Cardiorespiratory Effects of Added Dead Space in Patients With Heart Failure and Central Sleep Apnea*

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Background: Inhaled CO₂ has been shown to stabilize the breathing pattern of patients with central sleep apnea (CSA) with and without congestive heart failure (CHF). Added dead space (DS) as a form of supplemental CO₂ was effective in eliminating idiopathic CSA. The efficacy and safety of DS has not yet been evaluated in patients with CHF and CSA.

Methods: We examined the respiratory and cardiovascular effects of added DS in eight patients with CHF and CSA. The DS consisted of a facemask attached to a cylinder of adjustable volume. During wakefulness, the cardiorespiratory response to 200 to 600 mL of DS was tested. Cardiac output and stroke volume were measured using echocardiography with and without DS. During the nocturnal study, patients slept with and without DS, alternating at approximately 1-h intervals.

Results: Values are expressed as the mean ± SE. The wakefulness study revealed a plateau in the partial pressure of end-tidal CO₂ (PETCO₂) and the partial pressure of end-tidal O₂ between DS amounts of 400 and 600 mL. The mean stroke volume index (33 ± 7 vs 34 ± 7 mL/m², respectively) and the mean cardiac index (1.9 ± 0.3 vs 1.9 ± 0.4 L/min/m², respectively) were not affected by DS. Neither heart rate nor BP showed a significant change in response to DS of ≤ 600 mL. During sleep, DS increased the PETCO₂ (40.7 ± 2.7 vs 38.9 ± 2.6 mm Hg, respectively; p < 0.05), reduced apnea (1 ± 1 vs 29 ± 7 episodes per hour, respectively; p < 0.01) and arousal (21 ± 8 vs 30 ± 8 arousals per hour, respectively; p < 0.05), increased the mean arterial oxygen saturation (Sao₂) [94.4 ± 1.0% vs 93.5 ± 1.1%, respectively; p < 0.01], and reduced Sao₂ oscillations (ΔSao₂ from maximum to minimum, 1.8 ± 0.4% vs 5.5 ± 0.9%, respectively; p < 0.01).

Conclusion: DS stabilized CSA and improved sleep quality in patients with CHF without significant acute adverse effects on the cardiovascular function.

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Key words: dead space; heart failure; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; CHF = congestive heart failure; CPAP = continuous positive airway pressure; CSA = central sleep apnea; DS = dead space; FETO₂ = fraction of inspired O₂; FEtCO₂ = fraction of end-tidal CO₂; FICO₂ = fraction of inspired CO₂; PETO₂ = partial pressure of end-tidal O₂; PETCO₂ = partial pressure of end-tidal CO₂; SaO₂ = arterial oxygen saturation; V/Q = ventilation-perfusion; VT = tidal volume

Central sleep apnea (CSA) is a common form of sleep-disordered breathing in patients with congestive heart failure (CHF)¹ and is associated with increased morbidity and mortality.²³ Patients with systolic dysfunction, higher end-diastolic left ventricular volumes, and a greater degree of pulmonary congestion are at increased risk of developing this form of sleep apnea.⁴⁵ The negative cardiovascular effects of CSA are probably related to a combination of episodic hypoxemia, surges in arterial pressure, and frequent arousals.⁶

Therapy with nasal continuous positive airway pressure (CPAP) has been shown to reduce CSA and to reverse some of its negative pathophysiologic consequences, but it is not clear whether these beneficial effects are due to the elimination of the CSA or to a direct effect of CPAP on improving cardiac function.⁷ Compliance with nasal CPAP is also a problem in some patients. Thus, alternative
therapy directly focused at the elimination of CSA would not only clarify the link between CSA and morbidity but also may provide a new therapy for patients who cannot tolerate nasal CPAP.

The narrow difference between eupneic PaCO₂ and the hypocapnic apneic threshold is a critical determinant of the periodic breathing in patients with CHF. Widening this difference by elevating the eupneic PaCO₂ by administering exogenous CO₂ has been highly effective in eliminating CSA in patients with CHF or without CHF. However, the cumbersome delivery system associated with exogenous CO₂ was poorly suited for home use. The alternative of adding a small amount of dead space (DS) has been tested for its ability to stabilize the breathing pattern in patients with idiopathic CSA syndrome. Since DS is able to “boost” PaCO₂ with no requirement for exogenous CO₂, this technique might be more feasible for long-term home use and, therefore, may provide an intriguing approach to therapy for CSA.

We investigated the cardiovascular and ventilatory response to various levels of DS during wakefulness and sleep in patients with CHF and CSA. The daytime DS study enabled us to determine the patient tolerance of the DS system and to titrate the amount of DS needed to normalize the partial pressure of end-tidal CO₂ (PETCO₂). We then evaluated the effectiveness of DS in eliminating CSA along with its short-term effects on cardiac function.

**Materials and Methods**

**Subjects**

We studied eight stable male patients with CHF and recurrent CSA, who had a mean (± SE) age of 64 ± 4 years and a body mass index of 29 ± 2. Pulmonary function tests showed normal arterial blood gas levels (FIO₂ 0.20 ± 0.04; PaCO₂ 39 ± 1 mm Hg; and pH 7.4 ± 0.06) and no obstructive or restrictive abnormalities (FEV₁, 79 ± 4%; FVC, 86 ± 4%; and FEV₁/FVC ratio, 80.3%). Seven patients had ischemic cardiomyopathy, and one patient had dilated cardiomyopathy. The average left ventricular ejection fraction was 26 ± 3%. All patients had an apnea-hypopnea index (AHI) of >15 events per hour of sleep, with at least 75% of the events being of central origin. Seven of the eight patients were receiving therapy with angiotensin-converting enzyme inhibitors and beta-blockers. The University of Wisconsin Health Sciences Human Subjects Committee approved the study, and all patients provided informed written consent prior to entering the study.

**Measurements**

Ventilation was measured during wakefulness with a pneumotachograph (model 5719; Hans Rudolph; Kansas City, MO) coupled to a differential pressure transducer (Validyne; Northridge, CA). ECG was recorded using a monitor (model 78553 B; Hewlett-Packard Medical Products; Andover, MA). An automated sphygmomanometer (Dinamap, 1846SX; Critikon; Tampa, FL) was used to measure BP. Echocardiography was performed with an echocardiography device (SONOS model 5000; Hewlett-Packard Medical Products). Stroke volume was derived from a left ventricular outflow, Doppler flow velocity integral multiplied by the cross-sectional area derived from a parasternal view of a two-dimensional echocardiogram. Five consecutive Doppler flow images were obtained in each individual, and the values were averaged.

Overnight sleep studies were performed on each patient using standard polysomnographic techniques10,12 to identify sleep stage and arousals. Respiratory effort was monitored by respiratory inductive plethysmography (Respitrace; Ambulatory Monitoring Inc; Ardsley, NY) that was calibrated with an isovolumic maneuver. Arterial oxyhemoglobin saturation was measured continuously by pulse oximetry (Biox model No. 3740; Ohmeda; Madison, WI). The fraction of inspired O₂ (FIO₂) and the fraction of inspired CO₂ (FICO₂), as well as the partial pressure of end-tidal O₂ (PETO₂) and PETCO₂ were sampled from the mask and were measured by a gas analyzer (model CD-3A; AMETEK; Pittsburgh, PA), which was calibrated with known gases before and after each experiment. All the signals were recorded continuously for off-line analysis of the data.

Central apneas were identified by the absence of the excursion of the sum tracing of the calibrated inductive plethysmography (ie, tidal volume [VT]) for at least 10 s with no movement of the rib cage or abdomen. The fraction of end-tidal CO₂ (FETCO₂) was used as a secondary method to confirm the plethysmographic output. Obstructive apneas were defined as the absence of VT excursion for >10 s in the presence of paradoxical chest wall motion. Hypopneas were defined by ≥50% reduction in VT with a reduction of arterial oxygen saturation (SaO₂) of >4% for >10 s.

**Protocol**

The DS system (Fig 1) consisted of a tightly sealed facemask attached to an adjustable plastic cylinder. The cylinder consisted of an inner extensible piece. The volume of the system could be increased from 400 to 800 mL by extending the inner piece. Both the cylinder and the inner piece had a relatively large diameter to avoid any resistive load.

**Daytime Study:** This independent evaluation of the cardiorespiratory effects of DS was performed on both the day before and the day after the nocturnal sleep study. On the morning before the nocturnal sleep study, measurement of BP, heart rate, VT, respiratory frequency, and end-tidal gas levels were obtained during a 10-min period of quiet spontaneous room air breathing. Subjects then received DS from 200 to 600 mL in 200-mL increments. Each level of DS was used for 10 min, with baseline measurements repeated at the end of the trial.

In the morning after the nocturnal study, all subjects received an echocardiogram while breathing room air to measure baseline stroke volume and cardiac output. Then the same amount of DS as used during the nocturnal study was applied to each subject for 15 min before repeating the same echocardiographic measurements.

**Nocturnal Study:** Subjects underwent a nocturnal polysomnography that consisted of 30 to 60-min periods of room air breathing alternating with 30 to 60-min periods of DS breathing (Fig 2). Each DS or room air trial was terminated by either awakening the subject when it had lasted 60 min or at the moment when the subject spontaneously awakened after at least 30 min in the same trial. Then a new trial was always started while the subject was awake. DS titration was repeated during the first portion of the night to determine the minimum amount of DS required to stabilize the breathing pattern. All subjects required...
DS levels between 400 and 600 mL, which was within the previously evaluated level of DS during the daytime study. At the end of each trial, throughout the night, an investigator entered the room to either add or remove the DS from the mask, which was left on the patient for the room air trial.

Statistical Analysis

During wakefulness, all cardiovascular and respiratory parameters were measured and averaged at each volume of DS and were compared by using analysis of variance with repeated measurement analysis. When the overall p value was significant, Student-Newman-Keuls post hoc tests were used to identify significant differences at each value of DS. For the nocturnal study, sleep stages and arousals were scored according to standard criteria, with each epoch of 30 s being assigned a single stage score. End-tidal PCO₂ was measured breath-by-breath and was averaged for the last 2-min period of stable breathing after each intervention. For each 1-min epoch of sleep recording, we measured the maximum, minimum, and mean SaO₂ as well as the oscillation of SaO₂ (ie, the difference between maximum and minimum SaO₂ values), and then we averaged each of these measurements during the room air and DS periods. The time to the return to sleep was defined as the time between the beginning of a DS or room air trial, which was always started in wakefulness, and the first 1-min epoch of any sleep stage. This time was measured and averaged for all trials and in both conditions. The comparison of measurements was made during DS breathing and non-DS breathing in non-rapid eye movement sleep using a paired t test. Values were expressed as the mean ± SE.

RESULTS

Effects of DS During Wakefulness

Ventilatory Response: Vt increased with the use of DS, while the respiratory frequency remained unchanged throughout the experiment (Fig 3). With increasing DS, FiCO₂ increased and FIO₂ decreased progressively. The PETCO₂ increased initially (increase with DS of 200 mL, 37.2 ± 1.2 to 39.5 ± 1.1 mm Hg) after which there was no further increase despite the incremental increase in DS. Likewise, no further decrease in PETO₂ was noted beyond the 400-mL DS level.

Cardiovascular Response: With the increase in DS of ≤ 600 mL, no change was noted in heart rate (59 ± 6 vs 62 ± 6 beats/min) or arterial pressure (systolic BP, 116 ± 12 vs 115 ± 9 mm Hg, respectively; diastolic BP, 63 ± 5 vs 61 ± 4 mm Hg, respectively). On the morning after the nocturnal sleep study, echocardiography showed no difference between control and DS breathing in either stroke volume index (34 ± 7 vs 33 ± 7 mL/m², respectively) or cardiac index (1.9 ± 0.4 vs 1.9 ± 0.3 L/min/m², respectively).

Effects of DS During Sleep: Since one subject could not sleep during either room air or DS breathing, the nocturnal study data are reported for the remaining seven patients.

During the nocturnal study, subjects spent a mean duration of 122 ± 68 min breathing DS and 153 ± 63 min breathing room air. Of the total DS time, 100 ± 53 min was sleep time, and of the room air breathing time, 109 ± 59 min was sleep time.

Sleep Quality: The average time to the return to sleep following each spontaneous or investigator-induced awakening was much shorter with DS than with control breathing (11 ± 6 vs 25 ± 9 min, respectively; p < 0.01) [Fig 4]. Sleep stage distribution was not different with and without DS. Predominantly light sleep was present in both conditions,

**Figure 1.** The DS device. The mask is attached via a short connector to the plastic cylinder with extensible inner piece. The extensible inner piece contains a 4-cm hole in the distal end. The device can be adjusted to provide a DS of 200 to 800 mL.
Figure 2. Top, A: nocturnal polygraph of room air and DS breathing. The upper panel shows a segment of room air breathing followed by a segment of breathing through a face mask with 250 mL DS, then an additional 300 mL DS was added to the mask. In the lower panel, the mask and DS were removed, and the subject breathed room air again. The mask alone was added followed by an additional 250 mL DS. The segments with added DS show resolution of the fluctuations in SaO2, VT, and P(ET)CO2, indicating a decrease in arousals, oxygen desaturations, and apneas. Bottom, B: polygraph of the room air (upper panel) and DS segments (lower panel) shown in top, A. The upper panel demonstrates periodic breathing during room air conditions with fluctuations in SaO2, VT, and P(ET)CO2. The lower panel shows that the breathing pattern was stabilized by DS, with an increase in FICO2 of about 2%. No oxygen desaturations or excessive elevation in P(ET)CO2 occurred. VT did not exceed that observed during the hyperpnea phase of room air periodic breathing.
with stage 1 and 2 sleep occupying 70 to 75% of total sleep time. The arousal index decreased significantly with DS breathing compared to control breathing (21 ± 8 vs 30 ± 8 arousals per hour, respectively; p < 0.05) [Fig 4]. Although all patients had a decrease in the arousal index, two patients had a very modest reduction. The persistence of arousals in one of these patients could be attributed to the emergence of obstructive hypopneas after the complete resolution of the central apneas with DS breathing. The other patient had a significant number of nonrespiratory arousals that persisted with DS despite the significant reduction in the number of his respiratory events.

Respiratory Effects: DS breathing resulted in a consistent reduction in the apnea index from 29 ± 7 to 1 ± 1 events per hour (p < 0.01). The AHI also was significantly reduced (43 ± 7 vs 9 ± 4 events per hour, respectively; p < 0.01) [Fig 1, 5]. The Petco2 showed only a slight increase of 1.8 mm Hg during DS breathing compared to non-DS breathing (40.7 ± 2.7 vs 38.9 ± 2.6 mm Hg, respectively; p < 0.05). The minimum Sao2 (93.1 ± 1.0% vs 89.6 ± 1.3%, respectively; p < 0.01) and mean Sao2 (94.4 ± 1.0% vs 93.5 ± 1.1%, respectively; p < 0.01) improved significantly with DS breathing, with no change in the maximum Sao2 (95.0 ± 0.9% vs 94.9 ± 1.1%, respectively; p = 0.47). The magnitude of oscillation in the Sao2 was reduced with the DS breathing as well (ΔSao2 from maximum to minimum, 5.5 ± 0.9% vs 1.8 ± 0.4%, respectively; p < 0.01) [Fig 1, 6].

Cardiovascular Effects: DS breathing did not change the heart rate (65 ± 6 vs 66 ± 6 beats/min, respectively) or the number of ectopic beats (1.5 ± 0.7 vs 1.9 ± 0.8 events per hour) during sleep.

Discussion

The addition of 400 to 600 mL DS to patients with CHF and CSA during sleep resulted in a substantial decrease in AHIs, a reduction in the arousal index, and an improvement in sleep quality. The improvement in nocturnal breathing pattern and sleep quality was associated with a slight, but consistent, increase in Petco2 and Sao2. We consider the elevation of Petco2 as the primary mechanism underlying the DS-induced stabilization of breathing during sleep by keeping Paco2 above the apneic threshold. The virtual elimination of periodic breathing is very likely to account for the improvement of sleep quality and oxygenation. No acute adverse effects of DS breathing on cardiovascular hemodynamics were noted in terms of heart rate, BP, stroke volume, and cardiac index. Added DS has been described as an alternative way to augment PaCO2 and has been used in patients with idiopathic CSA. Because CSA secondary to CHF shares the same tendency toward hyperventilation as idiopathic CSA, a similar therapeutic effect in the present study is not surprising.

Studying CSA in patients with CHF allowed us to extend our previous observations about idiopathic CSA to the examination of the cardiovascular and respiratory effects of added DS in patients with abnormal cardiac function. We also extended our previous studies by examining the dose response of DS during wakefulness, which yielded the following useful information on the potential mechanisms for the beneficial effect of DS in these patients.

First, the addition of DS resulted in an increase in minute ventilation as a result of an increase in the Vt without a change in the breathing frequency. This effect of DS on breathing pattern is consistent with other reports in the literature. Since there is no difference in the Vt and frequency responses to 1,000 mL DS while breathing 100% O2 vs breathing room air, the high Vt breathing patterns appear to be uniquely related to the DS itself. Normally, large breaths are an effective way to clear the DS and to facilitate the entering of fresh air into the lungs during the subsequent breath. The increase in Vt without an associated increase in breathing frequency requires less respiratory muscle work for a given level of Vt than if breathing frequency also increased, as is the case with other ventilatory stimulants including inhaled CO2.18–20 If breaths are large enough during DS breathing, the Fico2 may actually be decreased if the DS is completely emptied with a large breath. In contrast, with exogenous CO2, large breaths are not able to further reduce the Fico2. Thus, while breathing with added DS, patients might subconsciously adopt large breaths to overcome the effect of DS in order to inhale less CO2. However, a potential adverse effect of this DS-induced increase in Vt also could occur. Since our patients were likely to have pulmonary congestion secondary to their severe left heart failure, the deep breaths induced by DS would need to overcome more elastic recoil pressure and thereby increase the work of breathing. In other words, the large breaths observed with added DS serve a useful function if heart function is normal but may be maladaptive in patients with CHF when using DS for the deliberate elevation of Paco2.

Second, the increase in DS was associated with a progressive increase in Fico2 and a progressive decrease in FiO2 However, there was no corre-
sponding increase in PETCO₂ or decrease in PETO₂, even at the higher level of DS (ie, 400 and 600 mL) as would have been expected. This interesting finding was most consistent with an improvement in the matching of ventilation and perfusion. An improvement of the relationship of ventilation-perfusion (V/Q) during DS breathing has been observed in unconscious patients who have received tracheostomies²¹ and in resting anesthetized dogs.²³ In addition to its favorable effect on V/Q matching,²⁴ DS might also promote gas mixing by improving blood flow distribution and reducing the dispersion of the V/Q distribution.²³²⁵

The improvement in gas exchange with added DS...
minimized the adverse effect on oxygenation that would have been expected in response to the increased PETCO₂. We actually found an increase in the mean and minimum SaO₂ in the nocturnal study with DS breathing. Therefore, oxygenation in patients with CSA can be expected to benefit from DS breathing as a result of the elimination of central apnea and from the improvement in gas exchange despite an associated slight increase in PaCO₂. Since hypoxia has been associated with augmented sympathetic nerve traffic and a carryover effect on arterial pressure,26,27 improvement in oxygenation has a potential beneficial effect on two important determinants of prognosis in patients with CHF.

Finally, DS breathing improved sleep quality by decreasing the number of arousals and by shortening the sleep latency following intervention-induced awakenings. The interaction between sleep instability and breathing instability has been well-described.28,29 Frequent arousals and sleep fragmentation often follow recurrent apneas due to the chemical and mechanical stimuli.30 On the other hand, repeated arousals and rapid sleep-state fluctuations facilitate the occurrence of apneas and hypopneas by causing abrupt hypventilation and consequent transient hypocapnia31 and by their direct effect on central neural oscillation.32 DS breathing may be able to break this cycle of instability by initially stabilizing the breathing pattern resulting in a secondary consolidation of the sleep state.

Added DS potentially could be associated with a number of adverse effects. First, DS breathing may increase ventilatory work and potentially may fatigue already compromised respiratory muscles. However, the VT in our patients during DS breathing was actually smaller than the postapneic VT following asphyxie stimulation during room air Cheyne-Stokes breathing (Fig 2). The frequent arousals and the postapneic hyperpneas during CSA may cause equal or even more work of breathing than that associated with DS breathing. Nevertheless, since we did not make precise ventilatory measurements during periodic breathing while the patients were not using DS breathing, we cannot rule out the possibility of an increased workload with added DS.

Second, the elevation of PaCO₂ by DS breathing could induce sympathetic excitation resulting in vasoconstriction, tachycardia, and an increase in myocardial contractility.33 DS-induced hyperventilation also causes the acceleration of heart rate due to the pulmonary vagal inflation reflex.34 This DS-induced cardiac stimulation might lead to poor long-term outcomes and morbidity. However, the increase in norepinephrine levels following the administration of exogenous CO₂ in previous studies35 was associated with a greater increase in end-tidal CO₂ (in-

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21993/ on 06/22/2017)
crease, 4 mm Hg) than was seen in our present study (increase, 1.8 mm Hg) and yielded no improvement in the arousal index. In the present study, DS resulted in a small increase in PETCO₂, which essentially returned the PaCO₂ to normal, eupneic levels and was unlikely to produce large changes in the circulation. In fact, CO₂ usually produces multiple offsetting effects on the cardiovascular system. In addition to its excitatory effect on sympathetic neural activity, it also causes bradycardia and vasodilatation by its direct action on the cardiac pacemaker and the vascular smooth muscle. Consequently, in healthy subjects, cardiac output and heart rate were predictably not affected by DS. In patients with CHF, we did not find any significant increase in either BP or heart rate with a DS of 600 mL during the daytime study. The night study did not show any increase in heart rate or number of ectopic beats with DS application. Although we did not measure BP or sympathetic activities during the nocturnal studies, we attribute the lack of acute negative cardiovascular effects in our nocturnal study to the improvement in apnea index, sleep quality, arousal index, and oxygen saturation.

The practical use of added DS in patients with CHF is associated with several positive and negative considerations. Compared to pharmacologic treatment, the DS is more physiologic. For example, acetazolamide is a respiratory stimulant that is effective in improving the breathing of patients with CSA. However, because it causes metabolic acidosis and has significant side effects, such as urinary frequency and paraesthesias, its usefulness is limited. Compared to exogenous CO₂, DS breathing is a more convenient, natural, and safer means of providing CO₂. Compared to CPAP, DS does not require the use of positive pressure in a tightly sealed mask, which can interfere with patient compliance. However, CPAP is able to improve left ventricular ejection fraction, which also could improve muscle strength independent of its effect on stabilizing the breathing pattern. Hence, DS may be easier to use but not necessarily superior to the use of CPAP. On the negative side, the long-term effect of the elevation of CO₂ is unknown in terms of cardiovascular outcomes and patient compliance. Patients with CHF and CSA are very sensitive to wearing any device on their face. A more comfortable DS system would be needed to replace the present device.

Taken together, the clinical significance of this study

![Figure 5. Effect of DS on apnea and AHI. Apnea was virtually eliminated with DS (29 ± 7 to 1 ± 1 events per hour, respectively). The AHI was also significantly reduced (43 ± 7 to 9 ± 4 events per hour, respectively). * = < 0.05 compared to control breathing.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21993/ on 06/22/2017)
remains uncertain. The approach remains experimental, and it should not be used routinely in clinical practice before a series of careful, long-term, follow-up studies are conducted. A single night study makes cardiorespiratory parameters comparable between room air and DS. The multiple trials in a randomized order avoided any artificial effect. However, the effect of DS breathing on sleep and its architecture has to be further studied in a full night setting.

In summary, our study reported several important conclusions. First, added DS administered through a facemask is a practical modality with which to increase PETCO₂ and to eliminate CSA in patients with CHF. Second, sleep quality improved with the stabilization of the breathing pattern. Third, no acute adverse cardiovascular effects were noted with DS administration. Long-term studies to determine the effect on cardiovascular outcomes and patient compliance are required before the DS device can be recommended for routine use in patients with CHF and CSA.

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