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

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 or 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. Thoracoabdomi-
inal motion was monitored by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, White Plains, NY). VT was taken as the electrical sum of the rib cage and abdominal displacements, which was calibrated against a spirometer by the two positions-simultaneous equations method (8, 28). Esophageal pressure was assessed by using a balloon-catheter system during the first night to accurately determine apnea type. Central 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 an ear oximeter (Oxyshuttle, Sensormedics, Anaheim, CA). Transcutaneous Pco₂ (Ptco₂) was continuously measured with a transcutaneous monitor (Kontron Medical, Hoffman-LaRoche, 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 Pco₂ of 23 and 55 Torr. The Ptco₂ during recalculation 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. Ptco₂ and SaO₂ were also recorded on a separate strip-chart recorder (type C7025A, Linseis, Princeton, NJ) at a speed of 1 cm/min. CO₂ delivery system. The FETco₂ was controlled by mixing a CO₂-enriched gas (3% CO₂-21% O₂-76% N₂) and compressed air in a Douglas bag with a capacity of 120 liters. The bag was maintained partially full during the period of CO₂ inhalation by supplying it with the gas mixture at a flow rate of ~10-15 l/min, which was varied according to each patient’s V̇l. The FETco₂ was measured between 1 and 2.3% by manually controlling the flow rates of the two gas streams. The patients breathed through a tight-fitting face mask, with separate inspiratory and expiratory valves (Downs CPAP Mask, Vital Signs). The Douglas bag was connected to a three-way stopcock, which was, in turn, connected to the inspiratory port of the face mask by vinyl tubing 2 min 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.

Dead-space system. The dead-space system consisted of a face mask with a single opening onto which were fitted various lengths of wide-bore tubing (65-mm ID) fitted to the port of the face mask (20-mm ID) to increase the FETco₂ by the rebreathing of expired gas. At the maximum volume used (700 ml), the dead-space apparatus had a negligible resistance (0.1 cmH₂O·l⁻¹·s⁻¹ at 3 Hz and 0.2 cmH₂O·l⁻¹·s⁻¹ at 7 Hz) measured by an airway hypersensitivity monitor (Astograph model TCK-6000M, Chest, Tokyo, Japan).

Protocol

The studies were conducted on four consecutive nights in the sleep laboratory. The first night (N1) served as a control night, during which 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% 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 Ptco₂ 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 V̇l were determined by averaging the FETco₂ and V̇l 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, V̇l 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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>AHÍ, no./h sleep</th>
<th>MA, no./h sleep</th>
<th>Pao₂, Torr</th>
<th>Pco₂, Torr</th>
<th>pH</th>
<th>Mean Sleep, SaO₂, %</th>
<th>Minimum Sleep, SaO₂, %</th>
<th>Mean Sleep, PtcCO₂, Torr</th>
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<td>37</td>
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<td>44.2</td>
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<td>7.44</td>
<td>93.2</td>
<td>85.7</td>
<td>39.6</td>
</tr>
</tbody>
</table>

All patients were men. BMI, body mass index; AHÍ, apnea-hypopnea index; MA, movement arousals; Pao₂, arterial Po₂; Pco₂, arterial Pco₂; SaO₂, oxyhemoglobin saturation; PtcCO₂, transcutaneous Pco₂.
Fig. 2. Group data for F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} during stable breathing (SB) and preapneic breathing while inhaling room air and during SB while inhaling CO\textsubscript{2} on N\textsubscript{2} during stage 2 sleep. Preapneic F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} (4.6 ± 0.2%) was significantly lower than F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} during stable breathing during inhalation of room air (5.3 ± 0.2%) or CO\textsubscript{2} (5.8 ± 0.1%). F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} was higher during stable breathing during CO\textsubscript{2} breathing than during room air breathing. ***P < 0.005 compared with stable breathing during room air and CO\textsubscript{2} 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 (T\textsubscript{tot}), and F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} between conditions of stable breathing during room air breathing (solid bars) and during CO\textsubscript{2} inhalation (open bars) during stage 2 sleep of N\textsubscript{2} study. CO\textsubscript{2} inhalation significantly reduced coefficients of variation of VT (from 34.4 ± 6.6 to 13.8 ± 3.8%) and F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} (from 4.7 ± 0.9 to 2.4 ± 0.3%) but not of T\textsubscript{tot} (from 11.2 ± 1.3 to 9.2 ± 1.4%). *P < 0.025 compared with stable breathing during room air breathing.

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, F\textsubscript{ET\textsubscript{CO\textsubscript{2}}} fell below the baseline level during stable breathing. This observation indicates that central apneas in ICSAS are critically dependent on reductions in P\textsubscript{T\textsubscript{tc\textsubscript{CO\textsubscript{2}}}} below the apneic threshold because of hyperventilation. Second, confirmation of this mechanism was provided by the observation that raising P\textsubscript{AC\textsubscript{O\textsubscript{2}}} above the apneic threshold, either by administering a CO\textsubscript{2}-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 V˙I 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. This decrease in FETCO2 averaged 0.70% (±0.5 Torr), but the maximum FETCO2 preceding central apneas was only 0.29% (±0.2 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>
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<tr>
<th>Patient No.</th>
<th>Total S2 Time, h</th>
<th>SBT, % of S2</th>
<th>AI, no/h</th>
<th>AHI, no/h</th>
<th>SaO2, %</th>
<th>PtcCO2, Torr</th>
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<tr>
<td>Air CO2</td>
<td>1.6</td>
<td>12.5</td>
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<td>43.8</td>
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<td>12.7</td>
<td>94.0</td>
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<td>Air CO2</td>
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<td>38.1</td>
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<td>Mean</td>
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<td>93.6</td>
<td>39.3</td>
</tr>
<tr>
<td>P Value</td>
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<td>0.0009</td>
<td>0.047</td>
<td>0.0008</td>
<td>0.0024</td>
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</table>

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

### Effects of Alternating Room Air and \( \text{CO}_2 \) Inhalation (N2)

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

Another important effect of \( \text{CO}_2 \) inhalation observed during the N2 study was the diminution of the breath-to-breath variability of VT and \( \text{FETCO}_2 \) (Figs. 1 and 3). This finding is in accord with the previous observation that \( \text{CO}_2 \) inhalation consistently lowers the breath-to-breath amplitudes of the oscillations in arterial pH (2). During breathing of room air, \( \text{PaCO}_2 \) fluctuates from breath to breath in association with fluctuations in VT (3, 27). However, during the breathing of \( \text{CO}_2 \), \( \text{PaCO}_2 \) is more stable and its breath-to-breath oscillations are less affected by \( \text{VT} \) because alveolar \( \text{PCO}_2 \) is not diluted by inhalation of the \( \text{CO}_2 \)-enriched gas as much as it would be by inhalation of room air. The reductions in the breath-to-breath oscillations of \( \text{PaCO}_2 \) 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 \( \text{PaCO}_2 \), pH (4, 6, 12), and fluctuations in \( \text{PaCO}_2 \) would stabilize their activity. This effect would be particularly important in patients with ICSAS because they have an increased peripheral ventilatory responsiveness to \( \text{CO}_2 \) 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>( \text{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>
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<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>
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<tr>
<td>S1 sleep time, %SPT</td>
<td>5.8 ± 1.2</td>
<td>7.1 ± 2.0</td>
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<tr>
<td>S2 sleep time, %SPT</td>
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<td>54.6 ± 5.4</td>
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<td>9.4 ± 2.1</td>
<td>0.87</td>
</tr>
<tr>
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<td>10.6 ± 2.8</td>
<td>8.1 ± 1.6</td>
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<tr>
<td>MAI, no./h</td>
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<td>0.12</td>
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<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 ( \text{SaO}_2 ), %</td>
<td>93.2 ± 0.5</td>
<td>95.3 ± 0.5</td>
<td>0.045</td>
</tr>
<tr>
<td>Mean ( \text{PtcCO}_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 (CO2 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;0.05</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 \( \text{CO}_2 \) 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, \( \text{CO}_2 \) night. Inhalation of \( \text{CO}_2 \) 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 CO₂ Inhalation (N3)

The N3 study allowed us to assess the influence of inhaled CO₂ on sleep structure, to analyze the sustained effects of inhaled CO₂ on respiration in all sleep stages, and to distinguish the effects of CO₂ 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 V₁ and lowering PCO₂ (30), during CO₂ inhalation, FETCO₂ did not decrease and, therefore, arousals did not trigger central apneas or hypopneas. Second, we confirmed the finding of the N2 study that raising PaCO₂ by CO₂ inhalation virtually abolished central apneas and hypopneas. However, we extended these findings by showing that the effect of CO₂ 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, CO₂ inhalation had no significant effect on the frequency of obstructive apneas or hypopneas, most of which occurred during REM sleep. This finding indicates that CO₂ 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...
central apneas were primarily related to fluctuations of PaCO₂ and is compatible with the observation that CO₂ inhalation eliminates central apneas in tracheostomized patients (1).

Effects of Added Dead Space (N4)

We demonstrated that addition of 400–700 ml of dead space to the ICSAS patients increased FICO₂ and PtcCO₂ to the same degree as did inhalation of the CO₂-enriched gas and, like the CO₂-enriched gas, virtually eliminated central apneas and hypopneas. Thus it was shown that raising PaCO₂ 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 PaCO₂ above the apnea threshold.

The dead-space protocol also provided additional information. During CO₂ inhalation because the fraction of inspired O₂ (FIO₂) was controlled at 21%, SaO₂ increased probably through augmentation of Vl due to CO₂ stimulation (Fig. 1), by improvement of ventilation-perfusion matching (19), and by elimination of apneas and associated dips in SaO₂. However, during dead-space breathing, our patients exhibited no significant change in mean SaO₂. This lack of effect of dead space on SaO₂ probably arose from the effects of increased Vl and abolition of apneas, which prevented dips in SaO₂, vs. the countervailing effect of rebreathing expired air, which reduces FIO₂. Therefore, the observations that the ICSAS patients in our study were normoxemic awake and had only mild dips of SaO₂ during apneas, in combination with the observation that dead space abolished central apneas without increasing mean SaO₂ during sleep, argue against a primary role of hypoxia in the pathogenesis of ICSAS. Rather, they strengthen the case that elevation of PaCO₂ was the primary mechanism underlying the inhaled CO₂-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 SaO₂ in association with increases in ventilation and reductions in PaCO₂ (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 O₂ administration but were eliminated by CO₂ inhalation. Therefore, the increase in SaO₂ during inhalation of the CO₂-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 ICSAS (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 CO₂-titration study was required to determine the FICO₂ required to eliminate central apneas for each patient before the overnight CO₂ 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 CO₂ inhalation study, and, therefore, we used the third night as the all-night CO₂ 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 CO₂ 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 AH1 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.

FETCO₂ measurements reflect breath-to-breath alveolar CO₂ fraction but are dependent on the generation of sufficient ventilation to obtain an alveolar plateau. Therefore, this technique cannot measure alveolar CO₂ fraction during apneas or hypopneas. Accordingly, we used PtcCO₂ monitoring as well, which continuously measures PtcCO₂ in the presence or absence of ventilation and provides a measure of PaCO₂ averaged over time. The two measurements of PtcCO₂ and FETCO₂ behaved in parallel fashion in our patients. However, during room air breathing, the value of end-tidal PCO₂ derived from FETCO₂ tends to be lower than PaCO₂ (13, 14), whereas PtcCO₂ tends to more accurately reflect PaCO₂ (21). In addition, during CO₂ inhalation, the increase in end-tidal PCO₂ is usually 2–3 Torr greater than the increase in PaCO₂ (13, 14). This explains why during the N2 study PtcCO₂ increased by 1.3 Torr but FETCO₂ increased by 0.5% (~3.6 Torr). Thus the use of FETCO₂ provides important information about relative changes in PaCO₂, but cannot necessarily be considered an accurate reflection of PaCO₂. Changes in PtcCO₂ likely provided a more accurate reflection of PaCO₂.

In summary, we have demonstrated that an abrupt reduction in FETCO₂ immediately precedes the onset of the central apneas in patients with ICSAS. Furthermore, we have shown for the first time that inhalation of a CO₂-enriched gas or addition of dead space eliminates central apneas and hypopneas in these patients in association with an increase in FETCO₂ and PtcCO₂ and a dampening of breath-to-breath oscillations of FETCO₂. 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 indi-
cate 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
therapies for this disorder. More studies over longer
time periods will be required to test the therapeutic
potential of these approaches.

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Address for reprint requests: T. D. Bradley 212-10 EN Toronto
Hospital, General Div., 200 Elizabeth St., Toronto, ON, Canada M5G
2C4.

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REFERENCES

refractory sleep apnea with supplemental carbon dioxide. Am. J.

different methods of CO₂ administration on oscillations of arte-

arterial pH with breathing in the cat. J. Appl. Physiol. 26:

and C. B. Wolff. Sensitivity of the carotid body to within-breath

5. Berssenbrugge, A., J. Dempsey, C. Iber, C. J. Skatrud, and
P. Wilson. Mechanisms of hypoxia-induced periodic breathing

chemoreceptor discharge in the control of breathing. Respir.


Schneider, M. A. Cohn, and M. A. Sackner. Validation of respira-
tory inductive plethysmography using different calibration

respiratory rhythm in humans. J. Physiol. (Lond.) 440: 17–33,

10. Dowell, A. R., C. E. Buckley, R. Cohen, R. E. Whalen,
and H. O. Sieker. Cheyne-Stokes respiration: a review of clinical
manifestations and critique of physiological mechanisms. Arch.

Alveolar CO₂ measured by expiration into the rapid infrared gas

12. Dutton, R. E., W. A. Hodson, D. G. Davies, and A. Fen
ner. Effect of the rate of rise of carotid body PO₂ on the time course of

13. Ellingsen, I., K. Liestol, G. Sydnes, A. Hauge, and
G. Nicolaysen. Arterial PCO₂ and lung ventilation in man
exposed to 1–5% CO₂ in the inspired gas. Acta Physiol. Scand.

14. Ellingsen, I., G. Sydnes, A. Hauge, J. A. Zwart, K. Liestol,
and G. Nicolaysen. CO₂ sensitivity in humans breathing 1 or

CO₂ on the response of laryngeal afferents to upper airway

Catterall, C. M. Shapiro, and N. J. Douglas. The sleep

17. Green, J. A. Clinical studies on respiration. iv. Some observa-
tions on Cheyne-Stokes respiration. Arch. Intern. Med. 52:
454–463, 1933.

18. Hugdell, D. W., C. Hendricks, and A. Dadley. Alteration in
obstructive apnea pattern induced by changes in oxygen and

19. Ingram, R. H., G. D. Finlay, and J. M. Bradford. Relationship of
PaCO₂ to airway PCO₂ in dog lungs. J. Appl. Physiol. 40:

20. Khoo, M. C. K., R. E. Kronauer, K. P. Strohl, and A. S.
Slutskey. Factors inducing periodic breathing in humans: a

21. Naughton, M. T., D. C. Benard, A. Tam, R. Rutherford,
and T. D. Bradley. The role of hyperventilation in the pathogenesis of
central sleep apnea in patients with congestive heart failure.

Stokes respiration. J. Physiol. (Lond.) 222 (Proc. xviii–xx,
1905.

minology, Techniques and Scoring System for Sleep Stages of
(Publ. No. 204)

Smith, and P. L. Smith. Reflex modulation of airflow dynamics

25. Skatrud, J. B., and J. A. Dempsey. Interaction of sleep state
and chemical stimuli in sustaining rhythmic ventilation. J. Appl.

M. Ahmed, and M. H. Kryger. Effect of inhaled 3% CO₂ on
Cheyne-Stokes respiration in congestive heart failure. Sleep

Phillipson. Control of expiratory duration by arterial CO₂
oscillations in vagotomized dogs. J. Appl. Physiol. 70: 1586–

and N. J. Douglas. Accuracy of respiratory inductive plethysmo-
graph in measuring tidal volume during sleep. J. Appl. Physiol.

29. Xie, A., R. Rutherford, F. Rankin, B. Wong, and T. D.
Bradley. Hypocapnia and increased ventilatory responsiveness
in patients with idiopathic central sleep apnea. Am. J. Respir.

Bradley. Interaction of hyperventilation and arousal in the
pathogenesis of idiopathic central sleep apnea. Am. J. Respir.