_2}$, Torr</td>
<td>39.6 ± 1.1</td>
<td>43.0 ± 1.3</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Values are means ± SE. SPT, sleep period time; W, awake time during sleep period; S1, stage 1; SW, slow-wave sleep; REM, rapid-eye-movement sleep; MAI, movement arousal index.

Table 4. AHI among sleep stages for nights 1 and 3

<table>
<thead>
<tr>
<th>Stage</th>
<th>Night 1 (RoomAir), no./h</th>
<th>Night 3 (CO$_2$ inhalation), no./h</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>56.1 ± 12.0</td>
<td>22.3 ± 8.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>S2</td>
<td>47.9 ± 8.3</td>
<td>6.0 ± 1.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SW*</td>
<td>28.8 ± 11.0</td>
<td>1.4 ± 0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>REM†</td>
<td>16.6 ± 5.9</td>
<td>9.4 ± 3.4</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Only 5 patients had SW on both nights. †Most apneas and hypopneas in REM were obstructive.

Fig. 5. Individual comparisons of apnea index (AI; ○) and apnea-hypopnea index (AHI; △) for each of the 6 patients between room air breathing (N1) and CO$_2$ breathing all night (N3). Compared with N1, all patients experienced reductions in AI and AHI during N3 (14.3 ± 5.5 vs. 0.7 ± 0.3 apneas/h and 43.7 ± 7.3 vs. 5.8 ± 0.9 apneas and hypopneas/h, respectively). *P < 0.05 and ***P < 0.005 compared with N1.

Fig. 6. Comparisons of central and obstructive AHIs between N1 and N3. Solid bars, air night; open bars, CO$_2$ night. Inhalation of CO$_2$ during N3 reduced central AHI (from 37.4 ± 5.7 to 2.5 ± 1.1; P < 0.005) but not obstructive AHI (from 5.9 ± 2.4 to 4.2 ± 1.0; P = 0.52). ***P < 0.005 compared with N1.
Effects of Overnight CO\textsubscript{2} Inhalation (N3)

The N3 study allowed us to assess the influence of inhaled CO\textsubscript{2} on sleep structure, to analyze the sustained effects of inhaled CO\textsubscript{2} on respiration in all sleep stages, and to distinguish the effects of CO\textsubscript{2} inhalation on central and obstructive respiratory events. First, we did not find significant differences in sleep-state distribution, frequency of movement arousals, or body position between N1 and N3 (Table 3). Therefore, any change in respiration between N1 and N3 could not be attributed to differences in sleep states, the frequency of arousals, or body position. Although we have previously shown that arousals can precipitate central apneas by increasing V\text{t} and lowering PCO\textsubscript{2} (30), during CO\textsubscript{2} inhalation, FETCO\textsubscript{2} did not decrease and, therefore, arousals did not trigger central apneas or hypopneas. Second, we confirmed the finding of the N2 study that raising PaCO\textsubscript{2} by CO\textsubscript{2} inhalation virtually abolished central apneas and hypopneas. However, we extended these findings by showing that the effect of CO\textsubscript{2} inhalation was evident over an entire night and in all sleep stages except REM, where most of the events were obstructive. Third, during the N3 study, we were able to show that in contrast to central events, CO\textsubscript{2} inhalation had no significant effect on the frequency of obstructive apneas or hypopneas, most of which occurred during REM sleep. This finding indicates that CO\textsubscript{2} inhalation did not stabilize periodic breathing in our patients with ICSA primarily by reducing pharyngeal collapsibility (15, 18, 24). Rather, it strengthens the assumption that

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**Fig. 7.** Polysomnographic recordings from same patient as in Fig. 1 during dead-space night (N4) study. A: off dead space. B: on dead space. Patient had periodic breathing with central apneas throughout baseline period while breathing room air, as shown in A. Preapnic FETCO\textsubscript{2} was ~4.5%, similar to that shown in Fig. 1. Later in the night when 500 ml of dead space were added, his FETCO\textsubscript{2} increased to 5.2% and his breathing became stable, as shown in B.

Fig. 8. Changes of mean PtcCO\textsubscript{2} (A), mean SaO\textsubscript{2} (B), AI (C), and AHI (D) from baseline to added dead-space period. In A and B, control values of PtcCO\textsubscript{2} (40.8 Torr) and SaO\textsubscript{2} (95.1%) were taken as zero. In trials with dead space, PtcCO\textsubscript{2} increased significantly by 1.3 ± 0.3 to 42.1 Torr, whereas SaO\textsubscript{2} increased, but not significantly, by 1.0 ± 0.4 to 96.1%. In C and D, changes of AI and AHI with dead space were expressed as percentage of baseline values. With dead space, AI decreased significantly to 5.2% of baseline level (27.1 vs. 1.5 apneas/h), and AHI decreased significantly to 11.6% of baseline level (60.1 vs. 7.1 apneas and hypopneas/h). *P < 0.05 and ***P < 0.005 compared with baseline values.

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central apneas were primarily related to fluctuations of \( \text{PaCO}_2 \), and is compatible with the observation that \( \text{CO}_2 \) inhalation eliminates central apneas in tracheotomized patients (1).

Effects of Added Dead Space (N4)

We demonstrated that addition of 400–700 ml of dead space to the ICSAS patients increased \( \text{FiCO}_2 \) and \( \text{PtcCO}_2 \) to the same degree as did inhalation of the \( \text{CO}_2 \)-enriched gas and, like the \( \text{CO}_2 \)-enriched gas, virtually eliminated central apneas and hypopneas. Thus, it was shown that raising \( \text{PaCO}_2 \) by two independent methods resulted in similar reductions in the frequencies of central apneas and hypopneas. These findings indicate that the most likely mechanism for abolition of central apneas by the addition of dead space was elevation of \( \text{PaCO}_2 \) above the apnea threshold.

The dead-space protocol also provided additional information. During \( \text{CO}_2 \) inhalation because the fraction of inspired \( \text{O}_2 \) (\( \text{FiO}_2 \)) was controlled at 21%, \( \text{SaO}_2 \) increased probably through augmentation of \( \dot{V} \text{I} \) due to \( \text{CO}_2 \) stimulation (Fig 1), by improvement of ventilation-perfusion matching (19), and by elimination of apneas and associated dips in \( \text{SaO}_2 \). However, during dead-space breathing, our patients exhibited no significant change in mean \( \text{SaO}_2 \). This lack of effect of dead space on \( \text{SaO}_2 \) probably arose from the effects of increased \( \dot{V} \text{I} \) and abolition of apneas, which prevented dips in \( \text{SaO}_2 \), vs. the countervailing effect of rebreathing expired air, which reduces \( \text{FiO}_2 \). Therefore, the observations that the ICSAS patients in our study were normoxic awake and had only mild dips of \( \text{SaO}_2 \) during apneas, in combination with the observation that dead space abolished central apneas without increasing mean \( \text{SaO}_2 \) during sleep, argue against a primary role of hypoxia in the pathogenesis of ICSAS. Rather, they strengthen the case that elevation of \( \text{PaCO}_2 \) was the primary mechanism underlying the \( \text{CO}_2 \)-induced and dead space-induced elimination of central sleep apneas. Further evidence for this was provided by previous work from our laboratory in which it was demonstrated that the initiation of periodic breathing was accompanied by increases in \( \text{SaO}_2 \) in association with increases in ventilation and reductions in \( \text{PaCO}_2 \) (30). In addition, Badr et al. (1) showed that central apneas observed after a tracheostomy in a patient with obstructive sleep apnea were not affected by \( \text{O}_2 \) administration but were eliminated by \( \text{CO}_2 \) inhalation. Therefore, the increase in \( \text{SaO}_2 \) during inhalation of the \( \text{CO}_2 \)-enriched gas was more likely the consequence rather than the cause of the abolition of central apneas. Nevertheless, we cannot rule out the possibility that apnea-related desaturation could secondarily facilitate further respiratory system instability in ICSA (20).

Ideally, the four night studies should have been conducted in randomized order. However, for practical reasons, the order of the studies was not randomized. An overnight study during room air breathing was required before any intervention to provide baseline data and to confirm the diagnosis of ICSAS. Hence, the first night served as an acclimatization night and control night. Also, a \( \text{CO}_2 \) titration study was required to determine the \( \text{FiCO}_2 \) required to eliminate central apneas for each patient before the overnight \( \text{CO}_2 \) inhalation study, and this was done on the second night. In addition, considering that two patients were not available for a fourth consecutive night, we gave priority to the \( \text{CO}_2 \) inhalation study and, therefore, we used the third night as the all-night \( \text{CO}_2 \) inhalation study. Although the above four studies were not conducted in random order, this should have no impact on the validity of the outcomes because the effects of \( \text{CO}_2 \) inhalation and addition of dead space were similar on different nights and because during the portions of N2 and N4 when patients were breathing room air, apneas and hypopneas were similar in frequency to N1. The N1 study was performed without a face mask to obtain baseline data with minimal perturbation. However, it should be noted that the AHI during the room air portion of N2, when the patients were wearing a face mask, was identical to N1, suggesting that the face mask had no important effect on breathing pattern. Therefore, comparisons of N3 and N1 can reasonably be made. The two patients who did not agree to undergo the dead-space protocol (patients 3 and 6 in Tables 1 and 2) did so because of the inconvenience. However, this should not affect our results because they did not differ in any important way from the other four patients who completed the protocol.

\( \text{FETCO}_2 \) measurements reflect breath-to-breath alveolar \( \text{CO}_2 \) fraction but are dependent on the generation of sufficient ventilation to obtain an alveolar plateau. Therefore, this technique cannot measure alveolar \( \text{CO}_2 \) fraction during apneas or hypopneas. Accordingly, we used \( \text{PtcCO}_2 \) monitoring as well, which continuously measures \( \text{PtcCO}_2 \) in the presence or absence of ventilation and provides a measure of \( \text{PaCO}_2 \) averaged over time. The two measurements of \( \text{PtcCO}_2 \) and \( \text{FETCO}_2 \) behaved in parallel fashion in our patients. However, during room air breathing, the value of end-tidal \( \text{PCO}_2 \) derived from \( \text{FETCO}_2 \) tends to be lower than \( \text{PaCO}_2 \) (13, 14), whereas \( \text{PtcCO}_2 \) tends to more accurately reflect \( \text{PaCO}_2 \) (21). In addition, during \( \text{CO}_2 \) inhalation, the increase in end-tidal \( \text{PCO}_2 \) is usually 2–3 Torr greater than the increase in \( \text{PaCO}_2 \) (13, 14). This explains why during the N2 study \( \text{PtcCO}_2 \) increased by 1.3 Torr but \( \text{FETCO}_2 \) increased by 0.5% (~3.6 Torr). Thus the use of \( \text{FETCO}_2 \) provides important information about relative changes in \( \text{PaCO}_2 \) but cannot necessarily be considered an accurate reflection of \( \text{PaCO}_2 \). Changes in \( \text{PtcCO}_2 \) likely provided a more accurate reflection of \( \text{PaCO}_2 \).

In summary, we have demonstrated that an abrupt reduction in \( \text{FETCO}_2 \) immediately precedes the onset of the central apneas in patients with ICSAS. Furthermore, we have shown for the first time that inhalation of a \( \text{CO}_2 \)-enriched gas or addition of dead space eliminates central apneas and hypopneas in these patients in association with an increase in \( \text{FETCO}_2 \) and \( \text{PtcCO}_2 \) and a damping of breath-to-breath oscillations of \( \text{FETCO}_2 \). These findings provide compelling evidence that the
mechanism for initiation of central hypopneas and apneas in ICSAS is a reduction in PaCO2 toward or below the apneic threshold, respectively. Our data further indicate that the mechanism for abolition of these events by CO2 inhalation and addition of dead space is by increasing and stabilizing PaCO2 above the apneic threshold. Taken together, these findings indicate that ICSAS is a disorder of respiratory control system instability that is PaCO2 dependent. Although the purpose of this study was not to test the clinical effects of increasing PaCO2, our findings that CO2 inhalation and addition of dead space eliminate central apneas and hypopneas point to their potential as treatments for this disorder. More studies over longer time periods will be required to test the therapeutic potential of these approaches.

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