Complex sleep apnoea in congestive heart failure

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Received 6 July 2010
Accepted 21 January 2011
Published Online First 10 March 2011

ABSTRACT

Background Sleep disordered breathing is common and of prognostic significance in patients with congestive heart failure (CHF). Complex sleep apnoea (complexSA) is defined as the emergence of central sleep apnoea during continuous positive airway pressure (CPAP) treatment in patients with obstructive sleep apnoea (OSA). This study aims to determine the prevalence and predictors for complexSA in patients with CHF with OSA, and to assess the effects of treatment with adaptive servoventilation.

Methods 192 patients with CHF (left ventricular ejection fraction (LVEF) ≤45%, New York Heart Association (NYHA) class ≥2) and OSA (apnoea–hypopnoea index (AHI) ≥15) were investigated using echocardiography, cardiopulmonary exercise testing, measurement of hyperoxic, hypercapnic ventilatory response, 6 min walk test and measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) prior to CPAP introduction. If patients demonstrated complexSA (AHI >15/h with <10% obstructive events) during CPAP titration, adaptive servoventilation was introduced and the investigations were repeated at 3 monthly follow-up visits.

Results ComplexSA developed in 34 patients (18%) during CPAP titration. After adjustment for demographic and cardiac parameters, measures of CO_2 sensitivity (higher hyperoxic, hypercapnic ventilatory response) were independently associated with complexSA. Patients using adaptive servoventilation had improved AHI, NYHA class, NT-proBNP concentration, LVEF, hyperoxic, hypercapnic ventilatory response, oxygen uptake during cardiopulmonary exercise testing and the relationship between minute ventilation and the rate of CO_2 elimination (V_E/V_{CO_2} slope) at last individual follow-up (14±4 months).

Conclusion There is a high prevalence of complexSA in patients with OSA and CHF, and those who develop complexSA have evidence of higher respiratory controller gain before application of CPAP. Treatment with adaptive servoventilation effectively suppressed complexSA and had positive effects on cardiac function and respiratory stability.

INTRODUCTION

With an overall 5 year mortality of 50%, congestive heart failure (CHF) is still associated with a poor prognosis.[1] Sleep disordered breathing (SDB) is common in patients with CHF, with approximately a third predominantly having obstructive sleep apnoea (OSA) and another third predominantly having central sleep apnoea with Cheyne–Stokes respiration (CSA).[2 3] Moreover patients with CHF who have SDB have increased mortality rates compared with those who do not.[4] Whereas in OSA complete cessation of airflow (apnoeas) and/or discernible reduction in airflow (hypopnoeas) is due to an upper airway collapse, CSA is recognised as a control dysfunction-related disease, an expression of respiratory instability.[5–7] In patients with CHF with CSA, heart failure therapy is the suggested first-line treatment, not only improving CHF but also reducing CSA effectively.[8] OSA does not respond to heart failure therapy. Thus, the European Society of Cardiology (ESC) recommends a specific continuous positive airway pressure (CPAP) ventilation treatment in patients with CHF with OSA, which has proven to have a positive prognostic impact in these patients.[9] However, not all patients respond to CPAP therapy, for example due to unresolved mask leaks or unsatisfactory positive airway pressure titration.[10] Some patients even develop Cheyne–Stokes respiration during CPAP administration, a finding labelled as complex sleep apnoea (complexSA).[11]

In heart failure patients, complexSA, though apparent in clinical practice, has never yet been investigated systematically.

The aim of this study was to investigate the prevalence and characteristics of patients with CHF with complexSA compared with patients with pure OSA, defining predictive factors for complexSA, and evaluating therapeutic effects of adaptive servoventilation on heart failure and SDB parameters.

MATERIALS AND METHODS

Patients

Between July 2003 and September 2009, 941 consecutive patients with moderate to severe OSA (apnoea–hypopnoea index (AHI) ≥15/h) underwent CPAP introduction. In total, 225 presented with stable CHF (left ventricular ejection fraction (LVEF) <45%, New York Heart Association (NYHA) class ≥II), and were included in a prospective registry. Of those, 192 patients (85.3%) were eligible to be included in this study. Exclusion criteria were current treatment for SDB (8 patients), evidence of significant pulmonary disease or hypercapnia (partial pressure of CO_2 (pCO_2) >45 mm Hg; 3 patients), pregnancy, acute coronary syndrome or acute myocardial decompensation within 3 months (22 patients). Some of the patients included also participated in other studies. ComplexSA was defined as ≥15 episodes of central apnoea or periodic breathing per hour during CPAP titration and <10% of events being obstructive. All patients undergoing CPAP titration had extensive baseline tests of cardiorespiratory function, described below. Patients diagnosed with complexSA were offered adaptive servoventilation therapy and were reassessed at 3 monthly intervals

(figure 1). The last assessment (mean 14±4 months) was used to assess changes with adaptive servoventilation therapy. If patients underwent cardiac surgery or invasive procedures (eg, percutanous coronary intervention) or heart failure medication changed (except for dosage adaption) the last assessment prior to the intervention was defined as the end point. Data from patients who died during follow-up were not analysed. All patients gave written informed consent, and the study was approved by the Ethical Review Board of the Ruhr University Bochum.

Sleep studies

Sleep studies were performed by either in-hospital cardiorespiratory polygraphy (Embletta; Embla, Amsterdam, The Netherlands) or polysomnography (N7000/S7000; Embla) as described previously.[12 13] SDB was defined in accordance with a modified version of the 2007 AASM (American Academy of Sleep Medicine) criteria for scoring respiratory events and the SERVE-HF trial study protocol.[14 15] In summary, apnoea was defined by a >90% reduction from baseline to peak amplitude of the signal from nasal cannula (pressure), lasting ≥10 s, while hypopnoea was defined as a ≥30% reduction in flow and a ≥3% desaturation from pre-event baseline for >10 s. Obstructive versus central hypopnoeas were determined on the presence/absence of inspiratory flow limitation and/or paradoxical abdominal/thoracic movements. Cheyne–Stokes respiration was defined as at least three episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apnoeas or hypopnoeas. If nasal pressure was not available (therapy introduction), XFlow complementary flow signal (sum of the amplitudes of the thoracic and abdominal movements) was referred to instead.

Continuous positive airway pressure

In this study an automatic positive airway pressure (APAP) device (S8 AutoSet Spirit II; ResMed, Martinsried, Germany) was used. APAP introduction was performed during wakefulness under continuous monitoring of blood pressure. Initial pressure support was set to 5–12 cm H_2O, unless the treating physician decided differently on the basis of individual clinical and demographic data (eg, massive obesity, which was not present in the vast majority of patients included (table 1)). Until 2008, therapy introduction was performed by in-hospital, unattended polygraphy (n=141, 73.4%) only. Since in-hospital full polysomnography is available at our institution (from 2008), CPAP introduction has been performed exclusively under attended polysomnography (n=51, 26.6%). In those undergoing polysomnography, attending technicians were encouraged to optimise pressure settings during sleep. If Cheyne–Stokes respiration occurred, maximum pressure support was reduced to the lowest possible level (threshold: sufficient suppression of obstructive events). If therapy introduction was unattended, pressure settings were optimised according to polygraphic results in the morning. Again, if Cheyne–Stokes respiration occurred, maximum pressure support was reduced and patients underwent a second therapy night with polygraphy. Only if the remaining central AHI under the lowest possible pressure support was ≥15/h were patients considered to have complexSA.

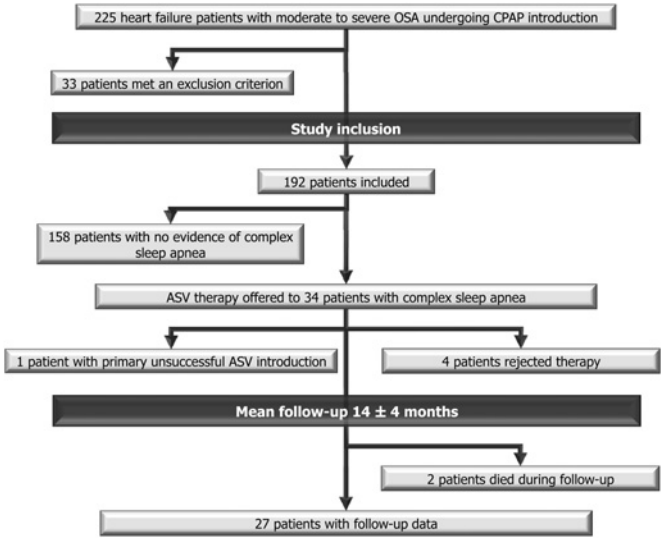

Figure 1 Study flow chart. ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea.

Adaptive servoventilation

Adaptive servoventilation (AutoSet CS2; ResMed) is a bi-level ventilation mode that changes pressure support to maintain target minute ventilation. Adaptive servoventilation was initiated during wakefulness under continuous monitoring of blood pressure. During a titration study using polysomnography, end expiratory pressure was manually adjusted to eliminate obstruction of the upper airways. Data on treatment efficacy and usage were collected from the device at follow-up visits (Res Scan; ResMed).

Echocardiography

Determination of the dimensions of the left atrium (LAD) and left ventricle (end-diastolic, LVEDD), biplane measurement of the left ventricular ejection fraction (LVEF) and estimation of systolic pulmonary artery pressure (sPAP) were performed (Vivid 7; GE Healthcare, Munich, Germany) following American Society of Echocardiography guidelines.[16]

Cardiopulmonary exercise testing

Symptom-limited bicycle cardiopulmonary exercise testing (ZAN Ferraris, Oberthulba, Germany) starting with 10 W and an increase of 10 W/min was performed at baseline and during each follow-up visit. Peak oxygen consumption (V_{O_2} peak), oxygen consumption at the individual aerobic–anaerobic threshold (V_{O_2}-AT), the relationship between minute ventilation and CO_2 production (VE/V_{CO_2}), maximum workload and total exercise time were recorded. The predicted V_{O_2} peak was calculated taking gender and age into account.

Six-minute walk test

A 6-min walk test was performed according to American Thoracic Society (ATS) guidelines.[17]

Standard laboratory measurement

Measurementd of haemoglobin (Hb) concentration, high sensitive C-reactive protein, potassium, creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) were performed at baseline and during follow-up visits.

Capillary blood gas analysis

Prior to CPAP introduction, the pCO_2, partial pressure of O_2 (pO_2), capillary pH and base excess were taken from hyperaemic ear lobe samples and measured using an ABL 330 (Radiometer, Copenhagen, Denmark).

Table 1 Demographic and clinical data of the study population before introduction of continuous positive airway pressure

	OSA (n=158)	ComplexSA (n=34)	p Value
Male, n (%)	134 (79.2)	33 (97.1)	0.79
Age, years	64.8±9.8	65.6±10.0	0.72
Ischaemic cause, n (%)	92 (0.58)	18 (0.53)	0.48
CRT device implanted, n (%)	93 (0.59)	18 (0.53)	0.63
Body mass index	29.4±5.3	28.2±4.7	0.23
Nocturia	1.4±1.6	1.5±2.6	0.57
NYHA class	2.5±0.6	2.7±0.7	<0.01
Heart rate	72±13	72±16	0.83
Systolic blood pressure	115±23	118±20	0.38
Diastolic blood pressure	74±12	69±13	0.02
Atrial fibrillation, n (%)	31 (19.6)	8 (23.5)	0.79
Arterial hypertension, n (%)	126 (79.7)	26 (76.5)	0.84
Diabetes, n (%)	47 (29.7)	6 (17.6)	0.10
Medication, n (%)			
β-Blockers	143 (90.5)	33 (97.1)	0.41
ACE/AT1 inhibitors	156 (98.7)	33 (97.1)	0.95
Aldosterone blockers	103 (65.2)	21 (61.8)	0.88
Amiodarone	42 (26.6)	10 (29.4)	0.86
Digitalis glycosides	57 (36.1)	14 (41.2)	0.74
Diuretics	151 (95.5)	27 (79.4)	<0.01
Blood gas analysis and sleep studies			
pH	7.428±0.03	7.442±0.03	0.03
pco_2, mm Hg	40.3±4.5	37.0±4.0	<0.001
po_2, mm Hg	75.6±10.0	77.6±11.6	0.34
BE	2.5±3.1	1.9±2.7	0.41
AHI, /h	33.1±15.1	30.4±13.2	0.32
Mean oxygen saturation (%)	91.9±3.1	92.6±3.0	0.54
Maximum oxygen desaturation (%)	80.5±6.5	80.7±6.5	0.89
Average oxygen desaturation (%)	5.6±5.2	5.8±4.0	0.70
Longest apnoea duration, s	38.5±21.3	35.5±19.3	0.43
Longest hypopnoea duration, s	53.1±27.1	51.2±22.0	0.67
Echocardiography			
LVEF (%)	31.6±7.4	30.1±7.5	0.31
LVEDD, mm	70.0±9.0	69.5±11.9	0.21
LAD, mm	50.0±8.8	50.2±7.5	0.89
sPAP	36.7±13.0	42.3±13.9	0.12
Cardiopulmonary exercise testing and six-minute walk			
Duration, min	7.5±3.0	7.4±2.4	0.91
Maximum workload, watts	82.5±35.2	90.6±32.5	0.25
Vo_2-AT, ml/min/kg	12.9±3.7	12.7±3.1	0.79
Vo_2 peak, ml/min/kg	14.7±4.1	14.4±3.9	0.73
Vo_2 predicted, %	60.3±18.3	63.7±17.6	0.32
VE/Vco_2 slope	30.5±4.0	33.7±5.3	0.001
Six-minute walk test, m	379±111	382±85	0.90
Laboratory measurement			
NT-proBNP, pg/ml	1662±3157	2789±3940	0.14
Hb, /ml	13.5±2.6	14.0±1.3	0.11
Sodium, μg/l	137.3±5.9	139.6±7.9	0.41
Creatinine, μg/l	1.3±0.5	1.3±0.4	0.70
CRP, ng/ml	0.8±0.9	0.8±0.8	0.92
HCVR, l/min/mm Hg	2.52±1.49	4.60±3.66	<0.001

ACE/AT1, angiotensin-converting enzyme/angiotensin 1 receptor; AHI, apnoea– hypopnoea index; BE, base excess; CRP, C-reactive protein; CRT, cardiac resynchronisation therapy; ComplexSDA, complex sleep apnoea; Hb, haemoglobin; HCVR, hyperoxic, hypercapnic ventilatory response; LAD, left atrium dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OSA, obstructive sleep apnoea; pco_2, partial pressure of CO_2; po_2, partial pressure of O_2; sPAP, systolic pulmonary artery pressure; VE/Vco_2 slope, the relationship between minute ventilation and the rate of CO_2 elimination; Vo_2, oxygen consumption; Vo_2-AT, oxygen consumption at the individual aerobic–anaerobic threshold.

Rebreathing test

The hyperoxic, hypercapnic ventilatory response testing (ZAN Ferraris) protocol is based on the Read rebreathing testing protocol.[18] Hyperoxic, HCVR sensitivity was determined as the slope of minute ventilation (l/min) plotted against PET_{CO_2} (mm Hg).

Statistics

Statistical analysis was performed with the Statview (Version 5.1) software (SAS Institute), and the SigmaPlot (Version 11) software. Differences between the OSA and complexSA group were compared by unpaired t test if testing for normal distribution (Kolmogorov–Smirnov) passed, and with the help of the Mann–Whitney test, if testing failed. In the case of categorial variables, χ^2 tests or the Fisher exact test was performed. A multiple logistic regression analysis including age, sex, body mass index (BMI), LVEF, Vo_2 peak, Hb concentration and hyperoxic, hypercapnic ventilatory response was conducted for recognising independent associations with complexSA. Changes from baseline to follow-up within the treatment group were analysed using the paired t test if testing for normal distribution passed, and with the help of the Wilcoxon test if testing failed. A value of $p<0.05$ was considered significant for all comparisons. Data are given as mean±SD unless stated otherwise.

RESULTS

Patients' characteristics

Of 192 patients with CHF with moderate to severe OSA undergoing CPAP titration, 34 (18%) developed complexSA. Though prevalence tended to be higher in those studied by polygraphy (27/141, 19%) compared with polysomnography (7/51, 14%), the χ^2 test did not reveal a significant difference. An additional 36 patients (19%) presented with mild central sleep apnoea (AHI 5–14/h), which was not considered a criterion for discontinuing CPAP therapy. Demographic and clinical data are included in table 1. Patients with complexSA had lower diastolic blood pressure, a lower rate of diuretic use and a higher NYHA classification than patients with OSA. They also had higher pH and lower pco_2 on capillary blood gas analysis, a higher VE/Vco_2 slope during cardiopulmonary exercise testing and higher hyperoxic, hypercapnic ventilatory response. Adjusted for clinical and demographic parameters including age, sex, BMI, LVEF, Vo_2 peak and Hb concentration, an independent association between hyperoxic, hypercapnic ventilatory response and complexSA (p=0.01; table 2) was found.

Adaptive servoventilation

Adaptive servoventilation was offered to all 34 patients with complexSA. Four patients (12%) refused to start treatment, and

Table 2 Multiple logistic regression analysis for complex sleep apnoea

Parameter	p Value
Age	0.83
Male gender	0.54
BMI	0.59
LVEF	0.75
Vo_2 peak	0.76
Haemoglobin	0.73
HCVR	0.01

BMI, body mass index; HCVR, hyperoxic, hypercapnic ventilatory response; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Vo_2, oxygen consumption.

adaptive servoventilation was unsuccessful in reducing AHI below 15/h in one patient (3%). Of 29 patients forming the study cohort, two died during follow-up (one major cardiac event, one non-cardiac cause). Baseline and follow-up data from 27 patients (26 male, 66±8 years) were analysed. Average minimum pressure support was 3.0 cm H_2O, maximum 9.7±1.6 cm H_2O, and end expiratory pressure level was 5.5±1.6 cm H_2O. Downloaded data from the device showed a mean usage of >4 h per day in 76.2±24.0% of all possible treatment nights, with an average use of 6.4±1.4 h per day. Average AHI for the entire treatment period was 5.2±7.1/h and the apnoea index was 0.5±1.4/h. Other results are presented in table 3. Adaptive servoventilation led to significant improvements in sleep apnoea parameters (AHI, apnoea index, central apnoea index, longest apnoea period and lowest oxygen saturation). Severity of CHF was significantly improved (NYHA class, LVEF, NT-proBNP). Exercise tolerance improved significantly (V_{O_2} peak, V_{O_2}-AT, V_{O_2} predicted). Ventilatory responses to CO_2 were decreased during rest (hyperoxic, hypercapnic ventilatory response) and during exercise (V_E/V_{CO_2}), but changes in CO_2 and pH were minimal.

DISCUSSION

This is the first cohort study of patients with CHF and complexSA. A high prevalence of complexSA was found in a cohort of patients with CHF who have OSA undergoing CPAP titration. In addition, increased respiratory sensitivity to CO_2 was independently associated with complexSA Treatment with adaptive servoventilation was associated with significant improvements in control of complexSA, cardiac function and exercise tolerance.

Table 3 Effects of adaptive servoventilation (ASV) in patients witch congestive heart failure and complex sleep apnoea (n=27)

	Baseline (at ASV introduction)	Last follow-up visit under ASV therapy (14±4 months)	Significance (p Value)
Sleep study results			
AHI, /h	34.0±14.7	8.1±9.6	<0.0001
AI, /h	18.3±13.4	2.0±3.9	0.008
cAI, /h	17.4±12.5	0.77±1.79	<0.0001
Average oxygen saturation, %	93.2±1.8	94.3±1.5	0.37
Lowest oxygen saturation, %	81.9±5.3	87.3±4.4	0.0004
Mean desaturation, %	5.6±2.0	4.6±1.8	0.26
Longest apnoea period, s	40.4±16.3	21.2±19.8	<0.0001
Longest hyponea period, s	43.9±16.6	41.6±22.7	0.92
BMI	28.3±4.2	28.2±3.6	0.88
NYHA class	2.7±0.7	1.9±0.9	<0.0001
Nocturia	1.5±1.5	1.4±1.4	0.08
Systolic blood pressure, mm Hg	120.1±22.4	117.1±21.7	0.52
Diastolic blood pressure, mm Hg	71.1±14.0	73.2±15.4	0.53
Heart rate	72.5±13.1	72.0±13.6	0.52
Blood gas analysis			
pH	7.441±0.03	7.439±0.03	0.37
p_{CO_2}, mm Hg	37.0±4.0	37.8±4.1	0.21
p_{O_2}, mm Hg	77.6±11.6	80.8±11.8	0.38
BE	1.9±2.7	2.0±2.4	0.77
Echocardiography			
LVEF (%)	31.1±7.1	34.8±12.1	0.04
LVEDD, mm	68.8±7.4	65.3±14.5	0.18
LAD, mm	49.5±8.5	51.3±9.6	0.34
sPAP	42.1±13.1	38.1±15.6	0.21
Cardiopulmonary exercise testing and six-minute walk			
Duration, min	7.4±2.4	8.3±2.1	0.10
Maximum workload, W	90.6±32.5	97.6±29.8	0.15
V_{O_2}-AT, ml/min/kg	12.7±3.6	14.3±3.9	0.03
V_{O_2} peak, ml/min/kg	14.8±4.3	16.5±5.2	0.04
V_{O_2} predicted, %	61.7±18.2	71.7±21.1	0.02
V_E/V_{CO_2} slope	33.7±5.3	31.8±5.2	0.08
Six-minute walk test, m	371±82	421±96	0.09
Laboratory measurement			
NT-proBNP, pg/ml	2518±3340	2118±1667	0.01
Hb, /ml	14.0±1.3	14.0±1.3	0.42
Sodium, µg/l	139.6±7.9	139.4±3.6	0.23
Creatinine, µg/l	1.3±0.4	1.4±0.5	0.33
CRP, ng/ml	0.8±0.8	0.6±0.7	0.27
HCVR, l/min/mm Hg	4.60±3.66	3.11±2.3	0.03

AHI, apnoea– hypopnoea index; AI, apnoea index; BE, base excess; BMI, body mass index; Hb, haemoglobin; cAI, central apnoea index; HCVR, hyperoxic, hypercapnic ventilatory response; LAD, left atrium dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; p_{CO_2}, partial pressure of CO_2; p_{O_2}, partial pressure of O_2; sPAP, systolic pulmonary artery pressure; V_E/V_{CO_2} slope; the relationship between minute ventilation and the rate of CO_2 elimination; V_{O_2}, oxygen consumption; V_{O_2}-AT, oxygen consumption at the individual aerobic–anaerobic threshold.

The potential importance of OSA in the pathogenesis and prognosis of CHF is increasingly recognised, and the most recent guidelines of the European Heart Failure Society recommend routine screening and treatment of OSA in patients with CHF.[9]

CSA also is very common in patients CHF,[2 3] and is caused by respiratory instability occurring as a result of heart disease.[5–7] In the presence of an unstable upper airway, mixtures of obstructive and central apnoea may be observed. Some patients display a mixture of obstructive and central events during sleep,[19] and the predominant type of event may change during the night.[20] Others may display obstructive events during sleep but develop CSA when obstruction of the upper airways is treated with CPAP, a condition labelled complexSA.[11]

ComplexSA has been the subject of a number of studies involving patients with OSA enrolled from sleep laboratory populations but has not previously been studied in a CHF population. Javaheri recently reported an overall incidence of 6.5% in a large-scale retrospective analysis (84/1286), whereas Morgenthaler reported a prevalence of 15% (34/223 patients), Lehman 13% (13/99) and Yaegashi 6% (18/297).[21–24] The definition of complexSA used in this study was considerably more demanding than in previously published series in that the threshold AHI was 15/h as opposed to 5/h. The prevalence of 18% observed in this study accompanied by an additional 19% of patients presenting with a central AHI of >5/h during CPAP introduction suggests that complexSA is considerably more common in CHF than in sleep laboratory populations with OSA, and that with increased numbers of patients with CHF being screened and treated for OSA it will be an increasing clinical problem.

CO_2 homeostasis in OSA is characterised by transient hypercapnia or eucapnia. This contrasts with the dominant CO_2 homeostasis in patients with Cheyne–Stokes respiration: these patients present with a highly sensitive hypocapnia-induced apnoeic threshold, whereby apnoea is initiated by small transient reductions in partial pressure of arterial carbon dioxide (Pa_{CO_2}).[2 25] The difference between eupnoeic Pa_{CO_2} and the apnoeic threshold is determined by the ventilatory increase required to produce a given reduction in Pa_{CO_2} (plant gain) and the ventilatory responsiveness to a given change in CO_2 mediated through chemoreceptors (controller gain).[26 27] The interactions of these components of the respiratory control system also seem to determine the individual predisposition to complexSA.

CHF causes a number of changes in ventilatory control including circulatory delay and enhanced chemoreceptor sensitivity.[5–7] Circulatory delay causes a delay in ventilatory responsiveness of the chemoreceptors and predisposes for Cheyne–Stokes respiration.[28] Indirect measures of circulatory delay, such as LVEF, tended to be lower among our complexSA cohort but did not turn out to be significant. In contrast, direct measures of the controller gain revealed an enhanced ventilatory responsiveness among patients with complexSA compared with those with pure OSA. Furthermore, the hyperoxic, hypercapnic ventilatory response was associated with complexSA even after adjustment for clinical, demographic and cardiac measures. A highly responsive chemoreceptor also predisposes to central apnoeas and periodic breathing by moving eupnoeic CO_2 closer to the apnoea threshold. Patients with complexSA thus presented with lower daytime p_{CO_2}. These Findings contribute to the proposed pathophysiological model of CSA as a control dysfunction-related disease. However, hyperoxic, hypercapnicventilatory response testing is not routinely employed in clinical practice. Hence, identifying complex SA at the time of CPAP titration is challenging.

Adaptive servoventilation is a novel ventilatory mode which treats CSA more effectively than oxygen, CPAP or bi-level positive airway pressure.[29 30] It is in extensive clinical use for the treatment of CSA in CHF, and most,[30 31] but not all[32] published series show an improvement in CHF severity associated with its use. However, data on the long-term effect on mortality or morbidity are lacking, and are the subject of an ongoing study.[15] There are fewer publications on the use of adaptive servoventilation in complexSA. Allam and co-workers demonstrated adaptive servoventilation to be most effective in reducing AHI and arousals among 63 patients with complexSA compared with CPAP and bi-level positive airway pressure.[33] A small study showed similar results in nine patients with complexSA.[34] A recent randomised, controlled trial also displayed superiority of adaptive servoventilation compared with CPAP in patients with CHF with co-existing obstructive and central events.[19]

In this study adaptive servoventilation effectively suppressed CSA, and the improvements in cardiac function were of similar magnitude to those found in previously published studies of CSA in CHF.[31] In the absence of a control arm it is impossible to ascribe these changes to adaptive servoventilation therapy. As our therapy group consisted of 27 patients only, some parameters (eg, 6 min walk distance, VE/V_{CO_2} slope) tended to improve but did not reach a level of significance. A large-scale, randomised, controlled study will be necessary to verify these results.

ComplexSA without CHF frequently resolves with CPAP therapy after 1–3 months, probably because elevated sensitivity to CO_2 and a narrow CO_2 reserve return to normal after days to weeks of CPAP treatment.[24 35] Over the course of adaptive servoventilation treatment there was an improvement in CO_2 sensitivity among our CHF cohort with complexSA but it remained greater than the baseline values of the group who had OSA. Whether these patients can be encouraged to continue CPAP use and be assured that CSA is transitory or should generally be switched to adaptive servoventilation treatment for an underlying tendency to respiratory instability remains to be clarified in future studies.

Limitations

The major limitation of this study is that patients with complexSA were not randomised to other treatments besides adaptive servoventilation. This is because it was not planned as a randomised, controlled therapy trial. As this is the first study ever investigating complexSA in patients with CHF, we also focused on the prevalence and predictors for complexSA in this cohort. However, changes in heart failure severity in the treatment group may be due to factors other than adaptive servoventilation therapy.

Most of our sleep studies were performed by polygraphy, not polysomnography, and AHI was derived from total recording time rather than total sleep time. This may have introduced a bias, although there is close correlation between results from the device used for polygraphy and polysomnography.[36]

We defined complex sleep apnoea as ≥15 episodes of central apnoeas or periodic breathing per hour of sleep during CPAP administration exclusive of a significant proportion (≥10%) of obstructive or mixed apnoeas or hypopnoeas. This definition is quite strict compared with others.[23 24] CPAP introduction was performed by APAP devices, which in not recommended in patients with CHF.[37] However, to avoid overtitration, we applied restrictive pressure settings at therapy introduction (5–12 cm H_2O) which were further reduced if central events

occurred. In addition, pressure levels applied were comparable with those of a recently published randomised, controlled trial involving similar patient cohorts.[19]

Summary

Beside a comparatively high prevalence, the main finding of this study is the documentation of a respiratory instability as a possible underlying mechanism of complexSA, which is veiled by recurrent upper airway obstructions. Thus, CPAP restores a 'normal' respiratory breathing pattern, which in terms of patients with complexSA means more efficient CO_2 excretion with a subsequent fall of pCO_2 below the apnoea threshold. Consequently we could confirm a higher hyperoxic, hypercapnic ventilatory response independently associated with complexSA. Adaptive servoventilation therapy proved not only to suppress complexSA effectively but also to have positive effects on subjective and objective cardiac functional parameters and to improve respiratory stability in our cohort. Whether similar effects could have emerged from ongoing CPAP therapy needs to be determined by future head-to-head comparisons.

Funding TB was supported by an unrestricted research grant from the Ruhr University, Bochum.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee of the Ruhr University Bochum, Germany.

Provenance and peer review Not commissioned; externally peer reviewed.

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