Resolution of exercise oscillatory ventilation with adaptive servoventilation in patients with chronic heart failure and Cheyne-Stokes respiration: preliminary study

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Abstract

Background: Exercise oscillatory ventilation (EOV) is a common pattern of breathing in heart failure (HF) patients, and indicates a poor prognosis.

Aim: To investigate the effects of adaptive servoventilation (ASV) on ventilatory response during exercise.

Methods: We studied 39 HF patients with left ventricular ejection fraction (LVEF) ≤ 45. Cardiorespiratory polygraphy, cardiopulmonary exercise testing (CPET), echocardiography, and measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration were performed. Twenty patients with Cheyne-Stokes respiration and apnoea–hypopnoea index (AHI) ≥ 15/h were identified. Of these, 11 patients were successfully titrated on ASV and continued therapy. In the third month of ASV treatment, polygraphy, CPET, echocardiography, and measurement of NT-proBNP concentration were performed again.

Results: The EOV was detected at baseline in 12 (31%) HF patients, including eight (67%) who underwent ASV. The EOV was associated with significantly lower LVEF, peak oxygen uptake (VO₂), and ventilatory anaerobic threshold (VAT), and a significantly higher left ventricular diastolic diameter (LVDD), slope of ventilatory equivalent for carbon dioxide (VE/VCO₂), AHI, central AHI and NT-proBNP concentration. In seven patients with EOV, reversal of EOV in the third month of ASV therapy was observed; only in one patient did EOV persist (p = 0.0156).

Conclusions: The EOV can be reversed with ASV therapy. The EOV in association with central sleep apnoea and Cheyne-Stokes respiration (CSA/CSR) is prevalent in HF patients and correlates with severity of the disease.

Key words: exercise oscillatory ventilation, sleep-disordered breathing

INTRODUCTION

Periodic breathing is a common ventilation pattern in heart failure (HF) patients. It has been observed both during sleep and exercise. The prevalence of central sleep apnoea associated with Cheyne-Stokes respiration (CSA/CSR) and exercise oscillatory ventilation (EOV) in HF patients has been reported to range from 28% to 40%, and from 7% to 35%, respectively [1–6]. Although EOV is present in only a minority of patients with CSA/CSR, almost all EOV patients have CSA/CSR [4]. Both CSA/CSR and EOV have been identified as strong predictors of mortality in HF patients, the latter being the most powerful one of all cardiopulmonary exercise testing-derived variables [4–9].

Adaptive servoventilation (ASV) is a novel effective therapeutic method for reducing CSA. The ASV provides low levels of background expiratory positive airway pressures to...
which a variable amount of inspiratory pressure support is added. The amount of ventilatory support depends on the actual breathing effort of the patient. It has been shown that by correcting periodic breathing, ASV may improve sleep quality and cardiovascular function [10–14]. Because CSA/CSR and EOV appear to have the same underlying pathophysiologic mechanism [4, 15], it seems reasonable to expect that correction of CSA/CSR may reverse EOV.

Therefore, the purpose of the present study was to investigate the effects of ASV on periodic breathing during exercise.

METHODS
Study population and design
We prospectively studied patients with systolic HF due to ischaemic or idiopathic dilated cardiomyopathy referred for sleep study and cardiopulmonary exercise testing (CPET) as part of comprehensive HF evaluation. Eligibility criteria were as follows: (1) echocardiographic left ventricular ejection fraction (LVEF) $\geq 45$%; (2) New York Heart Association (NYHA) class I–III; (3) clinical stability with optimal medical treatment for at least one month; and (4) ability to perform CPET. Exclusion criteria were: (1) acute coronary syndrome within the last month; (2) patients with pacemakers, cardioverter-defibrillators or cardiac resynchronisation devices implanted within the last six months; (3) severe chronic obstructive pulmonary disease; and (4) history of stroke. All patients underwent polygraphy, CPET, echocardiography and determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration. The ASV therapy was offered to patients with moderate to severe CSA/CSR — apnoea-hypopnoea index (AHI) $\geq 15$ and for whom there were no other conventional therapeutic options. In the third month of ASV therapy, polygraphy, CPET, echocardiography and measurement of NT-proBNP concentration were performed again.

Cardiopulmonary exercise testing
Symptom-limited CPET was performed on a cycle ergometer with a ramp protocol that was personalised with the aim of having each patient reach maximum exercise in 7 to 10 min. Breath-by-breath measurements of gas exchange were obtained by a metabolic cart (ZAN 680, ZAN Messgerate Gmbh, Germany). Minute ventilation (VE), oxygen uptake and carbon dioxide output (VCO$_2$) were averaged over 10 s. Peak VO$_2$ was expressed as the mean value of VO$_2$ during the last 60 s of the exercise test. Ventilatory anaerobic threshold (VAT) was detected by the V-slope method. The VE/VCO$_2$ slope was calculated as a linear regression function using the data points from the whole exercise period. Peak oxygen pulse ($O_2$ pulse) was delineated as peak VO$_2$ divided by peak heart rate. The EOV was defined according to the following criteria: (1) three or more regular oscillations in VE; (2) a regular oscillation as defined by the standard deviation of three consecutive cycle lengths within 20% of the average; and (3) minimal average amplitude of ventilatory oscillation of 5 L [7].

Echocardiography
Standard M-mode and two-dimensional (2D) echocardiography and Doppler blood flow measurements were performed in all patients (Vivid 7 Dimension, GE Healthcare, USA). The LVEF was calculated according to Simpson’s method from a 2D apical view.

Sleep study
All patients underwent in-hospital unattended polygraphy (Embleta™, Embla, The Netherlands) with recording of nasal air flow, chest and abdominal movement, pulse oximetry and body position. Analysis was performed automatically using standard software (Somnologica for Embleta™, Embla, The Netherlands) and subsequently reviewed and corrected by a sleep-disordered breathing specialist. Apnoea and hypopnoea were defined according to the American Academy of Sleep Medicine criteria [16]. Apneic events were detected when at least 10 s interval of the air flow signal dropped to $\leq 10$% of baseline. Hypopnoeic events were detected when at least 10 s interval of the air flow signal dropped to $\leq 70$% of baseline in combination with a $\geq 4$% oxygen desaturation. Apnoea and hypopnoea were classified as either central or obstructive, depending on the absence or presence of thorax and abdominal movements. Cheyne-Stokes breathing was scored when there were at least three consecutive cycles of crescendo-decrescendo breathing amplitude with coexisting one of the following: (1) central AHI $\geq 5$; (2) the cyclic crescendo-decrescendo change in breathing amplitude lasted for at least ten consecutive minutes. The CSA/CSR was classified as severe when AHI was at least 30, and moderate when the AHI was at least 15 and less than 30.

NT-proBNP
Blood samples were taken from all patients to determine NT-proBNP concentration (cobas e411, Roche, Switzerland).

Adaptive servoventilation
Servo-ventilation devices provide a mode of pressure support to treat obstructive and complex central sleep apnoea disorders. Dynamic bilevel pressure (BPAP) provides positive airway pressure support to sustain upper-airway patency. The expiratory pressure is set to eliminate obstructive apnoea/hypopnoea during sleep. The ASV device changes the inspiratory pressure above the expiratory pressure as required to normalise patients’ ventilation. When the device detects normal breathing, dynamic BPAP acts like fixed continuous positive airway pressure (CPAP) by providing minimal pressure support; when the patient does not maintain the target peak inspiratory airflow, the device increases the pressure support above the expiratory pressure up to a maximum pressure, which can be set by the user. The device also provides automatic, timed, backup breaths during central apneas. The optimal backup rate is automatically determined by the device (based on the patient’s sleep-disordered breathing presentation).
Therapeutic ASV was delivered from one of two devices (BIPAP AutoSV Advanced, Philips Respironics, Murrysville, PA, USA or AutoSet CS2, ResMed, Sydney, Australia) for three months. The therapy was initiated using the default settings and during the hospital stay was titrated with the aim of reducing the AHI to £10.

The study was approved by the Institutional Review Board of the Military Medical Chamber (IRB followed the Helsinki recommendations, approval number 38/07). All subjects provided informed consent.

**RESULTS**

Between January 2007 and September 2010, 39 patients met the inclusion criteria and were enrolled in this study. Demographic and clinical data for these patients are set out in Table 1. Moderate to severe CSA/CSR was observed in 20 (51%) of the study sample. Ten (26%) of these presented a severe form (AHI ≥30) of sleep-disordered breathing. The EOV was detected in 12 (31%) subjects. Of all EOV patients, ten (83%) had AHI ≥15, while the other two (17%) patients had mild CSA/CSR. Compared to patients without EOV, patients with EOV had a significantly lower LVEF, peak VO2, and VAT, and a significantly higher left ventricular diastolic diameter (LVDD), VE/VCO2 slope, AHI, central AHI and NT-proBNP concentration (Table 1). Moreover, patients with EOV were significantly older and more frequently had permanent atrial fibrillation. There were no significant between-group differences in relation to other demographic and clinical characteristics, including NYHA functional class and O2 pulse (Table 1).

Table 1. Demographic and clinical data of the studied population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population (n = 39)</th>
<th>EOV patients (n = 12)</th>
<th>No-EOV patients (n = 27)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>61 ± 10</td>
<td>67 ± 8</td>
<td>59 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender</td>
<td>39 (100%)</td>
<td>12 (100%)</td>
<td>27 (100%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>30.0 ± 4.9</td>
<td>28.4 ± 4.8</td>
<td>30.7 ± 4.9</td>
<td>0.19</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.4 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>2.3 ± 0.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Ischaemic aetiology</td>
<td>26 (67%)</td>
<td>9 (75%)</td>
<td>17 (63%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (21%)</td>
<td>6 (50%)</td>
<td>2 (7%)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVDD [cm]</td>
<td>31 ± 7</td>
<td>28 ± 6</td>
<td>33 ± 7</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak VO₂ [mL/kg/min]</td>
<td>13.8 ± 4.2</td>
<td>11.4 ± 1.9</td>
<td>14.9 ± 4.4</td>
<td>0.001</td>
</tr>
<tr>
<td>VAT [mL/kg/min]</td>
<td>10.7 ± 2.9</td>
<td>9.5 ± 1.4</td>
<td>11.1 ± 3.3</td>
<td>0.047</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>34.2 ± 8.6</td>
<td>41.1 ± 7.3</td>
<td>31.2 ± 7.4</td>
<td>0.002</td>
</tr>
<tr>
<td>NT-proBNP [pg/mL]</td>
<td>839 (315; 3,101)</td>
<td>3,164 (855; 4,722)</td>
<td>375 (228; 1,143)</td>
<td>0.002</td>
</tr>
<tr>
<td>AHI [h⁻¹]</td>
<td>22.0 ± 16.6</td>
<td>31.1 ± 15.3</td>
<td>17.9 ± 15.7</td>
<td>0.01</td>
</tr>
<tr>
<td>AHI central [h⁻¹]</td>
<td>16.3 ± 16.1</td>
<td>28.2 ± 15.8</td>
<td>11.1 ± 13.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Medications:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>38 (97%)</td>
<td>12 (100%)</td>
<td>26 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>38 (97%)</td>
<td>12 (100%)</td>
<td>26 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diuretics</td>
<td>36 (92%)</td>
<td>12 (100%)</td>
<td>18 (86%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>32 (82%)</td>
<td>11 (92%)</td>
<td>21 (78%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*EOV patients vs no-EOV patients; VO₂ — arterial oxygen saturation; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; LVDD — left ventricle diastolic diameter; VAT — ventilatory anaerobic threshold; VE/VCO₂ slope — slope of ventilatory equivalent for carbon dioxide; NT-proBNP — N-terminal pro-brain natriuretic peptide; AHI — apnoea-hypopnoea index; ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin-II receptor blocker

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**Statistical analysis**

Continuous data are expressed as mean ± SD or as median and first and third quartile in the case of skewed distributions (NT-proBNP). Characteristics of the study groups were compared by an unpaired Student t test or Mann-Whitney U test in case of non-normally distributed data. A Wilcoxon signed rank test or sign test were used for repeated measures (because of small sample size). For qualitative variables, the χ² test with Yates’ correction and Fisher exact test, if necessary, was employed. Statistical differences with a p value < 0.05 were considered significant. All calculations were performed with statistical software (SAS 9.2, SAS Institute Inc., Cary, NC, USA).
Adaptive servoventilation for exercise oscillatory ventilation in heart failure

Of 20 patients with moderate to severe CSA/CSR, 14 patients were offered ASV therapy (the remaining six patients had other conventional therapeutic options such as cardioverter-defibrillator or cardiac resynchronisation device implantation). Two patients declined ASV therapy because of mask intolerance, and one subject for no specific reason. A total of 11 patients were successfully titrated on ASV, continued ASV therapy and underwent a follow-up visit in the third month of therapy. Medical treatment remained unchanged throughout the whole study period.

Resolution of exercise oscillatory ventilation
Eight patients out of 11 treated with ASV had EOV before therapy. The EOV was reversed in seven (86%) patients, and only in one patient did EOV persist (p = 0.0156). An example of the EOV pattern and its resolution is shown in Figure 1.

Sleep study
The AHI normalised during therapy, and resolution of Cheyne-Stokes breathing pattern was observed in all patients. There was a trend towards an improvement in mean nocturnal oxygen saturation, minimum nocturnal oxygen saturation and mean oxygen desaturation, but these did not reach statistical significance (Table 2).

Exercise response
Oxygen pulse increased significantly. There were trends towards an increase in peak oxygen uptake and VAT, but these did not reach statistical significance. The VE/VCO₂ slope did not change significantly (Table 2).

History, echocardiography and NT-proBNP
The LVEF increased significantly. The LVDD remained unchanged. There was a significant fall in the NT-proBNP concentration. There was a trend towards an improvement in NYHA functional class, but this did not reach statistical significance (Table 2).

DISCUSSION
Although periodic breathing during exercise in HF patients was described for the first time over 20 years ago [17], its clinical significance has only recently been appreciated. Recent reports have shown that EOV holds a high prognostic value in HF risk stratification. The EOV is superior to other conventional CPET-derived variables, including peak VO₂ and VE/VCO₂ slope, in predicting mortality and major cardiac events [4–9].

In this prospective study, we have demonstrated resolution of EOV with ASV therapy. Indeed, in all patients except for one treated with ASV, abnormal ventilatory pattern at baseline reversed in the third month of therapy.

The ASV is a novel method of treating patients with CSA/CSR. In our study, the effects of reverting EOV with ASV were accompanied by effective suppression of sleep-disordered breathing. The mechanisms responsible for resolution of EOV with ASV therapy are now a matter of speculation. It seems that periodic breathing both during sleep and exercise are coupled by the same pathophysiological mechanism [4, 15]. Both EOV and CSA/CSR are strictly associated with severity of HF. It has been demonstrated that different methods of therapy improving cardiac function, including medical treatment [18], cardiac surgery [19] and cardiac resynchronisation [20], may resolve sleep-disordered breathing. Only one study has reported reversal of abnormal ventilatory pattern during exercise in three patients treated with milrinone and two patients who underwent heart transplantation [17].

We observed EOV in 31% of patients and all patients with EOV had CSA/CSR. Our findings are similar to previously published data reporting the prevalence of EOV in HF patients of between 7% and 35%, and the coexistence of nocturnal with exertional periodic breathing [4–6]. Our results also confirmed a previously found correlation between EOV and severity of HF and impaired functional capacity [4–9, 21]. In the current study, patients with EOV compared to those without EOV had significantly lower LVEF, peak VO₂,
and VAT, and significantly higher LVDD, VE/VCO₂ slope, AHI, central AHI and NT-proBNP concentration.

The ASV therapy not only reversed EOV and CSR, but also improved LVEF and decreased NT-proBNP concentration, which is in line with the findings of previous studies [10]. On the other hand, there was no significant improvement in NYHA functional class — which is probably a consequence of the short-term follow-up and small study group. Our results support the observation that ASV therapy does not change VE/VCO₂ slope [10].

**Limitations of the study**

The study was uncontrolled, the sample size was small, and the follow-up was short. The study showed that EOV could be reversed with ASV therapy, but the effects of EOV resolution on prognosis are unknown. Further studies are required to address this issue.

**CONCLUSIONS**

The present study provides original observation that periodic breathing during exercise could be reversed with ASV therapy. Because of the limitations of the study, further data is required.

**This study was supported by the Military Institute of Medicine. The ASV devices used in this study were properties of ResMed and Respironics. Neither ResMed nor Respironics had access to the results of the study. The study is a result of a project funded by the National Centre for Science (project number: N N 402 489 840).**

**Conflict of interest: none declared**

**References**

Ustąpienie periodycznego oddychania w czasie wysiłku u pacjentów z przewlekłą niewydolnością serca i oddychaniem typu Cheyne-Stokesa leczonych adaptoserwoventylacją: doniesienie wstępne

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Streszczenie

Wstęp: Periodyczne oddychanie jest częstym zjawiskiem u pacjentów z przewlekłą niewydolnością serca (HF). Występuje ono nie tylko w czasie snu, ale i podczas wysiłku. Periodyczne oddychanie w czasie wysiłku (EOV) jest silnym predyktorem śmiertelności z przyczyn sercowych u pacjentów z HF. Adaptoserwoventylacja (ASV) jest nową metodą leczenia osób z oddychaniem typu Cheyne-Stokesa. Wykazano, że znacznie redukuje ona centralne bezdechy senne i normalizuje patologiczny tor oddychania w czasie snu.

Cel: Celem badania była ocena wpływu ASV na tor oddychania w czasie wysiłku.

Metody: Do badania włączono 39 pacjentów z przewlekłą HF, z frakcją wyrzutową lewej komory (LVEF) £45%. U wszystkich chorych wykonano badanie poligraficzne, ergospirometryczną próbę wysiłkową, badanie echokardiograficzne i oznaczono stężenie N-końcowego propeptydu natriuretycznego typu B (NT-proBNP). Oddychanie typu Cheyne-Stokesa i wskaźnik AHI (apnea–hypopnea) > 15/h stwierdzono u 20 (51%) pacjentów. U 11 spośród nich skutecznie wdrożono leczenie ASV. W 3. miesiącu terapii ponownie wykonano badanie poligraficzne, ergospirometryczną próbę wysiłkową, badanie echokardiograficzne i oznaczono stężenie NT-proBNP.

Wyniki: U 12 (31%) pacjentów z HF stwierdzono EOV, w tym u 8 (67%) leczonych ASV. Chorzy z EOV w porównaniu z osobami z prawidłowym torem oddychania w czasie wysiłku charakteryzowali się istotnie niższą LVEF, szczytowym pochłanianiem tlenu (VO2), progiem beztlenowym oraz istotnie większym rozkurczowym wymiarem lewej komory, nachyleniem VE/VCO2, AHI, centralnym AHI i stężeniem NT-proBNP. W 3. miesiącu terapii ASV stwierdzono ustąpienie EOV u 7 pacjentów, tylko u 1 osoby nie zaobserwowano poprawy w zakresie toru oddychania (p = 0,0156). Wśród pozostałych parametrów ergospirometrycznych tylko puls tlenowy istotnie wzrósł. Szczegółowe pochłanianie tlenu i próg beztlenowy nieznacznie się poprawiły, ale różnice te nie osiągnęły istotności statystycznej. U wszystkich pacjentów leczonych ASV stwierdzono normalizację toru oddychania w czasie snu i zmniejszenie AHI do < 5/h. Ponadto w trakcie leczenia ASV zaobserwowano znaczną zwiększenie LVEF i istotną redukcję stężenia NT-proBNP.

Wnioski: Badanie pokazuje oryginalne zjawisko normalizacji toru oddychania w czasie wysiłku u pacjentów z centralnym bezdechem sennym leczonych ASV. Na podstawie powyższych danych można jednak wnioskować bezpośrednio o znaczeniu klinicznym tej obserwacji. Wpływ ustąpienia EOV w czasie leczenia ASV na rokowanie odległe wymaga przeprowadzenia dalszych badań. Również ze względu na ograniczenia tego badania (krótki okres obserwacji, mała grupa badana) jego wyniki wymagają potwierdzenia w kolejnych pracach.

Słowa kluczowe: oddychanie periodyczne w czasie wysiłku, zaburzenia oddychania w czasie snu

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