Adaptive servo-ventilation and deadspace: effects on central sleep apnoea

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SUMMARY Central Sleep Apnoea (CSA) occurs commonly in heart failure. Adaptive servo-ventilation (ASV) and deadspace (DS) have been shown in research settings to reverse CSA. The likely mechanism for this is the increase of PaCO2 above the apnoeic threshold. However the role of increasing FiCO2 on arousability remains unclear. To compare the effects of ASV and DS on sleep and breathing, in particular effects on Arousal Index (ArI), ten male patients with heart failure and CSA were studied during three nights with polysomnography plus measurements of PetCO2. The order of the interventions control (C), ASV and DS was randomized. ASV and DS caused similar reductions in apnoea–hypopnoea index [(C) 30.0 ± 6.6, (ASV) 14.0 ± 3.8, (DS) 15.9 ± 4.7 e h−1; both P < 0.05]. However, DS was associated with decreased total sleep time compared with C (P < 0.02) and increased spontaneous ArI compared to C and ASV (both P < 0.01). Only DS was associated with increased ΔPetCO2 from resting wakefulness to eupnic sleep [(C) 2.1 ± 0.9, (ASV) 1.3 ± 1.0, (DS) 5.6 ± 0.5 mmHg; P = 0.01]. ASV and DS both stabilized ventilation however DS application also increased sleep fragmentation with negative impacts on sleep architecture. We speculate that this effect is likely to be mediated by increased PetCO2 and respiratory effort associated with DS application.

KEYWORDS arousability, control of breathing, deadspace, heart failure

INTRODUCTION Central Sleep Apnoea (CSA) occurs commonly in the setting of congestive heart failure (CHF) (Javaheri et al., 1998; Solin et al., 1999). Apnoeas and hypopnoeas during sleep lead to repetitive hypoxia, arousals and excessive sympathetic nervous system activity, which in turn leads to increased cardiac decline in this patient group (Lanfranchi et al., 1999).

To date, a number of options have been investigated for the treatment of Sleep Disordered Breathing (SDB) in CHF, including continuous positive airway pressure (CPAP) (Naughton et al., 1995), bi-level positive pressure ventilation (Teschler et al., 2001), supplemental O2 (Teschler et al., 2001), supplemental CO2 (Andreas et al., 1998; Lorenzi-Filho et al., 1999; Steens et al., 1994; Villiger et al., 1993) and added external deadspace (DS) (Khayat et al., 2003; Xie et al., 1997).

Work by Teschler et al. (2001) has shown adaptive pressure support servo-ventilation (ASV) to be more effective in treating CSA than CPAP, bi-level positive pressure support and supplemental O2 in a group of patients with CHF. ASV provides a varying amount of ventilatory support that acts directly to stabilise ventilation with the aim of improving sleep architecture and sleep quality. It provides a background level of expiratory positive airway pressure (EPAP) to which a variable amount of inspiratory pressure support (IPAP) is added. The pressure support (IPAP-EPAP) applied varies from 4 to 10 cmH2O depending on the subjects’ ventilatory effort. If effort is reduced, ventilatory support is increased and when effort is increased, ventilatory support is reduced. It is the only form of ventilatory support that is specifically designed to maintain ventilation at 90% of the patient’s own...
long-term average ventilation and hence decrease the likelyhood of hyperventilation (Teschler et al., 2001).

Supplemental CO₂ has also been shown to decrease the apnoea–hypopnoea index (AHI) both in patients with idiopathic central sleep apnoea (ICSA) (Xie et al., 1997) and in those with CSA secondary to CHF (Andreas et al., 1998; Lorenzi-Filho et al., 1999; Steens et al., 1994). Xie and colleagues have demonstrated that raising FiCO₂ with an added external DS in patients with ICSA has a similar effect to that induced by inhalation of supplemental CO₂. More recently these researchers have also shown that DS is as effective as supplemental CO₂ in reducing AHI and improving sleep quality in patients with CSA secondary to CHF (Khayat et al., 2003).

It is thought that raising FiCO₂ stabilizes ventilation by keeping PaCO₂ above the apnoeic threshold leading to improvements in sleep quality. However, Andreas et al. (1998) reported that despite reductions in AHI using both supplemental O₂ and CO₂, sleep quality remained poor and sympathetic activation as measured by plasma noradrenalin was high. Indeed, increasing CO₂ has been shown to cause arousal through its effect on increasing ventilatory effort (Gleeson et al., 1990). Ayas et al. (2000) have demonstrated that hypercapnia alone can induce arousal from sleep in the absence of changes in mechanoreceptor activity. Based on these observations, the effect of increasing the level of inspired CO₂ on sleep architecture remains unclear.

In the present study we reasoned that although DS may improve AHI, the accompanying hypercapnia may disrupt sleep. We have compared the effects of ASV and DS on both AHI and sleep architecture in a group of patients with CSA secondary to CHF. We have tested the hypothesis that sleep fragmentation will remain high with the use of DS, despite significant improvements in ventilation.

METHODS
Subjects
Ten male patients with stable CHF and evidence of CSA (AHI > 5 events h⁻¹, with <10% obstructive events on previous polysomnography were recruited for the study. All patients had: maximum oxygen consumption (MVO₂ – determined by symptom limited cardiopulmonary exercise testing) < 30 mL kg⁻¹ min⁻¹, left ventricular ejection fraction (LVEF – determined by echocardiogram) <50% and were classified as New York Health Association (NYHA) class II–III. Patients with unstable arrhythmias or using opiate/sedative drug treatments were excluded, as were patients with severe obstructive or restrictive lung disease (FEV₁, FVC ≤ 65% predicted), periodic leg movements or >10% obstructive events contributing to AHI. No changes to medications occurred during the study period. The Ethics Committee of the Royal Brompton & Harefield NHS Trust approved the study and written informed consent was obtained from each patient.

Measurements
Overnight polysomnography was performed (Jaeger Sleep Data System, Leicester, UK) and manually scored for sleep stages (Rechtschaffen and Kales, 1968) and arousals (Task Force of the American Sleep Disorders Association, 1992) according to standard criteria by a single scorer, blinded to the intervention applied. Arousals were classified as respiratory related if they occurred within 2 s of an apnoea or hypopnoea, and classified as spontaneous arousal if there was no respiratory event preceding it. Arterial oxygen saturation was measured by a pulse oximeter (Nellcor N-200E, Nellcor Inc., Hayward, CA, USA). The 2% dip rate in saturation was calculated as well as mean heart rate from ECG recording during sleep time. Apnoeas were defined as a 90% reduction in respiratory effort, with a 4% desaturation and/or arousal. Hypopnoeas were defined as 50–90% reduction in respiratory effort with a 4% desaturation and/or arousal. In-phase movements of chest and abdomen were used to score central hypopnoes and out of phase movements were scored as obstructive events. End tidal PCO₂ (PetCO₂) was measured using a nasal probe attached to an infrared rapid response capnograph (Morgan Capnograph; Morgan Medical Ltd, Kent, UK). The probe was positioned in the nares to ensure that plateaus were obtained in the signal during expiration. Oro-nasal flow was measured using a thermistor for baseline studies; mask pressure (MCI-3; Validyne Engineering Corporation, Los Angeles, CA, USA) was obtained on the ASV night. On the DS night a pneumotachograph (Fleisch No. 2, Hans Rudolph, Kansas City, MO, USA) attached to a differential pressure transducer (MCI-3; Validyne Engineering Corporation) was used to measure flow. All signals were collected simultaneously on the Spike II data acquisition system (Cambridge Electronic Design Ltd, Cambridge, UK) to allow additional analyses to be performed.

Protocol
All patients were enrolled for a three-night protocol with full polysomnography; one night each of control (C), ASV and added external DS in random order. These studies were conducted 7 ± 1 day apart such that each subject attended the sleep laboratory once per week for three consecutive weeks. Patients were allowed to sleep between 10 pm and 6 am. ASV was administrated using a full facemask (ResMed, North Ryde, Australia) and consisted of 5 cmH₂O EPAP and a minimum to maximum inspiratory support of 4–10 cmH₂O as per manufacturer settings.

The added external DS consisted of a full facemask (ResMed) with a single opening onto which wide-bore tubing with outer diameter of 35 mm was fitted. The total volume of the DS including the mask was approximately 500 mL. This volume has previously been used in our lab to stabilize ventilation in heart failure patients with CSA whilst previous studies have used 400–600 mL of DS to stabilize ventilation (Khayat et al., 2003; Szollosi et al., 2004). On both the ASV
and the DS night, patients had approximately 1 h to familiarize themselves with the apparatus before the studies began. PetCO₂ was measured on a breath by breath basis. The individual means for PetCO₂ were calculated using the fourth and fifth minute from a 5-min stable period of wakefulness without intervention, wakefulness with intervention and during stable eupnic NREM sleep. Only periods with a good plateau in the PetCO₂ trace were used for analysis. Mean minimum SpO₂ was calculated by averaging the minimum saturation associated with all events for each subject and then calculating the group mean. Thus this is the average desaturation associated with events and not the group mean for the single lowest saturation during sleep.

**Statistical analysis**

Based upon an alpha of 0.05 with power of 90% using the following formula: sample size = 16× (standard deviation²) / (difference expected²), a clinically significant difference in arousal index (ArI) of 10 h⁻¹ and SD 8 h⁻¹. The sample size required to show a difference between the two intervention nights with respect to the ArI is 10. We therefore recruited 10 patients for this study.

Statistical comparisons between C, ASV and DS nights were made using repeated measures analysis of variance using Stata9 (StataCorp LP, College Station, TX, USA). If the null hypothesis was rejected (χ < 0.05) we preformed post hoc comparisons using paired t-tests, adjusting for multiple comparisons using the Bonferroni step-down (Holm) adjustment. All data are given as mean ± standard error of mean (SEM).

**RESULTS**

The characteristics of the 10 patients are shown in Table 1 and the effects of intervention on sleep and breathing are presented in Table 2.

Figure 1 shows representative polygraphs, each of approximately 2.5 min duration, from one patient on each study night (C, ASV, DS). Central apnoeas of approximately 25 s in duration are clearly evident on the control night and each event was followed by arousal and desaturation. On the ASV night, respiration was stabilized and there was no evidence of arousals, whilst on the DS night respiration was stabilized but arousals still occur.

Figure 2 shows respiratory event and arousal data for each of the three study nights. Both the ASV and DS caused a similar reduction in AHI [(C) 30.0 ± 6.6, (ASV) 14.0 ± 3.8, (DS) 15.9 ± 4.7 e h⁻¹; both P < 0.05] (panel A). The majority of the events remaining during ASV and DS consisted predominantly of hypopnoeas with the Apnoea Index showing a significant improvement compared with C [(C) 17.0 ± 4.5, (ASV) 5.5 ± 3.2, (DS) 2.5 ± 1.4 e h⁻¹; both P < 0.05] (panel B). Both interventions were associated with similar improvements in ventilation, however DS was associated with a significant increase in ArI when compared with ASV [(C) 39.7 ± 7.3, (ASV) 23.7 ± 2.5, (DS) 38.4 ± 3.9 e h⁻¹; P < 0.005] (panel C). More specifically, the spontaneous ArI was found to be significantly higher with DS compared with both C and ASV [(C) 12.3 ± 3.4, (ASV) 12.3 ± 3.6, (DS) 22.7 ± 1.9 e h⁻¹; both P < 0.01] (panel D). Total sleep time (TST) was significantly decreased by DS compared with C (P < 0.02). Figure 3 shows the effects of intervention on PetCO₂ on each study night. Only DS caused a significant rise in PetCO₂ during wakefulness, which carried over into stable NREM sleep. There was also a moderate correlation between ΔPetCO₂ from wakefulness without intervention to stable eupnic sleep and the spontaneous ArI (r = 0.5). Mean saturation during sleep and the mean of the minimum saturation associated with events was not significantly different between ASV and DS.

**DISCUSSION**

This study is the first study to compare the effect of increasing CO₂ via an added external DS to the use of ASV on sleep architecture, across whole night recordings in a group of CHF patients with CSA. The novel finding is that both ASV and DS stabilized ventilation by a similar magnitude, however DS application was associated with a significant increase in the spontaneous ArI and a disruption of sleep architecture, despite a reduction in respiratory events.

Our results are consistent with the work of Teschler et al. (2001) who have shown that ASV is effective in decreasing AHI and ArI; however, the magnitude of the response in the present study is more modest. The likely explanation for this discrepancy is the shorter acclimatization period that our present study is more modest. The likely explanation for this discrepancy is the shorter acclimatization period that our patients had to pressure and mask use. Similarly, previous investigators (Khayat et al., 2003) have reported a greater reduction in AHI with the use of DS than we have observed in the present study. However, the rise in PetCO₂ with the application of DS was similar to that which occurred in the present study; therefore it is unlikely that we did not increase PetCO₂ sufficiently to exceed the apnoeic threshold. Indeed in the present study, apnoeas were virtually eliminated with DS.
and the contribution of hypopnoeas to the AHI was greatly increased. Instead, we believe that the difference in results of our study compared with those of Khayat et al. (2003) can be explained by the criteria applied to define hypopnoeas. Khayat et al. (2003) used a reduction in respiratory effort associated with a 4% desaturation to define hypopnoeas, whilst in the present study hypopnoeas were scored using a 4% desaturation and/or arousal criteria. We believe that our broader definition of hypopnoeas was responsible for the more modest decrease in AHI associated with the application of DS.

Our findings that DS improved AHI but not ArI are consistent with those of Andreas et al. (1998) who reported that sleep quality remained poor with the use of both supplemental CO2 and O2 despite a reduction in AHI. This is in contrast to the findings of Khayat et al. (2003) who reported a reduction in both AHI and ArI with the addition of external DS. However, these authors did not describe how arousals were defined and therefore it is unclear whether ASDA criteria (Task Force of the American Sleep Disorders Association, 1992) were applied or some other measure such as movement arousal. In the present study, a fixed amount of DS (500 mL) was applied and observations made across whole night recordings to identify the impact of intervention on sleep architecture. It may be argued that the lack of reduction in ArI with DS seen in our study may have been due to some of our patients having too much DS leading to increased arousability – we think that this is unlikely given the AHI we observed. It is however possible, that subsequent respiratory events may have contributed to the spontaneous ArI, or that differences in arousal scoring occurred. Taken together, these studies show that the number of spontaneous arousals is increased by DS application. If DS is to be considered a potential therapeutic option for patients with CSA secondary to CHF, the decrease in AHI and associated respiratory related arousals must outweigh the increase in general arousability and increase in sympathetic activation for patients to see an overall improvement in sleep quality.

The increase in spontaneous arousals that we have observed is in keeping with previous work (Ayas et al., 2000; Gleeson et al., 1990) showing that CO2 can induce arousal from sleep via several mechanisms, including increasing central drive with or without the direct involvement of lung mechanoreceptors. It has also been previously demonstrated that hypercapnic hyperventilation causes increased minute ventilation as well muscle sympathetic nerve activity (Van De Borne et al., 2001) and the application of DS has previously been shown to increase minute ventilation (Khayat et al., 2003). This increase in minute ventilation and therefore the work of breathing is a potential mechanism that may contribute to heightened arousability with DS. Our study was not designed to elucidate which specific mechanisms are involved in the arousal response. However, our results clearly indicate that the application of DS produced a significant increase in PetCO2 during wakefulness which carried over into stable NREM sleep. We speculate that the change in PetCO2 and its association with increased ventilatory drive is an important determinant of increased arousability that we have observed. This suggestion is supported by the observation that the change in PetCO2 from wakefulness without intervention, to eupnic sleep with intervention, showed a moderate positive correlation to the spontaneous ArI.

The application of DS produced a significant increase in eupnic sleep PetCO2 as well as an increase in mean overnight

<table>
<thead>
<tr>
<th>n = 10</th>
<th>Control</th>
<th>ASV</th>
<th>DS</th>
<th>Post hoc (Holm)</th>
<th>C/ASV</th>
<th>C/DS</th>
<th>ASV/DS</th>
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<tbody>
<tr>
<td>TST (h)</td>
<td>4.9 ± 0.4</td>
<td>4.7 ± 0.4</td>
<td>3.8 ± 0.4</td>
<td>0.034</td>
<td>ns</td>
<td>0.013</td>
<td>ns</td>
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<tr>
<td>SE (%)</td>
<td>72.4 ± 5.9</td>
<td>76.9 ± 4.0</td>
<td>64.2 ± 4.2</td>
<td>0.006</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>S1 (% TST)</td>
<td>22.8 ± 4.4</td>
<td>12.6 ± 1.8</td>
<td>20.5 ± 2.0</td>
<td>0.037</td>
<td>0.017</td>
<td>0.034</td>
<td>ns</td>
</tr>
<tr>
<td>SWS (% TST)</td>
<td>7.9 ± 1.8</td>
<td>9.8 ± 1.9</td>
<td>6.0 ± 1.1</td>
<td>0.006</td>
<td>ns</td>
<td>0.020</td>
<td>0.008</td>
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<td>0.034</td>
<td>ns</td>
<td>0.013</td>
<td>ns</td>
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<tr>
<td>Heart rate (sleep)</td>
<td>63.4 ± 2.8</td>
<td>61.3 ± 3.4</td>
<td>63.0 ± 2.5</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>2% DI (h⁻¹)</td>
<td>32.6 ± 7.8</td>
<td>18.6 ± 4.7</td>
<td>20.1 ± 7.3</td>
<td>0.020</td>
<td>0.034</td>
<td>0.038</td>
<td>ns</td>
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<tr>
<td>Mean sleep SpO2</td>
<td>94.8 ± 0.8</td>
<td>96.2 ± 0.5</td>
<td>96.6 ± 0.4</td>
<td>0.024</td>
<td>ns</td>
<td>0.038</td>
<td>ns</td>
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<tr>
<td>Mean min SpO2 (during events)</td>
<td>90.3 ± 1.2</td>
<td>93.2 ± 0.6</td>
<td>93.3 ± 0.6</td>
<td>0.005</td>
<td>0.021</td>
<td>0.007</td>
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<tr>
<td>Eupnic sleep PetCO2</td>
<td>34.8 ± 2.0</td>
<td>34.7 ± 2.2</td>
<td>37.8 ± 1.7</td>
<td>0.043</td>
<td>ns</td>
<td>ns</td>
<td>0.050</td>
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</table>

TST, total sleep time; SE, sleep efficiency; S1, stage 1; S2, stage 2; SWS, slow wave sleep; REM, rapid eye movement; AHI, apnoea-hypopnoea index; AI, apnoea index; ArI, arousal index; RArI, respiratory related arousal index; SArI, spontaneous arousal index; DI, desaturation index; ns, not significant.

Table 2. Effect of interventions on sleep and breathing
SpO\textsubscript{2} during sleep. The increase in mean sleep SpO\textsubscript{2} is explained by the reduction in respiratory events due to raising PetCO\textsubscript{2} above the apnoeic threshold. The sleep-related increase in PetCO\textsubscript{2} during DS application was modest (see Fig. 3) but larger than may have been anticipated given the rise in SpO\textsubscript{2}. However, SpO\textsubscript{2} was measured overnight and as such included periods of apnoea, hypopnoea and hyperpnoea; the eupnic sleep PetCO\textsubscript{2} was sampled from periods of sleep free of apnoeas, hypopnoeas and movement arousals. Therefore our analysis of wake to sleep changes in PetCO\textsubscript{2} reflects the changes in PetCO\textsubscript{2} during periods of ventilatory stability and is not directly comparable with the sleep SpO\textsubscript{2}. We believe the wake-to-sleep change in the PetCO\textsubscript{2} to be an important determinant of the spontaneous ArI and our results confirm that an association exists between the magnitude of the sleep-related increase in PetCO\textsubscript{2} following the application of the DS and the ArI. It is also possible that the increase in PetCO\textsubscript{2} associated with DS application produced an increase in spontaneous arousals due to a slight reduction in FiO\textsubscript{2} as predicted by the alveolar air equation.
In conclusion this study demonstrates that both ASV and DS reduce AHI in CSA due to CHF. ASV also improves objective measures of sleep quality whilst the application of DS increased sleep fragmentation. Our results support previous findings that increasing FiCO₂ reverses SDB but at the cost of enhanced arousability. Finally, the interaction between ventilation, arousability and sympathetic activation needs to be further investigated when considering the effectiveness of treatment options for CSA.

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