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Sleep apnoea in heart failure - results of a German survey

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ABSTRACT : US-American studies have reported that sleep apnoea is common in congestive heart failure (CHF) with Cheyne-Stokes respiration (CSR) being the most frequent type of sleep-disordered breathing (SDB) in these patients. Within the present study, we sought to assess the prevalence and type of SDB among CHF patients in Germany.

203 CHF patients participated in this prospective multi-center study. All of them were stable in NYHA classes II and III and had a left ventricular ejection fraction (LVEF) < 40%. The patients were investigated by polygraphy and all data centrally analyzed. Patient enrollment was irrespective of sleep-related symptoms.

The majority of patients was hospitalized and of male gender, mean age was 65 years. 71% had an apnoea-hypopnoea-index > 10/h (n = 145), obstructive sleep apnoea (OSA) occurred in 43% (n = 88) and CSR in 28% (n = 57).

The prevalence of SDB is high in stable severe CHF patients from a European population. As SDB may have a negative impact on the prognosis of CHF, a sleep study should be performed in every patient with CHF and a LVEF < 40%. Probably, this diagnostic approach should be adopted for all of these patients irrespective of the presence of sleep-related symptoms.

Key words : congestive heart failure; obstructive sleep apnoea; Cheyne-Stokes respiration

Abstract word count : 200

INTRODUCTION

Congestive heart failure (CHF) is a very common disorder carrying a poor prognosis. In Europe, it is estimated that about 14 million people suffer from CHF and each year more than 3 million new cases are diagnosed [1]. The five-year-mortality rates of CHF range between 40 and 60% [2].

Sleep-disordered breathing (SDB) has been reported to occur frequently in CHF patients with a left ventricular ejection fraction (LVEF) < 40%. Epidemiological studies performed in the U.S. in the 1990's have described prevalence rates for SDB in these patients of 40-70% [3-5]. These studies have mainly investigated ambulatory male patients in NYHA classes II and III. Most authors have found Cheyne-Stokes respiration (CSR) as the predominant type of SDB, whereas obstructive sleep apnoea (OSA) was less frequently observed.

For some reasons, the results of the above cited studies might not be valid for patients outside the U.S. For example, ethnicity may influence the occurrence of SDB due to differences in respiratory chemosensitivity, craniofacial morphology and the level of obesity. Furthermore, pharmacotherapy of CHF might differ between countries which may also impact on the frequency and severity of SDB in these patients. Up to now, however, there is a paucity of large-scale European studies investigating the epidemiology of SDB in CHF. Within the present study we sought to address this issue. We performed a prospective multi-center study to determine the prevalence of SDB and its relative distribution (i.e. occurrence of CSR vs. OSA) among stable CHF patients in Germany.

PATIENTS AND METHODS

Patient recruitment

The patients participating in this study were prospectively enrolled at 10 medical centers located throughout Germany (see appendix for a list of study centres). The main inclusion criterion was the presence of CHF with a LVEF < 40% (as determined by transthoracic echocardiography). Furthermore, the patients had to be stable in NYHA classes II or III. Exclusion criteria were the following : age < 18 years or > 80 years, clinical signs of decompensated CHF (i.e. oedema etc.), myocardial infarction within the last 6 months, significant chronic obstructive pulmonary disease (i.e. FEV_1 / IVC < 65% of predicted) and known drug addiction. Patient enrollment was independent of the presence of sleep-related symptoms (i.e. snoring, witnessed apnoeas, excessive daytime sleepiness). Patients were allowed to enter the study being ambulatory or hospitalized. The study was started in April 2004 and completed in January 2005. The study protocol had been approved by the local ethics committees and all patients had given their informed written consent.

Patient assessement

The anthropometric parameters of the patients were determined, i.e. age, sex and body mass index. The main cause of CHF was specified, i.e. coronary artery disease, idiopathic dilated cardiomyopathy, arterial hypertension etc., and the NYHA class was determined.

The current use of cardiac-specific medications was evaluated, i.e. ACE inhibitors or angiotensin II blockers, ß-blockers, aldosterone antagonists, diuretics and digitalis. It was noted if an implantable cardioverter-defibrillator or a biventricular assist device had been inserted. All patients were investigated by transthoracic echocardiography to determine LVEF (in %, normal : 60-70%). Furthermore, a standard 12-lead electrocardiogram was obtained to see if the patient was in sinus rhythm or atrial fibrillation. Finally, pulmonary function testing with arterial blood gas analysis was performed. Among others, the following data were achieved : FEV_1, IVC, the ratio of FEV_1/IVC as well as pO_2 and pCO_2 (in mm Hg).

Polygraphy

Prior to polygraphy, all patients filled in the Epworth Sleepiness Scale (range : 0-24) to assess their level of daytime sleepiness. The STARDUST II system (Respironics, Inc., Germany) was used for polygraphy. This device records oxygen saturation (SaO_2) and heart rate by pulse oximetry at the finger tip. Airflow is monitored by a pressure cannula attached to the patient's nostrils. Breathing efforts are measured by an inductive plethysmographic belt tightly wrapped around the chest. Finally, snoring and body position are registered. All data were stored on CD-ROM's for later visual analysis. This was carried out centrally at the sleep laboratory of the Charité University Hospital, Berlin with the investigator (A.B.) blinded to the patients' characteristics.

All apnoeas / hypopnoeas had to last more than 10 sec. and an apnoea-hypopnoea-index (AHI) > 10 / hour of time in bed was considered as diagnostic of SDB. In the case of apnoeas, there had to be an absence of airflow.

Obstructive apnoeas were diagnosed if the respiratory efforts continued during the breathing pauses, otherwise these events were classified as central apnoeas. Hypopnoeas were defined by a reduction in respiratory amplitude of at least 50% when compared to the preceding signals. Obstructive hypopnoeas had to display persistent and / or increasing effort and snoring during the event, with associated inspiratory flow limitation on the nasal pressure signal. Hypopnoeas were scored as central when there was an absence of these findings. According to the criteria established by Javaheri et al. [3, 4], OSA was supposed to be present if the obstructive AHI was > 10/h and the central AHI accounted for less than 50 percent of the total AHI. CSR was diagnosed if the obstructive AHI was < 10/h and the central AHI comprised 50 percent or more of the total AHI. In addition, CSR was requested to show a typical waxing-and-waning pattern of hyperventilatory phases.

Data analysis

All data were entered into a web-based questionnaire for later statistical analysis. They are reported as mean ± SEM unless otherwise indicated. Direct comparisons of data among the groups with OSA, CSR and without SDB (i.e. without OSA and CSR) were made by analysis of variance with post hoc correction for multiple comparisons by Tukey's test. A p-value < 0.05 was regarded as statistically significant.

RESULTS

Patient characteristics

A total of 203 patients were enrolled. The characteristics of the study population are summarized in **table 1.** The majority of patients was hospitalized and of male gender, mean age was 65 years. Almost equal proportions were in NYHA classes II and III. Echocardiography showed marked impairment of left ventricular systolic function. The main cause of CHF was ischaemic heart disease. ACE inhibitors / angiotensin II blockers and ß-blockers were taken by 91% and 90% of patients, respectively. Pulmonary function testing excluded significant ventilatory deficits in all patients studied (data not shown).

Prevalence and type of sleep-disordered breathing

Polygraphy revealed SDB in 71% of patients (n = 145). The mean AHI was 34 ± 3 / h, mean SaO_2 was 93.1 ± 0.3 %, lowest SaO_2 was 75.5 ± 0.4 % and the time spent with $SaO_2 < 90\%$ was 8.7 ± 0.7 % of time in bed. OSA was observed in 43% (n = 88) and CSR in 28% (n = 57) of patients (for further details see **table 2**). When comparing hospitalized to ambulatory patients, a similar proportion of SDB was observed (118 of the 166 hospitalized patients and 27 of the 37 ambulatory patients had SDB, i.e. 71% vs. 73%, respectively; p = n.s.). Women with CHF less frequently suffered from SDB than male CHF patients (31 of the 51 women and 114 of the 152 men had SDB, i.e. 61% vs. 75%; $p < 0.05$).

Comparison of patients with OSA, CSR and without SDB

The characteristics of the patients with OSA, CSR and without SDB are compared in **tables 3** and **4.** In general, patients with SDB tended to be of male gender. Patients with OSA were more obese than the patients of the other two groups. In addition, they suffered from more severe daytime sleepiness (i.e. they had higher Epworth scores, see table 2). Patients with CSR more often had atrial fibrillation and lower pCO_2 values. There were no statistically significant differences regarding NYHA classes, LVEF and the leading causes of CHF between the three groups. Except for the use of digitalis, the spectrum of medications was similar in the patients with OSA, CSR and undisturbed nocturnal breathing.

DISCUSSION

This study represents one of the largest European surveys performed to date on the occurrence of SDB in CHF patients. We enrolled participants irrespective of the presence of sleep-related symptoms and found a high prevalence of SDB of 71%. It might be speculated that the percentage of patients with SDB would have been even higher if we had only investigated CHF patients with snoring, witnessed apnoeas and excessive daytime sleepiness. Probably, such an approach would have further increased the proportion of patients with OSA as these are usually more symptomatic than those with CSR. This was also the case in our series with the OSA patients displaying higher Epworth scores than the CSR patients.

As in other studies [5, 6], patients with OSA were more obese than those with CSR or without SDB, whereas CSR was more often observed in patients who were in atrial fibrillation and / or were hypocapnic. We believe that these characteristics can be used in clinical practice to identify those CHF patients who are at a higher risk for SDB.

Recognizing that a patient with CHF suffers from SDB may have important clinical implications. OSA can contribute to the worsening of CHF through various mechanisms. The intrathoracic pressure swings associated with OSA may directly depress cardiac contractility. Furthermore, OSA may lead to CHF by promoting the development of arterial hypertension and ischaemic heart disease [7, 8]. Likewise, some studies suggest that CSR has a negative impact on the prognosis of CHF [9, 10]. This effect is presumably mediated by an enhancement of the neurohumoral changes characteristic of CHF such as sympathetic and natriuretic peptide activation [11, 12]. Furthermore, CSR might trigger malignant arrhythmias leading to sudden cardiac death [13].

The prevalence of SDB in our CHF patients was similar or even higher than that reported in the literature. However, due to several reasons, it is difficult to compare the results of our survey to those obtained in earlier studies. First, most earlier studies were performed at single well-known referral centers whereas our patients were enrolled at different clinical institutions of pulmonary and general internal medicine located throughout Germany. Second, studies employed different scoring criteria for SDB. For example, the AHI cut-off value in our study was 10/h, whereas Javaheri et al. used a cut-off of 15/h. It has also to be considered that in our study the AHI was expressed as number of apnoeas and hypopnoeas per hour of time in bed (and not per hour of total sleep time as in most preceding studies). Third, the sleep recordings from the different studies were scored by different investigators thus introducing inter-rater variabilities. Fourth, there were differences in monitoring techniques of sleep and breathing between studies. In contrast to the other studies which mainly employed in-hospital polysomnography, we used a polygraphic device. Due to the lack of electroencephalographic channels we might have missed some hypopnoeas associated with arousals rather than with oxygen desaturations. On the other hand, we employed pressure cannulae for the detection of apnoeas / hypopnoeas which are more sensitive than the thermistors used in the earlier studies [14].

In contrast to most preceding studies on the epidemiology of sleep apnoea in CHF, the predominant type of SDB in our study was OSA and not CSR. Sometimes it is difficult to classify cases of SDB as OSA or CSR. For instance, differentiating between obstructive and central apnoeas / hypopnoeas can be very challenging especially when one only relies on the signals of inductive plethysmography.

In our study, however, scoring of SDB was more refined by additionally using informations from the snoring and airflow channels (i.e. obstructive events had to display snoring and / or flattening of the inspiratory flow contour). A further point to consider is that some CHF patients may exhibit features of both OSA and CSR, i.e. mixed sleep apnoea, however, all patients of our study either had predominant OSA or CSR. Therefore, we suggest that the observed shift in the spectrum of SDB can not be explained by relevant misclassification of SDB but is primarily related to differences in patient characteristics between studies. In this context, it is known that more severely reduced LVEF and higher NYHA classes are associated with an increased risk to develop CSR [15, 16]. In our patients, however, left ventricular function was better preserved and all of them were stable in NYHA classes II and III. This might have contributed to a higher proportion of OSA cases in our study. In addition, when compared to the earlier studies, the patients of our survey were characterized by a more widespread use of ß-blockers. We speculate that this optimization in pharmacotherapy of CHF led to the disappearance of CSR in a subset of our patients. ß-blockers might suppress CSR not only by decreasing circulation times and pulmonary venous congestion but also by altering chemoreflex regulation of ventilatory control [17]. Of note, this assumption is supported by two recent studies showing that CHF patients taking ß-blockers have a lower prevalence and severity of CSR than those who do not [18, 19].

Similarly to pharmacotherapy, mechanical devices used for the treatment of advanced CHF such as cardiac resynchronisation therapy have been reported to improve or even abolish CSR [20]. In our study, only a minority of patients received this form of therapy and therefore, we are not able to address this issue. However, it should be kept in mind that an

optimization of CHF treatment in a more general sense might impact on the occurrence of SDB in these patients.

It should be acknowledged that our study has some possible limitations. As already stated, we performed polygraphy which might be inferior to polysomnography. However, a study investigating the ability of polygraphy to detect SDB in patients with CHF showed that there was no significant difference when compared with polysomnography [21]. Furthermore, we performed blinded visual analysis of all polygraphic data at a single center thus minimizing possible bias induced by inter-observer variabilities. Second, as we mainly included hospitalized CHF patients of male gender, our findings might not be extrapolated to outpatients and females with CHF. Although we observed a similar proportion of SDB in ambulatory vs. hospitalized patients, it has to be taken into account that ambulatory CHF patients frequently do not receive medical therapy according to established guidelines [22]. One may suspect that this may lead to a higher percentage of CSR in these patients. As far as concerning the effects of gender on the occurrence of SDB in CHF, it has been reported that male sex is associated with a higher likelihood to develop both OSA and CSR [5]. We also found a higher percentage of males in those patients suffering from SDB. Thus, if we had included more females, the proportion of patients with sleep apnoea probably would have been lower.

In summary, we have shown that the prevalence of SDB is high in stable severe CHF patients from a European population. Due to the potential adverse effects of SDB on the clinical course of CHF, we suggest that a sleep study should be performed in every patient with CHF and a LVEF < 40% . Probably, this diagnostic approach should be adopted for all of these patients irrespective of the presence of sleep-related symptoms.

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Tables

Table 1

Patient characteristics of the whole study population (n = 203)

males [n (%)]	152 (75)
hospitalized [n (%)]	166 (82)
age [years]	65.3 ± 1.1
body mass index [kg/m^2]	27.6 ± 0.6
NYHA II / III [n (%)]	112 (55) / 91 (45)
LVEF [%]	28.0 ± 1.0
main cause of CHF	
• coronary artery disease [n (%)]	115 (57)
• dilated cardiomyopathy [n (%)]	61 (30)
• hypertension [n (%)]	27 (13)
atrial fibrillation [n (%)]	57 (28)
pCO_2 [mm Hg]	39.7 ± 0.8
ß-blockers [n (%)]	183 (90)
ACE inhibitors / AT II blockers [n (%)]	185 (91)
diuretics [n (%)]	164 (81)
aldosterone antagonists [n (%)]	93 (46)

digitalis glycosides [n (%)]	85 (42)
ICD [n (%)]	43 (21)
CRT [n (%)]	17 (8)

Data are given as mean +/- SEM or as total and relative (i.e. %) numbers.

Abbreviations :

CRT = cardiac resynchronisation therapy, ICD = implantable cardioverter defibrillator,

LVEF = left ventricular ejection fraction, pCO_2 = partial pressure of arterial carbon dioxide.

Table 2

Results of polygraphy

	OSA	CSR	no SDB
number of pts. [n (%)]	88 (43)	57 (28)	58 (29)
Epworth score	8.5 ± 0.7 #	6.7 ± 0.7	5.8 ± 0.8
AHI [n/h]	34 ± 2	35 ± 3	4 ± 1 *
OAI [n/h]	28 ± 2 *	4 ± 2	2 ± 1
CAI [n/h]	2 ± 1	27 ± 3 *	1 ± 1
HI [n/h]	4 ± 2	4 ± 2	1 ± 1
SaO_2 mean [%]	93.1 ± 0.3	93.0 ± 0.4	94.1 ± 0.4

lowest SaO_2 [%]	74.4 ± 0.4	77.3 ± 0.5	88.1 ± 0.5 *
SaO_2 < 90% [% of TIB]	10.6 ± 0.7 *	5.8 ± 0.7	3.8 ± 0.9

Data are given as mean +/- SEM or as total and relative (i.e. %) numbers.

# denotes a p-value < 0.05 and * a p-value < 0.01 in comparison to the other two groups

Abbreviations :

AHI = apnoea-hypopnoea-index, OAI = obstructive apnoea-index, CAI = central apnoea-index,

HI = hypopnoea-index, SaO_2 = oxygen saturation, TIB = time in bed.

Table 3

Anthropometric data, NYHA classes, LVEF and causes of cardiac failure in the patients with OSA, CSR and without sleep-disordered breathing

	OSA	CSR	no SDB
number of pts.	88	57	58
males [n (%)]	67 (76)	47 (82)	38 (66) #
hospitalized [n (%)]	69 (78)	49 (86)	48 (83)
age [years]	64.7 ± 1.1	67.2 ± 1.2	64.2 ± 1.2
body mass index [kg/m^2]	29.0 ± 0.5 #	26.7 ± 0.6	26.5 ± 0.6

NYHA II [n (%)]	50 (57)	32 (56)	30 (52)
NYHA III [n (%)]	38 (43)	25 (44)	28 (48)
LVEF [%]	28.6 ± 0.9	26.8 ± 1.0	28.4 ± 1.0
main cause of CHF			
• coronary artery disease [n (%)]	51 (58)	33 (58)	31 (53)
• dilated cardiomyopathy [n (%)]	25 (28)	17 (30)	19 (33)
• hypertension [n (%)]	12 (14)	7 (12)	8 (14)
atrial fibrillation [n (%)]	19 (22)	25 (44) #	13 (22)
pCO_2 [mm Hg]	40.6 ± 0.8	36.8 ± 0.8 *	41.3 ± 0.9

Data are given as mean +/- SEM or as total and relative (i.e. %) numbers.

# denotes a p-value < 0.05 and * a p-value < 0.01 in comparison to the other two groups

Table 4

Therapy of heart failure in the patients with OSA, CSR and without sleep-disordered breathing

	OSA	CSR	no SDB
number of pts.	88	57	58
ß-blockers [n (%)]	81 (92)	52 (91)	50 (86)
ACE inhibitors / AT II blockers [n (%)]	83 (94)	52 (91)	50 (86)

diuretics [n (%)]	71 (81)	46 (81)	47 (81)
aldosterone antagonists [n (%)]	40 (45)	25 (44)	28 (48)
digitalis glycosides [n (%)]	34 (39)	30 (53) #	21 (36)
ICD [n (%)]	18 (20)	14 (25)	11 (19)
CRT [n (%)]	8 (9)	5 (9)	4 (7)

Data are given as total and relative (i.e. %) numbers.

# denotes a p-value < 0.05 in comparison to the other two groups

APPENDIX

The following study centers participated in the study :

- Universitätsklinikum Gießen / Marburg, Standort Gießen, Medizinische Klinik II, R. Schulz (n = 23 pts.)
- Charité Universitätsmedizin Berlin, Schlafmedizinisches Zentrum, Medizinische Klinik und Poliklinik, Schwerpunkt Kardiologie - Pulmologie - Angiologie, A. Blau, I. Fietze (n = 12 pts.)
- Universitätsklinik der Ruhr-Universität Bochum; St. Josefshospital, Medizinische Klinik II, Kardiologie, J. Börgel and BG-Kliniken Bergmannsheil, Medizinische Klinik III (Pneumologie, Allergologie, Schlaf-und Beatmungsmedizin), H.W. Duchna (n = 30 pts.)
- Sana Kliniken Ostholstein, Klinik Oldenburg, Innere Medizin-Pneumologie, I. Koper (n = 19 pts.)

- Pius-Hospital Oldenburg / Niedersachsen, Klinik für Innere Medizin, R. Prenzel (n = 19 pts.)
- Städtisches Krankenhaus Martha-Maria Halle-Dölau, Klinik für Innere Medizin II, S. Schädlich (n = 21 pts.)
- Theresienkrankenhaus Mannheim, Abteilung Innere Medizin III, J. Schmitt (n = 39 pts.)
- Universitätsklinikum Bonn, Medizinische Klinik II, Kardiologie / Pneumologie, S. Tasci (n = 10 pts.)
- Georg-August-Universität Göttingen, Zentrum für Innere Medizin, Abteilung Kardiologie / Pneumologie, S. Andreas (n = 30 pts.)

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