Effects of inhaled CO_2 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 CO_2 and added dead space on idiopathic central sleep apnea. *J. Appl. Physiol.* 82(3): 918–926, 1997.—We hypothesized that reductions in arterial P_{CO_2} (Pa_{CO_2}) below the apnea threshold play a key role in the pathogenesis of idiopathic central sleep apnea syndrome (ICSAS). If so, we reasoned that raising Pa_{CO_2} would abolish apneas in these patients. Accordingly, patients with ICSAS were studied overnight on four occasions during which the fraction of end-tidal CO_2 and transcutaneous P_{CO_2} were measured: during room air breathing (*N1*), alternating room air and CO_2 breathing (*N2*), CO_2 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 CO_2. Both administration of a CO_2-enriched gas mixture and addition of dead space induced 1- to 3-Torr increases in transcutaneous P_{CO_2}, 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 CO_2 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 Pa_{CO_2} through two different means virtually eliminated central sleep apneas, we conclude that central apneas during sleep in ICSA are due to reductions in Pa_{CO_2} below the apnea threshold.

carbon dioxide inhalation; periodic breathing

IDIOPATHIC CENTRAL SLEEP APNEA SYNDROME (ICSAS) is an uncommon disorder characterized by recurrent central apneas during sleep in the absence of ventilatory failure, cardiac failure, or neuromuscular diseases and in association with symptoms of central sleep apnea (7). Central apneas in patients with ICSAS are precipitated by abrupt increases in tidal volume (V_T) and minute ventilation ($\dot{V}_I$), often in association with arousals from sleep, which are accompanied by reductions in P_{CO_2} (30). These observations indicate that central apneas in ICSAS are posthyperventilatory in nature. In addition, our laboratory has previously demonstrated that compared with healthy control subjects, those with ICSAS chronically hyperventilate in association with hypocapnia both while they are asleep and while awake (29). Furthermore, both central and peripheral chemoresponsiveness in patients with ICSAS are increased compared with healthy control subjects, suggesting that increased ventilatory responsiveness to chemical respiratory stimuli may play a role in provoking hyperventilation and hypocapnia (29, 30). Taken together, these data led us to propose that chronic and acute hyperventilation interact in such a way as to precipitate central apneas during sleep: the former may maintain arterial P_{CO_2} (Pa_{CO_2}) close to the apnea threshold, and the latter may drive Pa_{CO_2} below this threshold, resulting in central apneas. Arousals may facilitate this process by causing abrupt increases in $\dot{V}_I$ and reductions in Pa_{CO_2}.

If recurrent reductions in Pa_{CO_2} below the threshold for apnea are the mechanism responsible for central apneas during sleep in patients with ICSAS, we reasoned that raising and maintaining Pa_{CO_2} above the apneic threshold should abolish central apneas in these patients. To test this hypothesis, we examined the effects of raising Pa_{CO_2} on central apneas in patients with ICSAS. This was accomplished either by having them inspire a CO_2-enriched gas mixture or by having them breathe through a face mask with added dead space during sleep to increase the fraction of inspired CO_2 ($F_{I_{CO_2}}$). To this end, patients with ICSAS were studied overnight under four different conditions: *1*) room air breathing; *2*) alternating room air and CO_2 inhalation, *3*) CO_2 inhalation all night, and *4*) breathing through a face mask with added dead space all night.

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 CO_2 retention (a daytime $Pa_{CO_2} \leq$ 45 Torr), hypoxia (arterial $P_{O_2} >$70 Torr), lung disease, heart failure, neurological disease, or renal dysfunction in association with two or more 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. Thoracoabdom-

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 (Sa_{O_2}) was continuously measured by an ear oximeter (Oxyshuttle, Sensormedics, Anaheim, CA). Transcutaneous P_{CO_2} (Ptc_{CO_2}) was continuously measured with a transcutaneous monitor (Kontron Medical, Hoffman-LaRoche, Basel, Switzerland) with the CO_2 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 P_{CO_2} of 23 and 55 Torr. The P_{CO_2} during recalibration 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 CO_2 ($F_{ET_{CO_2}}$) was measured by an infrared CO_2 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% CO_2. 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. Ptc_{CO_2} and Sa_{O_2} were also recorded on a separate strip-chart recorder (type C7025A, Linseis, Princeton, NJ) at a speed of 1 cm/min.

CO_2 delivery system. The $F_{I_{CO_2}}$ was controlled by mixing a CO_2-enriched gas (3% CO_2-21% O_2-76% N_2) and compressed air in a Douglas bag with a capacity of 120 liters. The bag was maintained partially full during the period of CO_2 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 $\dot{V}_I$. The $F_{I_{CO_2}}$ was adjusted 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 m in length and 17 mm in internal diameter. Therefore, the circuit allowed the subjects to breathe either room air or the CO_2-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 CO_2 in the Douglas bag and the switching of the inspired gas between room air and the CO_2 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 $F_{I_{CO_2}}$ by the rebreathing of expired gas. At the maximum volume used (700 ml), the dead-space apparatus had a negligible resistance (0.1 $cmH_2O \cdot l^{-1} \cdot s$ at 3 Hz and 0.2 $cmH_2O \cdot l^{-1} \cdot s$ 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 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 CO_2-enriched gas mixture was administered for 1 h, after which room air and the CO_2 mixture were alternated at 1-h intervals for the rest of the night. The initial $F_{I_{CO_2}}$ was 1% and was then gradually increased if apneas persisted. Because during the *N2* study we found that an $F_{I_{CO_2}}$ of 1.0–2.0% was sufficient to abolish central apneas in all patients, on the third night (*N3*), the patients were administered an $F_{I_{CO_2}}$ slightly higher than during *N2* (1.5–2.3%) to ensure that Ptc_{CO_2} 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). $F_{ET_{CO_2}}$ was taken from the end of the expiratory plateau (11). Baseline $F_{ET_{CO_2}}$ and VT were determined by averaging the $F_{ET_{CO_2}}$ 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 $F_{ET_{CO_2}}$ was determined by averaging the $F_{ET_{CO_2}}$ of the last three breaths of the hyperpnea preceding every central apnea in S2 sleep for the *N2* study. The mean preapneic $F_{ET_{CO_2}}$ was calculated and the maximum preapneic $F_{ET_{CO_2}}$ was measured for each subject during S2 sleep of the *N2* study. The coefficients of variation of $F_{ET_{CO_2}}$, 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 CO_2 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 $F_{ET_{CO_2}}$ for preapneic breaths, during stable breathing during room air breathing

Table 1. *Characteristics of the patients*

Patient No.	Age, yr	BMI, kg/m²	AHI, no./h sleep	MA, no./h sleep	Awake Blood Gases			Mean Sleep, Sa_{O_2}, %	Minimum Sleep, Sa_{O_2}, %	Mean Sleep, Ptc_{CO_2}, Torr
					Pa_{O_2}, Torr	Pa_{CO_2}, Torr	pH			
1	57	37	37.9	26.8	80	35	7.44	90.4	80.0	42.3
2	60	26	27.6	16.6	84	38	7.43	95.6	91.0	36.2
3	61	35	44.9	17.5	71	38	7.43	91.7	81.0	40.5
4	55	23	46.8	25.8	101	37	7.44	94.3	92.0	43.0
5	54	28	79.1	28.8	82	35	7.45	92.9	84.0	38.3
6	71	27	28.8	25.0	86	35	7.44	94.0	86.0	37.0
Mean	60	29	44.2	23.4	84	36	7.44	93.2	85.7	39.6

All patients were men. BMI, body mass index; AHI, apnea-hypopnea index; MA, movement arousals; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; Sa_{O_2}, oxyhemoglobin saturation; Ptc_{CO_2}, transcutaneous P_{CO_2}.

and during stable breathing during CO_2 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 O_2 desaturation and a low mean Ptc_{CO_2} 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.

CO_2 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 V_T and consequently lower $F_{ET_{CO_2}}$ just before the onset of apnea. In fact, reductions in $F_{ET_{CO_2}}$ invariably preceded central apneas during S2 sleep. The maximum preapneic $F_{ET_{CO_2}}$ in the patients, which should be close to the apneic threshold, was on average 0.29% (2 Torr) lower than baseline $F_{ET_{CO_2}}$ during stable breathing in S2 sleep. $F_{ET_{CO_2}}$ during stable breathing during room air breathing did not fall lower than this without precipitating a central apnea. In addition, inhalation of the CO_2-enriched gas caused an increase in $F_{ET_{CO_2}}$ and reduced its variability compared with stable breathing during room air breathing. Similarly, the group data in

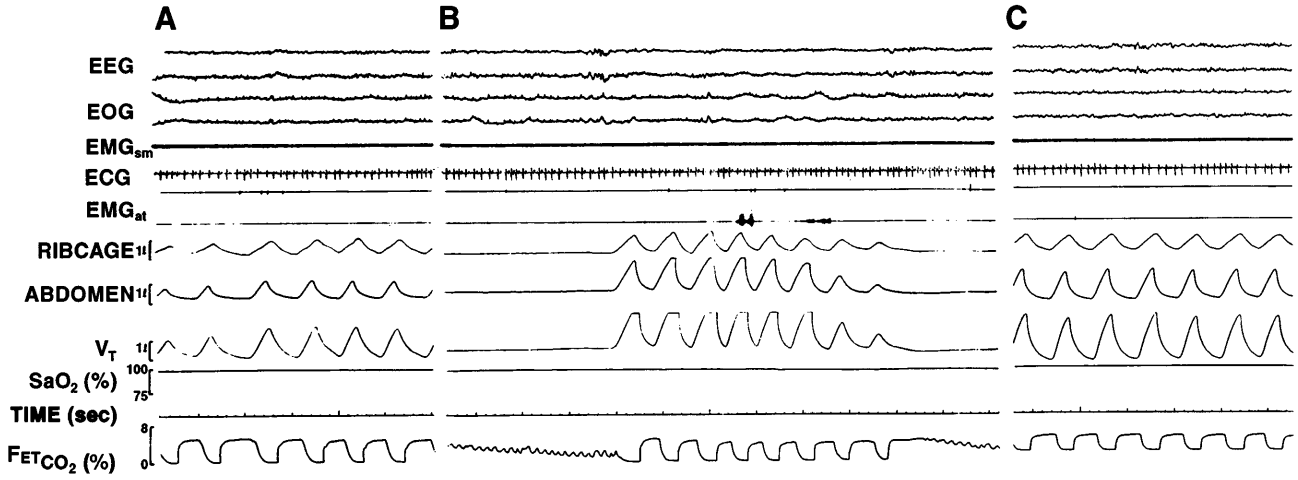

Fig. 1. Polysomnographic recordings from 1 patient in stage 2 sleep during alternating room air and CO_2 breathing (*N2*) study. *A*: stable breathing during room air breathing. *B*: periodic breathing with central apneas during room air breathing. *C*: stable breathing while inhaling CO_2-enriched gas (fraction of inspired CO_2 is 2.2%). Note that fraction of end-tidal CO_2 ($F_{ET_{CO_2}}$) is lower during preapneic breaths (*B*) than during stable breathing during either room air or CO_2 breathing. In addition, $F_{ET_{CO_2}}$ and tidal volume (V_T) are higher and variability in V_T and $F_{ET_{CO_2}}$ among breaths is lower during CO_2 breathing than during stable breathing during room air breathing. EOG, electrooculogram; EMGsm, submental electromyogram; EMGat, anterior tibial EMG; Sa_{O_2}, oxyhemoglobin saturation.

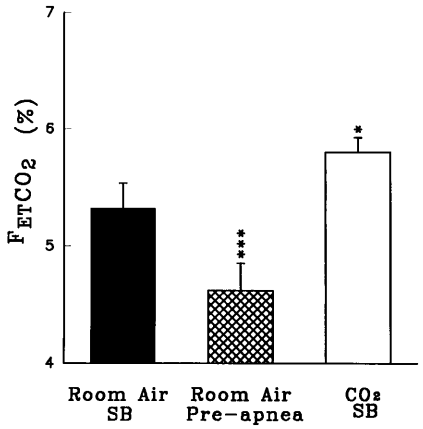

Fig. 2. Group data for $F_{ET_{CO_2}}$ during stable breathing (SB) and preapneic breathing while inhaling room air and during SB while inhaling CO_2 on *N2* during stage 2 sleep. Preapneic $F_{ET_{CO_2}}$ (4.6 ± 0.2%) was significantly lower than $F_{ET_{CO_2}}$ during stable breathing during inhalation of room air (5.3 ± 0.2%) or CO_2 (5.8 ± 0.1%). $F_{ET_{CO_2}}$ was higher during stable breathing during CO_2 breathing than during room air breathing. ***$P < 0.005$ compared with stable breathing during room air and CO_2 breathing. *$P < 0.05$ compared with stable breathing during room air breathing.

Fig. 2 show that the preapneic $F_{ET_{CO_2}}$ was significantly lower than during stable breathing during room air breathing and that $F_{ET_{CO_2}}$ during CO_2 inhalation was higher than during both stable breathing and preapneic breaths. Moreover, group data in Fig. 3 show that CO_2 inhalation reduced the coefficients of variation of VT and $F_{ET_{CO_2}}$ but not of Ttot. The stabilizing effect of CO_2 inhalation on breathing was further evidenced by abolition of periodic breathing and dips in Sa_{O_2} (Fig. 4). Individual data for S2 sleep during the *N2* study are presented in Table 2. Central apneas and hypopneas were virtually abolished by CO_2 inhalation. The few isolated central apneas that were observed during CO_2 inhalation in *patients 2* and *5* occurred as $F_{ET_{CO_2}}$ was being titrated upward and when $F_{ET_{CO_2}}$ decreased below the room air preapneic level. At higher $F_{ET_{CO_2}}$

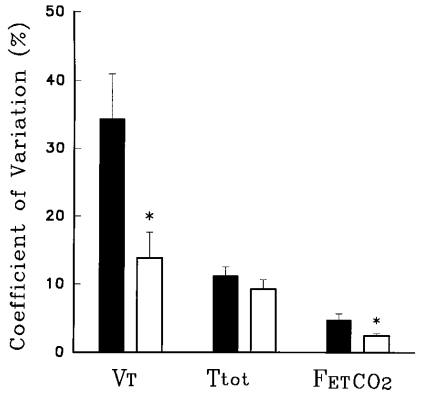

Fig. 3. Comparison of coefficients of variation of VT, total respiratory cycle time (Ttot), and $F_{ET_{CO_2}}$ between conditions of stable breathing during room air breathing (solid bars) and during CO_2 inhalation (open bars) during stage 2 sleep of *N2* study. CO_2 inhalation significantly reduced coefficients of variation of VT (from 34.4 ± 6.6 to 13.8 ± 3.8%) and $F_{ET_{CO_2}}$ (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.

values, this did not occur. Because of the reduction in central events, the proportion of time spent in stable breathing during S2 sleep was significantly longer during CO_2 inhalation than during room air breathing. The improvement of breathing during CO_2 inhalation was associated with significant increases in mean Ptc_{CO_2} and mean Sa_{O_2}, averaging 1.3 Torr and 2.1%, respectively, above the values during room air breathing.

Overnight CO_2 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 CO_2 during *N3* caused significant increases during sleep in mean Ptc_{CO_2} and mean Sa_{O_2} 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 $F_{ET_{CO_2}}$ and stabilization of breathing similar to that induced by CO_2 inhalation. As shown in Fig. 8, addition of 400–700 ml of dead space to the face mask caused a significant increase in Ptc_{CO_2} during S2 sleep, averaging 1.4 Torr, but no significant increase in mean Sa_{O_2}. The increase in Ptc_{CO_2} was accompanied by significant reductions in AI and AHI similar to those seen during CO_2 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, $F_{ET_{CO_2}}$ fell below the baseline level during stable breathing. This observation indicates that central apneas in ICSAS are critically dependent on reductions in Pa_{CO_2} below the apneic threshold because of hyperventilation. Second, confirmation of this mechanism was provided by the observation that raising Pa_{CO_2} above the apneic threshold, either by administering a CO_2-enriched gas mixture or by adding dead space to a face mask, virtually abolished central apneas and hypopneas in these patients.

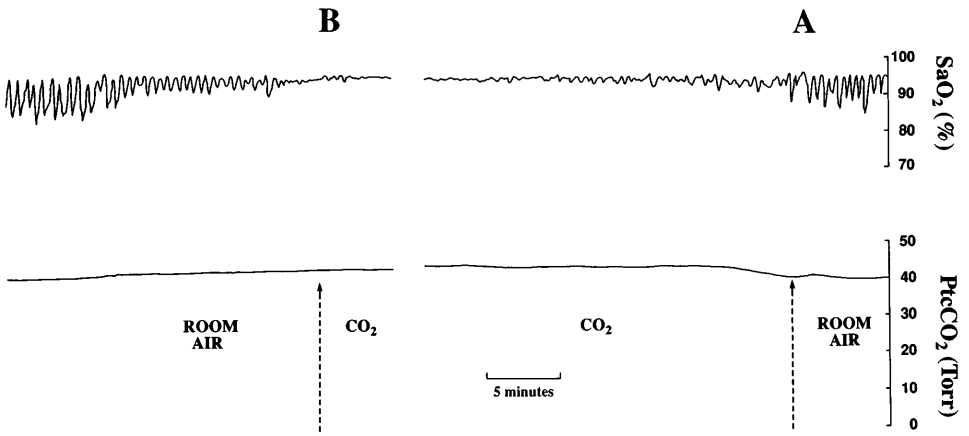

Fig. 4. Recording of Sa_{O_2} (*top*) and transcutaneous P_{CO_2} (Ptc_{CO_2}; *bottom*) from 1 patient in stage 2 sleep during *N2* study. Recording proceeds from *right* to *left*. *A*: transition from air to CO_2. *B*: transition from CO_2 to air. Initially, during room air breathing, Ptc_{CO_2} was 40 Torr, and dips in Sa_{O_2} corresponded with central apneas. With switch from room air to CO_2 breathing (fraction of inspired CO_2 = 1.2%) as indicated by arrow on *right*, Ptc_{CO_2} increased to 43 Torr in association with stabilization of Sa_{O_2} at 95%, which corresponded to abolition of central apneas. Arrow on *left* indicates switching from CO_2 to room air breathing. As Ptc_{CO_2} gradually decreased, Sa_{O_2} again began to fluctuate in association with recurrence of central apneas.

Preapneic $F_{ET_{CO_2}}$

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 Pa_{CO_2} during sleep than did normal control subjects (29). These observations strongly suggested that the Pa_{CO_2} of patients with ICSAS during NREM sleep was close to their apneic threshold, such that abrupt increases in $\dot{V}_I$ were sufficient to drive Pa_{CO_2} below the apneic threshold. However, in these previous studies, breath-by-breath $F_{ET_{CO_2}}$ was not measured, and, therefore, it was not possible to determine how far Pa_{CO_2} fell before the onset of central apneas. In the present study we have clearly demonstrated that $F_{ET_{CO_2}}$ abruptly decreased below the baseline level just before the onset of central apneas. This decrease in $F_{ET_{CO_2}}$ averaged 0.70% (~5 Torr), but the maximum $F_{ET_{CO_2}}$ preceding central apneas was only 0.29% (~2 Torr) below the baseline level during stable breathing. These data indicate that the reduction in Pa_{CO_2} 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 Pa_{CO_2} 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 $F_{ET_{CO_2}}$ 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 CO_2 response and the threshold for apnea (5, 9, 25).

If periodic reductions in Pa_{CO_2} were responsible for triggering central apneas in patients with ICSAS, raising Pa_{CO_2} above apneic threshold should eliminate central apneas. Our data confirmed this hypothesis. Although CO_2 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, CO_2 was administered for

Table 2. *Night 2 study: CO_2 vs. air during S2 sleep*

Patient No.	Total S2 Time, h		SBT, % of S2		AI, no./h		AHI, no./h		Sa_{O_2}, %		Ptc_{CO_2}, Torr	
	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2
1	1.6	2.3	12.5	69.6	7.0	0.0	52.5	12.7	92.3	94.0	37.8	38.5
2	2.2	1.7	31.8	94.1	36.5	1.1	48.2	2.3	95.5	96.7	36.5	38.8
3	2.6	1.7	50.0	94.1	2.4	0.0	27.8	5.4	94.1	96.7	37.9	38.1
4	2.2	0.8	22.7	100.0	3.2	0.0	44.1	1.2	94.6	95.8	43.2	43.7
5	2.1	2.7	33.3	55.6	23.9	3.0	68.3	14.0	92.5	95.3	42.3	44.1
6	1.4	0.6	50.0	100.0	12.3	0.0	21.7	0.0	92.3	95.8	37.8	40.5
Mean	2.0	1.6	33.4	85.6	14.2	0.7	43.8	5.9	93.6	95.7	39.3	40.6
P Value	0.32		0.0009		0.047		0.0008		0.0024		0.023	

S2, stage 2; SBT, stable breathing time in S2 sleep (% of total S2 sleep time); AI, apnea index.

Table 3. *Data for nights 1 and 3*

Parameter	Air Night	CO_2 Night	*P* Value
Total time asleep, h	5.0 ± 0.4	4.9 ± 0.5	0.85
SPT, h	6.2 ± 0.4	6.7 ± 0.5	0.27
W time, %SPT	19.7 ± 5.6	19.7 ± 4.3	0.99
S1 sleep time, %SPT	5.8 ± 1.2	7.1 ± 2.0	0.64
S2 sleep time, %SPT	54.2 ± 5.7	54.6 ± 5.4	0.96
SW time, %SPT	9.1 ± 2.5	9.4 ± 2.1	0.87
REM time, %SPT	10.6 ± 2.8	8.1 ± 1.6	0.38
MAI, no./h	23.4 ± 2.1	17.0 ± 2.6	0.12
Time supine, %SPT	63.7 ± 14.0	67.6 ± 15.0	0.85
Mean Sa_{O_2}, %	93.2 ± 0.5	95.3 ± 0.5	0.045
Mean Ptc_{CO_2}, Torr	39.6 ± 1.1	43.0 ± 1.3	0.013

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.

only a few minutes, FET_{CO_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 Ptc_{CO_2} of only 1.3 Torr and Sa_{O_2} by 2.1% during S2 sleep. The concurrent increase in FET_{CO_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 Pa_{CO_2}. The stabilization of breathing by a small increase in Pa_{CO_2} is in agreement with Berssenbrugge and colleagues' observation (5) that increasing the FI_{CO_2} just enough to augment Pa_{CO_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 Pa_{CO_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 FET_{CO_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, Pa_{CO_2} fluctuates from breath to breath in association with fluctuations in VT (3, 27). However, during the breathing of CO_2, Pa_{CO_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 Pa_{CO_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 Pa_{CO_2} and pH (4, 6, 12), reduced breath-to-breath fluctuations in Pa_{CO_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 4. *AHI among sleep stages for nights 1 and 3*

Stage	*Night 1* (Room Air), no./h	*Night 3* (CO_2 inhalation), no./h	*P* Value
S1	56.1 ± 12.0	22.3 ± 8.9	<0.05
S2	47.9 ± 8.3	6.0 ± 1.0	<0.005
SW*	28.8 ± 11.0	1.4 ± 0.9	<0.05
REM†	16.6 ± 5.9	9.4 ± 3.4	0.32

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

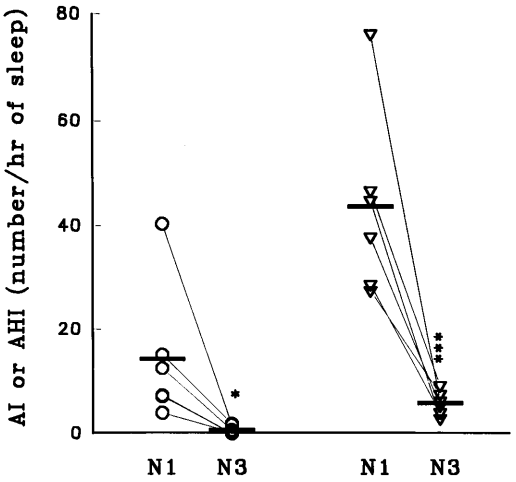

Fig. 5. Individual comparisons of apnea index (AI; ○) and apnea-hypopnea index (AHI; ▽) for each of the 6 patients between room air breathing (*N1*) and CO_2 breathing all night (*N3*). Compared with *N1*, all patients experienced reductions in AI and AHI during *N3* (14.3 ± 5.5 vs. 0.7 ± 0.3 apneas/h 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*.

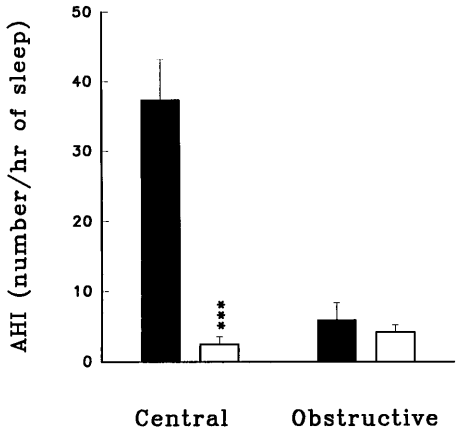

Fig. 6. Comparisons of central and obstructive AHIs between *N1* and *N3*. Solid bars, air night; open bars, CO_2 night. Inhalation of CO_2 during *N3* reduced central AHI (from 37.4 ± 5.7 to 2.5 ± 1.1; $P < 0.005$) but not obstructive AHI (from 5.9 ± 2.4 to 4.2 ± 1.0; $P = 0.52$). ***$P < 0.005$ compared with *N1*.

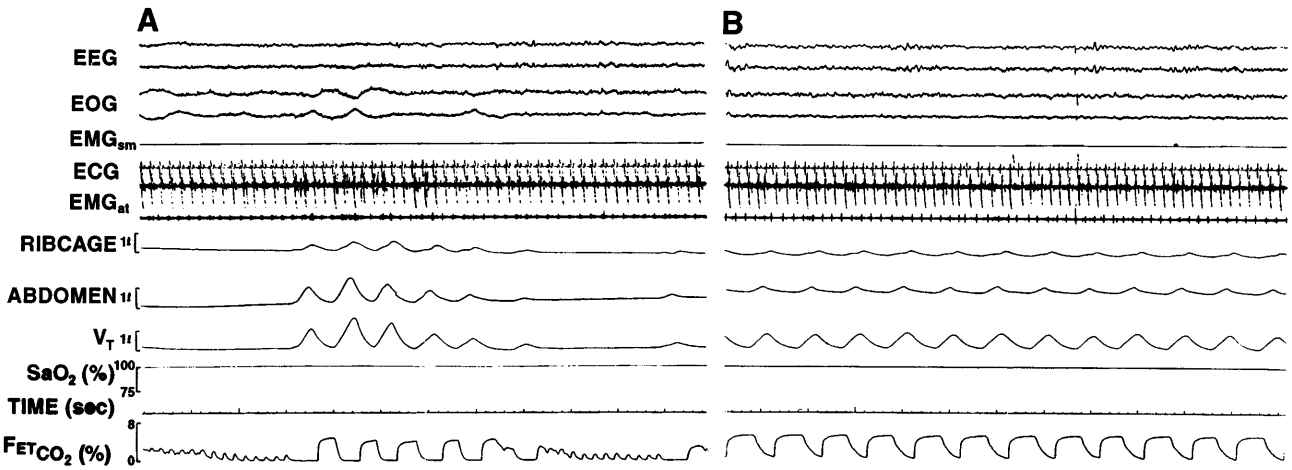

Fig. 7. Polysomnographic recordings from same patient as in Fig. 1 during dead-space night (*N4*) study. *A*: off dead space. *B*: on dead space. Patient had periodic breathing with central apneas throughout baseline period while breathing room air, as shown in *A*. Preapneic $F_{ET_{CO_2}}$ was ~4.5%, similar to that shown in Fig. 1. Later in the night when 500 ml of dead space were added, his $F_{ET_{CO_2}}$ increased to 5.2% and his breathing became stable, as shown in *B*.

Effects of Overnight CO_2 Inhalation (N3)

The *N3* study allowed us to assess the influence of inhaled CO_2 on sleep structure, to analyze the sustained effects of inhaled CO_2 on respiration in all sleep stages, and to distinguish the effects of CO_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 $\dot{V}_I$ and lowering P_{CO_2} (30), during CO_2 inhalation, $F_{ET_{CO_2}}$ did not decrease and, therefore, arousals did not trigger central apneas or hypopneas. Second, we confirmed the finding of the *N2* study that raising Pa_{CO_2} by CO_2 inhalation virtually abolished central apneas and hypopneas. However, we extended these findings by showing that the effect of CO_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_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_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

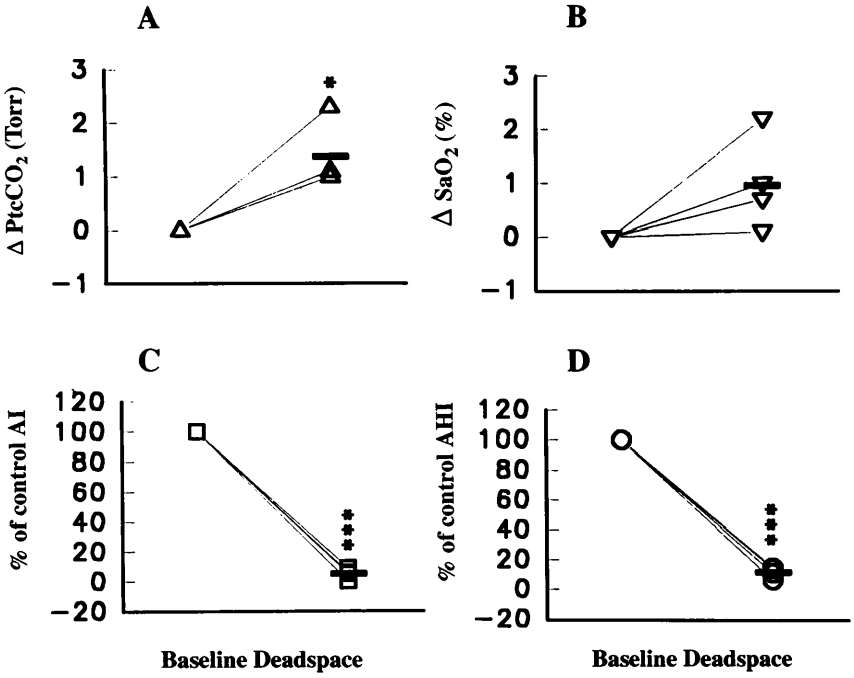

Fig. 8. Changes of mean Ptc_{CO_2} (*A*), mean Sa_{O_2} (*B*), AI (*C*), and AHI (*D*) from baseline to added dead-space period. In *A* and *B*, control values of Ptc_{CO_2} (40.8 Torr) and Sa_{O_2} (95.1%) were taken as zero. In trials with dead space, Ptc_{CO_2} increased significantly by 1.3 ± 0.3 to 42.1 Torr, whereas Sa_{O_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.

central apneas were primarily related to fluctuations of Pa_{CO_2} and is compatible with the observation that 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 FI_{CO_2} and Ptc_{CO_2} to the same degree as did inhalation of the CO_2-enriched gas and, like the CO_2-enriched gas, virtually eliminated central apneas and hypopneas. Thus it was shown that raising Pa_{CO_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 Pa_{CO_2} above the apnea threshold.

The dead-space protocol also provided additional information. During CO_2 inhalation because the fraction of inspired O_2 (FI_{O_2}) was controlled at 21%, Sa_{O_2} increased probably through augmentation of $\dot{V}I$ due to CO_2 stimulation (Fig. 1), by improvement of ventilation-perfusion matching (19), and by elimination of apneas and associated dips in Sa_{O_2}. However, during dead-space breathing, our patients exhibited no significant change in mean Sa_{O_2}. This lack of effect of dead space on Sa_{O_2} probably arose from the effects of increased $\dot{V}I$ and abolition of apneas, which prevented dips in Sa_{O_2}, vs. the countervailing effect of rebreathing expired air, which reduces FI_{O_2}. Therefore, the observations that the ICSAS patients in our study were normoxic awake and had only mild dips of Sa_{O_2} during apneas, in combination with the observation that dead space abolished central apneas without increasing mean Sa_{O_2} during sleep, argue against a primary role of hypoxia in the pathogenesis of ICSAS. Rather, they strengthen the case that elevation of Pa_{CO_2} was the primary mechanism underlying the inhaled 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 Sa_{O_2} in association with increases in ventilation and reductions in Pa_{CO_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 O_2 administration but were eliminated by CO_2 inhalation. Therefore, the increase in Sa_{O_2} during inhalation of the 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 CO_2-titration study was required to determine the FI_{CO_2} required to eliminate central apneas for each patient before the overnight 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 CO_2 inhalation study, and, therefore, we used the third night as the all-night 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 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.

FET_{CO_2} measurements reflect breath-to-breath alveolar CO_2 fraction but are dependent on the generation of sufficient ventilation to obtain an alveolar plateau. Therefore, this technique cannot measure alveolar CO_2 fraction during apneas or hypopneas. Accordingly, we used Ptc_{CO_2} monitoring as well, which continuously measures Ptc_{CO_2} in the presence or absence of ventilation and provides a measure of Pa_{CO_2} averaged over time. The two measurements of Ptc_{CO_2} and FET_{CO_2} behaved in parallel fashion in our patients. However, during room air breathing, the value of end-tidal PCO_2 derived from FET_{CO_2} tends to be lower than Pa_{CO_2} (13, 14), whereas Ptc_{CO_2} tends to more accurately reflect Pa_{CO_2} (21). In addition, during CO_2 inhalation, the increase in end-tidal PCO_2 is usually 2–3 Torr greater than the increase in Pa_{CO_2} (13, 14). This explains why during the *N2* study Ptc_{CO_2} increased by 1.3 Torr but FET_{CO_2} increased by 0.5% (~3.6 Torr). Thus the use of FET_{CO_2} provides important information about relative changes in Pa_{CO_2} but cannot necessarily be considered an accurate reflection of Pa_{CO_2}. Changes in Ptc_{CO_2} likely provided a more accurate reflection of Pa_{CO_2}.

In summary, we have demonstrated that an abrupt reduction in FET_{CO_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 CO_2-enriched gas or addition of dead space eliminates central apneas and hypopneas in these patients in association with an increase in FET_{CO_2} and Ptc_{CO_2} and a dampening of breath-to-breath oscillations of FET_{CO_2}. These findings provide compelling evidence that the

mechanism for initiation of central hypopneas and apneas in ICSAS is a reduction in Pa_{CO_2} toward or below the apneic threshold, respectively. Our data further indicate that the mechanism for abolition of these events by CO_2 inhalation and addition of dead space is by increasing and stabilizing Pa_{CO_2} above the apneic threshold. Taken together, these findings indicate that ICSAS is a disorder of respiratory control system instability that is Pa_{CO_2} dependent. Although the purpose of this study was not to test the clinical effects of increasing Pa_{CO_2}, our findings that CO_2 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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