AUS DEM LEHRSTUHL
FÜR INNERE MEDIZIN II
DIREKTOR: PROF. DR. MED. GÜNTER RIEGGER
DER FAKULTÄT FÜR MEDIZIN
DER UNIVERSITÄT REGENSBURG

PROGNOSTIC IMPACT OF SLEEP DISORDERED BREATHING AND ITS TREATMENT IN HEART FAILURE: AN OBSERVATIONAL STUDY

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Fakultät für Medizin
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vorgelegt von
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Für

meine Mutter Ingeborg Kral,

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1. Abstract

1.1. Aims:

Sleep disordered breathing (SDB) may contribute to disease progression in patients with chronic heart failure (CHF). The objective of this observational study was to evaluate whether SDB is a risk factor for mortality in CHF patients and whether this risk can be attenuated by treatment with positive airway pressure (PAP).

1.2. Methods and results:

We studied 296 CHF patients (median left ventricular ejection fraction 33%) who underwent in-lab polysomnography between January 2002 and December 2009. We compared (i) mortality between patients with severe SDB [apnoea–hypopnoea index (AHI) ≥ 22.5 h^{-1}] vs. those without severe SDB (AHI < 22.5 h^{-1}) and (ii) evaluated the impact of PAP treatment on mortality in those with severe SDB. After accounting for significant confounding factors (age, NYHA class, cause of CHF, diabetes, and PAP treatment), patients with severe SDB (n = 176) had a 2.0-fold increased hazard ratio for death compared with those without severe SDB [95% confidence interval (CI) 1.1–3.5, *P* = 0.023]. In an adjusted on-treatment analysis of the group with severe SDB, mortality was significantly less in patients using PAP (18%) compared with those with untreated SDB (52%; hazard ratio 0.4, 95% CI 0.2–0.6, *P* = 0.001). Mortality in the PAP-treated group was lower compared with the untreated group at any time-point of the follow-up period.

1.3. Conclusion:

The presence of severe SDB in CHF patients constitutes a significantly increased risk for death, independent of established risk factors. In CHF patients with SDB, use of PAP therapy was associated with a decreased mortality rate at any time point of the follow-up, suggesting that PAP can be safely used in such patients.

2. Introduction

Sleep disordered breathing (SDB) is highly prevalent (51–71%) among patients with chronic heart failure (CHF).[1 – 4] By exposing the failing heart to intermittent hypoxia, increased preload and afterload,[5] sympathetic nervous system activation,[6] and vascular endothelial dysfunction, SDB may promote disease progression.[7] The main clinical significance of SDB in CHF is its potential to contribute to mortality.[7] However, published data evaluating the impact of SDB on mortality in CHF patients are controversial. Some studies suggest that SDB is an independent predictor of mortality in this patient group.[8 – 13] In contrast to those findings, Andreas et al. and Roebuck et al. did not observe a significantly increased mortality rate in CHF patients with SDB compared with those without.[14, 15] Yumino et al.[16] recently reported that SDB is only an independent risk factor for death in patients with ischaemic cardiomyopathy, and not in patients with non-ischaemic cardiomyopathy.

In addition, the conclusions that can be drawn from the above studies are limited due to (i) small sample size, (ii) use of portable monitoring devices that do not allow the distinction between obstructive and central sleep apnoea (OSA and CSA),[8,11] and (iii) unknown[9,11,17] or limited use (10–53%)[8,10,12,18] of beta-blockers, which have an impact on survival in heart failure patients.[19,20] The results of previous studies with limited use of beta-blockers cannot be extrapolated to patients on contemporary optimal CHF therapy.

The application of different forms of positive airway pressure (PAP) is an effective treatment of SDB in CHF patients that also improves surrogates of long-term cardiac outcome such as cardiac afterload, heart rate, sympathetic tone[21] as well as left ventricular ejection fraction (LVEF).[22 – 24] However, in the largest randomized trial evaluating the effects of continuous PAP in CHF patients with CSA on transplant-free survival, the total number of events in both arms of the trial (control and continuous PAP) was identical. Due to an increased early event rate in the continuous PAP arm, deleterious effects of PAP therapy in some CHF patients could not be ruled out.[22] We therefore evaluated the following hypotheses in a large sample of CHF patients on contemporary medical therapy, who underwent full in-laboratory

polysomnography: (i) SDB including CSA and OSA is an independent risk factor for death in patients with CHF. (ii) Treatment with PAP is associated with a decreased mortality rate in patients with severe SDB and CHF. The in-hospital initiation of PAP therapy targeted at suppression of SDB is not associated with an increased early mortality rate.

3. Methods

3.1. Patients

We studied 411 CHF patients who underwent polysomnography and objective assessment of LVEF within 3 months at the University Hospital Regensburg between January 2002 and December 2009. Inclusion criteria were: (i) objective evidence of a structural and functional abnormality of the heart (impaired LVEF ≤ 50%)[25] and (ii) CHF due to either ischaemic, non-ischaemic, or hypertensive cardiomyopathy.[25] Exclusion criteria were (i) CHF due to valvular heart disease, (ii) listing for heart transplantation, (iii) severe pulmonary disease or cancer, as well as (iv) oxygen or PAP treatment. The study was planned according to the declaration of Helsinki and approved by the local ethics committee, and the subjects gave written informed consent.

3.2. Polysomnography

During polysomnography body position, eye and leg movements, cardiotachography, nasobuccal airflow, chest and abdominal effort, and arterial oxyhaemoglobin saturation assessed by pulse oximetry were recorded (Alice 3.5, Respironics, Pittsburgh, USA). Sleep stages were determined according to Rechtschaffen and Kales.[26] Apnoea was defined as a cessation of inspiratory airflow for ≥ 10 s. Central apnoeas were those that occurred with an absence of thoracic and abdominal effort, while obstructive apnoeas were those that occurred in the presence of thoracic and abdominal motion. Hypopnoea was defined as a reduction in airflow of more than 50% or thoracoabdominal effort lasting at least 10 s resulting in a ≥ 4% drop in arterial oxyhaemoglobin saturation (SaO_2). The oxygen desaturation index was defined as the number of ≥ 4% oxygen desaturations per hour of

sleep. Patients were classified as having OSA, when the predominant type of apnoea (≥ 50%) was obstructive in nature. Central sleep apnoea was defined as < 50% obstructive apnoeas.

3.3. Treatment

A trial of continuous PAP treatment was offered to patients with an apnoea–hypopnoea index (AHI) ≥15 h^{-1} or AHI ≥5 h^{-1} plus SDB-related symptoms, e.g. excessive daytime sleepiness.[27] To acclimatize patients, continuous PAP was applied to patients at 4 cmH_2O for 1 hour while awake. During the night, continuous PAP was started under attended polysomnographic control at 4 cmH_2O, and was slowly increased in 1–2.5 cmH_2O increments to reach the target pressure (usually 8–10 cmH_2O) or the highest pressure the patient could tolerate (< 8 cmH_2O). Patients were sent home at the lowest CPAP level leading to optimal suppression of SDB and were instructed to use CPAP for at least 6 hours per night. Other forms of PAP (bi-level PAP, 2002–2005, and adaptive servoventilation, 2005–2009) were used in patients whose SDB was not sufficiently suppressed by CPAP. The use of adaptive servoventilation in patients with an AHI >15 h^{-1} on continuous PAP treatment was based on a subanalysis of the CANPAP trial showing that continuous PAP was only associated with improved cardiac function and transplant-free survival, when it suppressed the AHI below 15 h^{-1}.[28] In addition, Kohnlein et al.[29] showed that continuous and bi-level PAP are equally effective in suppressing central respiratory events.

3.4. Outcome

The primary outcome was all-cause mortality between the day of the baseline polysomnography until December 2009. Physicians assessed the outcome by phone interview. In order to verify the causes of death of patients who died in hospital, documents relating to the hospital stay were evaluated. For patients with out-of-hospital death, documents available from the family physician were evaluated.

3.5. Statistical analysis

Data distribution was assessed by the Kolmogorov–Smirnov test. Continuous data are expressed as means ± standard deviation, unless otherwise indicated. Student's t-test was used to compare the means of groups for continuous variables, if appropriate. For proportions, the χ^2-test with Yates' correction was used, if necessary. A two-sided *P*-value < 0.05 was considered statistically significant. In an exploratory analysis, the cut-off value of the AHI was calculated using the receiver operating characteristic (ROC) in regular intervals in order to identify the best discriminative threshold to predict outcome. The area under the curve was obtained according to Hanley.[30] The AHI value with the maximum expression of the Youden index (defined as sensitivity + specificity - 1) was defined as the threshold for classifying patients into two groups with regard to the AHI. Kaplan–Meier estimates were used to visualize survival. A Cox proportional hazard model was used to compare survival between groups. All independent variables shown in *Table 1* were introduced one at a time in the model. Confounding variables (*Table 1* in bold) were those that conferred at least a 10% change in the hazard ratio for death according to the SDB category.[31] Therefore, age, NYHA class, cause of CHF, diabetes, and PAP treatment were entered in addition to SDB category in the final multivariate analyses.

To test hypothesis 1, we compared the mortality rate of the two SDB categories. To test hypothesis 2, we performed an intention-to-treat and an on-treatment analysis (continued PAP treatment for at least 6 months or until a primary event) for all patients in the severe SDB group.

A propensity score was created using a logistic regression model with PAP treatment as the independent variable and the following covariates: age, NYHA, ischaemic cardiomyopathy as cause of CHF, and diabetes. The propensity score was then entered into a Cox-PH model as a continuous variable. All analyses were performed with the Statistical Package for the Social Sciences (SPSS 15.0, Chicago, IL, USA).

Table 1 Possible confounders for death

Age, gender, body-mass index (BMI)
LVEF, **NYHA class, cause of CHF (ischaemic/non-ischaemic),** Atrial fibrillation
History of hypertension, **diabetes**, and hyperlipidaemia
Biventricular pacemaker, defibrillator
ACE-inhibitors/AT1-receptor antagonists, spironolactone, ß-receptor-blockers, digitalis, diuretics, lipid reducers
Positive airway pressure treatment

Significant confounders (> 10% change in hazard ratio for death according to category of sleep-disordered breathing) are marked in bold.

4. Results

Four hundred and eleven patients with a diagnosis of CHF underwent polysomnography and evaluation of LVEF between 1 January 2002 and 31 December 2009. Two hundred and ninety-six patients with CHF were eligible for analysis, 115 were excluded due to either LVEF > 50%, listing for heart transplantation, severe lung disease, or cancer (*Figure 1*).

On the basis of ROC analysis, the best cut-off value for detecting mortality was an AHI ≥ 22.5 h^{-1}, indicating severe SDB (n = 176). Patients with an AHI < 22.5 h^{-1} had absent-to-moderate SDB and were defined as the group without severe SDB (n = 97). The baseline characteristics of patients are listed in *Table 2*.

The severe SDB group was significantly older, more obese, and had more severe heart failure, indicated by significantly higher NYHA-functional class than the group without severe SDB. Additionally, the proportion of men and the prevalence of diabetes and implanted pacemakers were significantly higher in the severe SDB group. In the group without severe SDB, the percentage of patients receiving spironolactone was higher than in the severe SDB group.

With respect to sleep characteristics (*Table 3*), the severe SDB group had a higher AHI and arousal index as well as lower minimum oxygen saturation. The mean oxygen saturation was similar in both groups. Sleep efficiency and sleep time were lower in the severe SDB group

than in group without severe SDB. Neither sleep onset latency nor subjective sleepiness assessed by the Epworth Sleepiness Scale (ESS) differed significantly between groups and did not indicate excessive daytime sleepiness in either group (*Table 3*). Patients with severe SDB were more often PAP treated than those from the group without severe SDB (52 vs. 22%, *Table 3*).

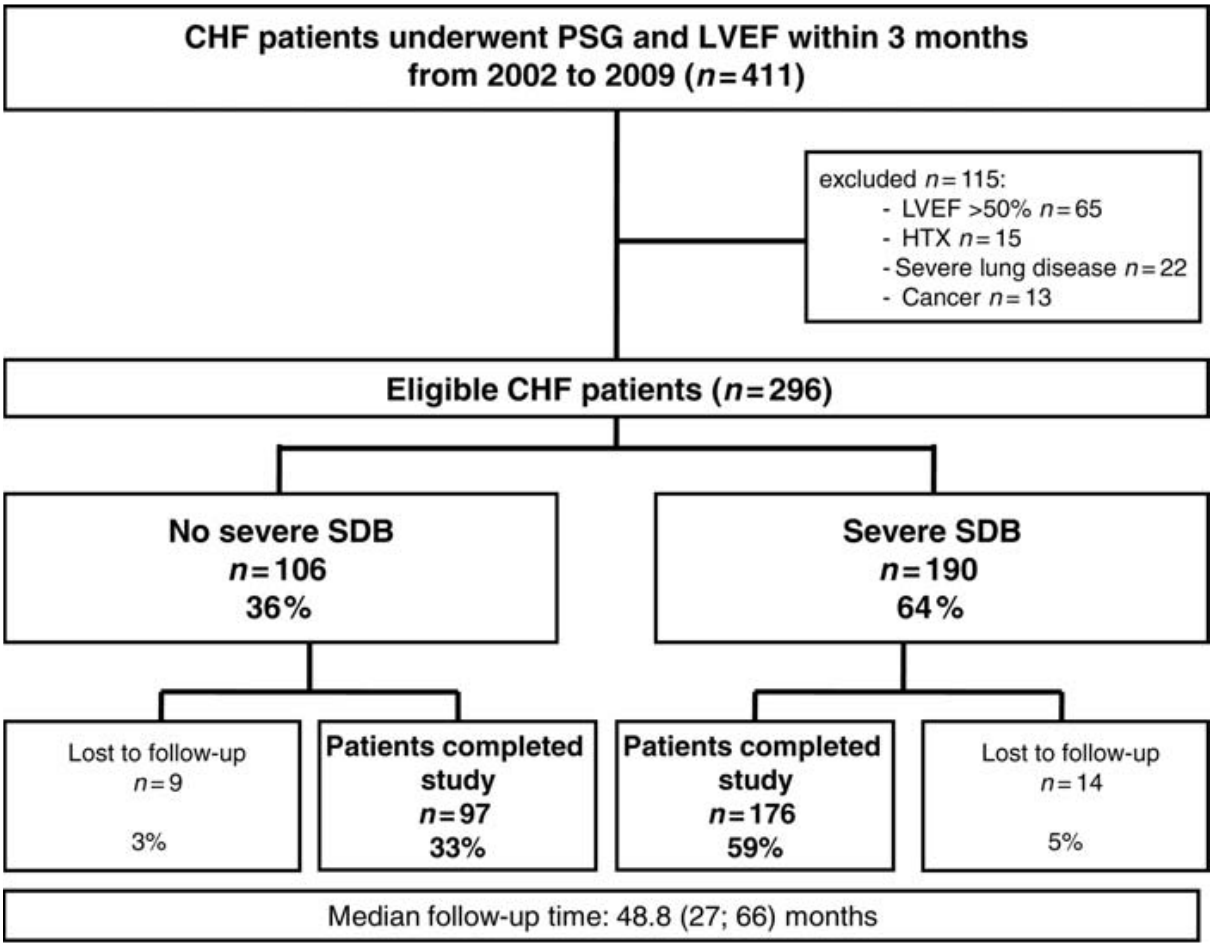

Figure 1 Progress of the cohort through the study. CHF, chronic heart failure; PSG, polysomnography; mo, months; LVEF, left ventricular ejection fraction; no severe SDB, sleep-disordered breathing defined as apnoea–hypopnoea index < 22.5 h^{-1}; severe SDB, severe sleep disordered breathing defined as apnoea–hypopnoea index ≥ 22.5 h^{-1}.

Table 2 Baseline characteristics of patients without severe sleep disordered breathing (AHI < 22.5 h^{-1}) and severe sleep disordered breathing (AHI ≥ 22.5 h^{-1})

	AHI< 22.5 h^{-1}	**AHI ≥ 22.5 h^{-1}**	***P*-value**
n	97	176	
Age (years)	59 ± 11	65 ± 9	0.028
Female (%)	16	11	< 0.001
BMI (kg/m^2)	27.9 ± 4.4	30.3 ± 5.6	0.002
LVEF (%)[a]	30 (25; 38)	34 (25; 44)	0.349
NYHA class	2.2 ± 0.5	2.4 ± 0.5	< 0.001
Ischaemic cardiomyopathy (%)	39	59	0.569
Atrial fibrillation (%)	21	25	0.322
Cardiovascular risk factors			
Hypertension (%)	45	57	0.645
Diabetes (%)	26	39	< 0.001
Hyperlipidaemia (%)	57	66	0.011
Rhythm devices			
Pacemaker (%)	19	30	< 0.001
Biventricular pacemaker (%)	8	5	0.042
Defibrillator (%)	26	27	0.59
Medications			
ACE-inhibitors/ AT1-antagonists (%)	94	93	0.688
Diuretics (%)	88	90	0.169
ß-blockers (%)	91	88	0.105
Spironolactone (%)	62	49	0.001
Digitalis (%)	29	25	0.178
Lipid lowering agents (%)	46	63	0.017

[a]LVEF is not normally distributed, reported as median (interquartile range), and differences between groups were compared with the Mann–Whitney U-test.

Table 3 Polysomnographic data of patients

	AHI< 22.5 h^{-1}	**AHI ≥ 22.5 h^{-1}**	***P*-value**
AHI (h^{-1})	12 ± 7	45 ± 17	< 0.001
Obstructive events (%)	30 ± 34	25 ± 30	0.078
Mean O_2 saturation (%)	93 ± 2	92 ± 3	0.122
Minimum O_2 saturation (%)	85 ± 6	76 ± 10	< 0.001
Total sleep time (min)	343 ± 49	320 ± 70	0.006
Sleep latency (min)	36 ± 29	38 ± 28	0.504
Sleep efficiency (%)	85 ± 10	81 ± 14	0.007
Arousals (h^{-1})	21 ± 14	33 ± 19	< 0.001
Slow and REM sleep (%)	35 ± 4	26 ± 2	0.008
Nocturnal heart rate (min^{-1})	61 ± 3	60 ± 2	0.616
Daytime sleepiness (ESS)	6.5 ± 4.3	7.9 ± 4.4	0.757
PAP treatment, n (%)	21 (22)	91 (52)	0.001

4.1. Impact of sleep disordered breathing on survival

Sixty CHF patients with severe SDB died (34%), whereas in the group without severe SDB 17 deaths occurred (18%, *P* = 0.003; *Figure 2*). After accounting for significant confounding factors (age, NYHA-functional class, cause of CHF, diabetes, and PAP treatment), patients with severe SDB had a two-fold increased hazard ratio for death [2.0, 95% confidence interval (CI) 1.1–3.5; *P* = 0.023], indicating significantly higher mortality of patients with severe SDB compared with patients without severe SDB. Other variables listed in *Table 1* were not significant confounders and were not included in the final model.

In the group with severe SDB, 53% of the deaths occurred due to progressive heart failure, 5% due to stroke, 3% due to sudden cardiac death, and 7% were related to a surgical procedure (coronary bypass surgery, mitral valve reconstruction, or carotid thrombarterectomy). Of the remaining patients (15%), causes of death were non-cardiovascular (pneumonia, pancreatitis, and cancer). The causes of 17% of deaths were unknown.

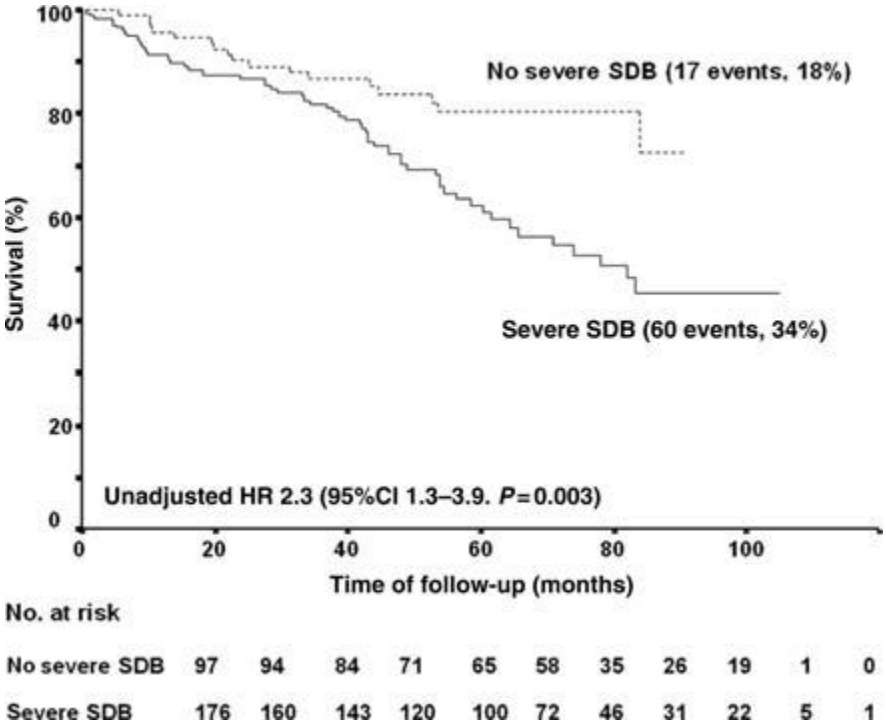

Figure 2 Kaplan–Meier plots for patients without severe sleep-disordered breathing (SDB, defined as apnoea–hypopnoea index < 22.5 h^{-1}) and severe sleep-disordered breathing (apnoea–hypopnoea index ≥ 22.5 h^{-1}). Survival was computed using unadjusted Cox proportional hazard analysis. HR, hazard ratio; CI, confidence interval.

4.2. Impact of sleep disordered breathing on survival in patients with ischaemic and non-ischaemic cardiomyopathy

In patients with ischaemic (n = 142, 53 deaths) and non-ischaemic cardiomyopathy (n = 131, 24 deaths), severe SDB was associated with a similarly increased hazard ratio for death (1.8, 95% CI 0.9 – 3.5, *P* = 0.107 vs. 2.2, 95% CI 0.9 – 3.5, *P* = 0.078).

4.3. Impact of obstructive and central sleep apnoea on survival

In the severe SDB group (n = 176), 22% of patients had predominantly OSA and 78% CSA. Comparing the severe and the mild OSA group, mortality was similar (19 vs. 21%, *P* = 0.884). In contrast, mortality was significantly higher in the severe CSA group compared with the mild CSA group (38 vs. 16%; unadjusted *P* = 0.002 and adjusted for the significant confounders age and NYHA class *P* = 0.035).

4.4. Impact of positive airway pressure support on survival: intention-to-treat analysis

In an intention-to-treat analysis of the severe SDB group, we compared patients who started a trial of PAP at home after in-hospital treatment initiation (74%) with patients who did not start a trial of PAP at home (26%). Mortality was not significantly different between the treated and untreated groups (28 vs. 51%, *P* = 0.247). With a total of 60 events, this analysis had 62% power to detect the above decrease of mortality in favour of the PAP-treated group at a two-sided alpha level of 0.05.

4.5. Impact of positive airway pressure support on survival: on-treatment analysis

An on-treatment analysis compared patients with severe SDB who used PAP for at least 6 months or until death (PAP-treated, 52%) and those who used PAP for less than 6 months (untreated, 48%; *Table 4*). Nine percent of the patients with untreated SDB terminated PAP therapy during initiation. Eleven percent of the patients terminated PAP therapy until the next clinical visit after 3 months. Baseline characteristics and polysomnographic data are shown in *Tables 4 and 5*.

Untreated patients had advanced diseases with respect to the underlying cardiovascular disease: ischaemic cardiomyopathy, atrial fibrillation, and biventricular pacing were more frequent in the untreated compared with the treated group. Patients with untreated SDB were significantly more often treated with beta-blockers compared with patients treated with PAP therapy (*Table 4*). In contrast, PAP-treated patients had more severe SDB than untreated patients, a higher percentage of obstructive episodes, and were more obese. Forty-eight percent of the PAP-treated patients were treated with continuous PAP, 13% with bi-level PAP, and 39% with adaptive servoventilation.

Table 4 Baseline characteristics of patients with use of positive airway pressure therapy vs. untreated sleep disordered breathing

	PAP-treated severe SDB	**Untreated severe SDB**	***P*-value**
n	91	85	
Age (years)	65 ± 10	65 ± 9	0.68
Female (%)	7	6	0.699
BMI (kg/m^2)	30.6 ± 6.2	29.9 ± 4.9	0.006
LVEF (%)[a]	35 (28; 45)	30 (25; 36)	< 0.001
NYHA class	2.3 ± 0.5	2.5 ± 0.5	0.009
Ischaemic cardiomyopathy (%)	55	64	0.033
Atrial fibrillation	20	29	0.04
Cardiovascular risk factors			
Hypertension (%)	57	57	0.893
Diabetes (%)	36	41	0.196
Hyperlipidaemia (%)	64	68	0.212
Rhythm devices			
Biventricular pacemaker (%)	3	7	0.032
Defibrillator (%)	25	29	0.223
Medications			
ACE-inhibitors/ AT1-antag. (%)	94	92	0.343
Diuretics (%)	89	92	0.218
Spironolactone (%)	55	44	0.843
ß-Blocker (%)	85	91	0.016
Digoxin (%)	23	27	0.227
Lipid lowering agents (%)	64	62	0.707

[a]LVEF is not normally distributed, reported as median (interquartile range), and differences between groups were compared with the Mann–Whitney U-test.

Table 5 Polysomnographic data of patients with use of positive airway pressure therapy vs. untreated sleep disordered breathing

	PAP-treated severe SDB	Untreated severe SDB	*P*-value
AHI (h^{-1})	48.9 ± 19	41.9 ±13	0.017
Obstructive events (%)	31 ±32	18 ±27	0.011
Mean O_2 saturation (%)	92 ±3	92 ±2	0.076
Minimum O_2 saturation (%)	75 ±11	78 ±7	0.001
Total sleep time (min)	323 ±72	317 ±69	0.791
Sleep latency (min)	36 ±27	40 ±29	0.793
Sleep efficiency (%)	81 ±16	80 ±16	0.085
Arousals (h^{-1})	38 ±21	29 ±16	0.063
Slow and REM sleep (%)	26 ±3	25 ±2	0.741
Nocturnal heart rate (min^{-1})	60 ±4	59 ±3	0.554
Daytime sleepiness (ESS)	7.9 ±4.5	7.8 ±4.1	0.591

Mortality in the PAP-treated group (18%, 16 deaths) was lower than the mortality of patients with untreated SDB (52%, 44 deaths, $P < 0.001$, *Figure 3 A*). In the PAP-treated group, eight deaths occurred due to progressive heart failure, three due to acute myocardial infarction, one due to stroke, one due to pneumonia, and one death was temporally related to coronary bypass surgery. None of the reported deaths was sudden cardiac death. The causes of death remain unknown in two patients.

Positive airway pressure-treated patients had a significantly decreased hazard ratio for death (0.3, 95% CI 0.2–0.6; $P < 0.001$), indicating significantly better survival in patients undergoing PAP treatment. In a multivariate Cox-proportional hazard model accounting for the significant confounders age, NYHA class, cause of CHF, and diabetes through a propensity score, PAP-treated patients still had a significantly decreased hazard ratio for death (0.4, 95% CI 0.2–0.6; $P = 0.001$). Other variables listed in *Table 1* were not significant confounders and were not included in the final model.

In the subgroup of patients with severe CSA, the PAP-treated group showed a lower hazard ratio for death compared with the untreated group at any time point of the follow-up period (unadjusted HR 0.4, 95% CI 0.2–0.7; *P* = 0.001; adjusted HR 0.4, 95% CI 0.2–0.7; *P* =0.004; *Figure 3 B*).

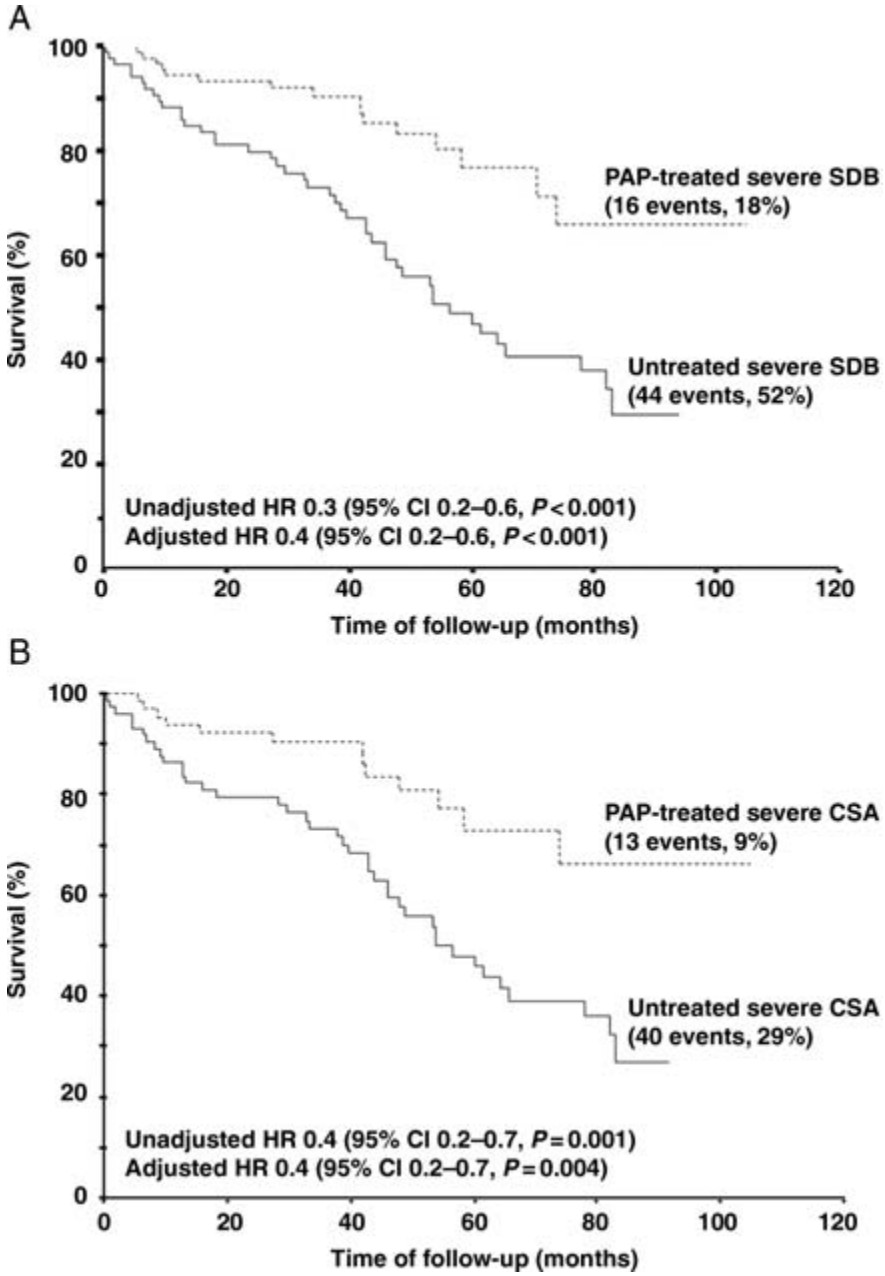

Figure 3 (A and B) Kaplan–Meier plots for patients with severe sleep-disordered breathing (SDB, apnoea–hypopnoea index ≥ 22.5 h^{-1}, A) and the subgroup of patients with severe central sleep apnoea (CSA, B) with and without positive airway pressure (PAP, defined as treatment .6 months or until a primary event). The unadjusted and adjusted Cox proportional hazard model is shown. The adjusted Cox proportional hazard model accounts for the significant confounders age, NYHA-class, cause of CHF, and diabetes through a propensity score. HR, hazard ratio; CI, confidence interval.

5. Discussion

This observational study of a large sample of CHF patients on contemporary medical therapy, who were evaluated for SDB by in-lab polysomnography, has given rise to several important findings: (i) SDB confers an increased risk for death in patients with CHF independently of conventional risk factors, (ii) PAP treatment of patients with severe SDB, which was initiated with attended polysomnographic monitoring and targeted to suppression of SDB, was not associated with an increased mortality rate at any time point of the follow-up period, and (iii) patients with severe SDB who used PAP treatment had a significantly lower mortality rate compared with those with untreated SDB.

In accordance with previously published data, we found that SDB and specifically CSA are a risk factor for increased mortality in patients with CHF, independent of known risk factors for death in heart failure patients.[8,10 – 13] Since in the group with severe SDB, only 7% of the deaths were due to sudden cardiac death, our data do not support a link between SDB and increased risk for sudden cardiac death.[32] The finding in the present analysis that medication did not significantly influence the hazard ratio for death according to the SDB category suggests that improvements in CHF medication reduced overall mortality, but did not alter the impact of SDB and CSA on the outcome among this group of patients. In line with previous studies, [7, 33] neither CHF patients in the group without severe SDB nor in the severe SDB group reported excessive daytime sleepiness assessed with the ESS (Table 3).

Our study in CHF patients with polysomnographic assessment of SDB extends the findings of previous studies in several important ways: (i) while in previously published studies the level of beta-blocker use was either not reported[9, 11, 17] or as low as 10 – 53%, [8, 10, 12, 17, 18] in our study it was 91 and 88% in the group without severe SDB and the severe SDB group, respectively. Beta-blocker use is of crucial importance for outcome studies in CHF patients, since the implementation of beta-blockers in medical therapy for CHF has significantly improved survival.[19, 20] (ii) In contrast to previous studies using portable sleep apnoea monitoring devices,[8, 11] the use of in-lab polysomnography with quantitative measurements of airflow and thoraco-abdominal effort enabled us to distinguish between CSA and OSA. By

this means we could attribute the association of SDB and poor prognosis in CHF patients in the reported sample to CSA. (iii) Our observational study included a significant proportion of patients in whom PAP therapy was initiated.

While treatment effects can hardly be proved by observational studies, this study type can add important information with respect to the safety of a treatment. The concern that PAP therapy may be harmful in some CHF patients with CSA, which was raised by the results of the CANPAP trial showing an increased event rate in the CPAP-treated compared with the control group in the first 18 months after treatment initiation,[22] is not supported by our observational data (*Figure 3 B*). One potential reason for this is that at our centre, PAP treatment in CHF patients with SDB was always initiated in hospital under polysomnographic monitoring, which was not mandatory in the CANPAP trial.[22]

The present study is subject to several limitations. First, due to the fact that the majority of CHF patients referred for full in-laboratory polysomnography in our study had suspected SDB, our study is limited by a shortage of patients without SDB to serve as a control group. We therefore compared patients with severe SDB vs. patients with absent-to-moderate SDB (group without severe SDB). This may have caused a conservative bias which would tend to underestimate the true mortality risk of severe SDB rather than identifying a false positive mortality risk. Secondly, although we studied a larger sample compared with previously published outcome studies of CHF patients with the assessment of SDB, our study ultimately lacked the statistical power to draw firm conclusions about the impact of OSA on mortality in such patients. Thirdly, in observational studies, differences in mortality rates between patients who adhere to PAP therapy and those who do not use PAP therapy cannot imperatively be attributed to treatment effects: e.g. the adherence to PAP therapy may be paralleled by adherence to heart failure medication. Enhanced adherence to medical therapy for heart failure is known to be associated with improved survival.[34]

6. Conclusions

We conclude that CHF patients on contemporary medical therapy with severe SDB have a significantly higher mortality risk than patients with absent or less severe SDB. Our data show that SDB contributes to progression of CHF and mortality, independent of established risk factors. Patients with CHF and severe SDB (CSA and OSA) who adhered to PAP treatment had a good prognosis, and PAP treatment was not associated with increased mortality at any time point during the follow-up period. In view of the multiple associations of SDB to known risk factors for death and worsening of CHF, randomized treatment trials with PAP are warranted to establish a causal relationship between SDB and worsening of CHF and to assess the effects of PAP treatment as a non-pharmacological adjunct to heart failure therapy on long-term morbidity and mortality in such patients.

Anhang:

Deutsche Zusammenfassung der Arbeit:

Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study

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Prognostischer Einfluss von schlafbezogenen Atemstörungen und deren Behandlung bei Herzinsuffizienz: eine Beobachtungsstudie

Schlaf bezogene Atemstörungen (SDB) können zum Progress der Erkrankung bei Patienten mit chronischer Herzinsuffizienz beitragen. Der Ansatz dieser Beobachtungsstudie besteht darin zu evaluierten, ob schlafbezogenen Atemstörungen ein Risikofaktor für Mortalität bei Patienten mit chronischer Herzinsuffizienz ist und ob dieser Risikofaktor durch eine Behandlung über Applikation eines positiven Atemwegsdruck (PAP) gesenkt werden kann.

Wir untersuchten 296 Patienten mit chronischer Herzinsuffizienz (mittlere linksventrikuläre Ejektionsfraktion 33%) retrospektiv von Januar 2002 bis Dezember 2009. Bei all diesen Patienten war in einem Schlaflabor eine Polysomnographie durchgeführt worden. Im Anschluss verglichen wir zum einen die Mortalität zwischen Patienten mit einer schwerwiegenden schlafbezogenen Atemstörung [Apnoe-Hypopnoe-Index (AHI) ≥ 22,5 h^{-1}] mit solchen ohne schwerwiegende SDB (AHI < 22,5 h^{-1}). Desweiteren bewerteten wir den Einfluss der Behandlung mit PAP auf die Mortalität bei Patienten mit schwerwiegender SDB. Nach der Berechnung der signifikanten Einflussgrößen (Alter, NYHA-Klasse, Ursache der Herzinsuffizienz, Diabetes mellitus und Behandlung mit PAP) zeigte sich, dass Patienten mit

schwerer SDB (n = 176) verglichen mit Patienten ohne schwerwiegende SDB eine 2,0-fach höhere Hazard-Ratio hinsichtlich eines letalen Verlaufes hatten [95% Confidenz-Intervall (CI) 1,1 – 3,5; p = 0,023). In einer adjustierten On-Treatment-Analyse derjenigen Patienten mit schwerwiegender SDB zeigte sich eine signifikant niedrigere Mortalitätsrate bei mit PAP-behandelten Patienten (18%), verglichen mit denjenigen, welche als unbehandelt eingestuft wurden (52%; Hazard-Ratio 0,4; 95% CI 0,2 – 0,6; p = 0,001). Insgesamt war die Mortalität in der mit PAP-therapierten Gruppe verglichen mit der unbehandelten Gruppe zu jedem Zeitpunkt im gesamten Follow-up niedriger.

Das Vorliegen einer schwerwiegenden SDB stellt somit unabhängig von bereits etablierten Risikofaktoren ein signifikant erhöhtes Mortalitätsrisiko bei Patienten mit chronischer Herzinsuffizienz dar. Bei chronisch herzinsuffizienten Patienten mit schlafbezogenen Atemstörungen war die Anwendung von PAP-Therapie assoziiert mit einer reduzierten Mortalitätsrate zu jedem Zeitpunkt des Follow-up, was nahelegt, dass die PAP-Therapie gefahrlos bei eben diesen Patienten eingesetzt werden kann.

Abkürzungsverzeichnis:

ACE	Angiotensin-converting enzyme
AHI	Apnoea-hypopnoea index
BMI	Body mass index
CHF	Chronic heart failure
CI	Confidence interval
CANPAP	Canadian continuous positive airway pressure for patients with central sleep apnoea and heart failure trial
Cox-PH	Cox proportional hazard
CPAP	Continuous positive airway pressure
CSA	Central sleep apnoea
ESS	Epworth Sleepiness Scale
HR	Hazard ratio
HTX	Heart transplantation
LVEF	Left ventricular ejection fraction
NYHA	New York heart association
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
REM	Rapid eye movement
ROC	Receiver operating characteristics
SaO_2	Arterial oxy-haemoglobin saturation
SDB	Sleep disordered breathing

Abbildungsverzeichnis:

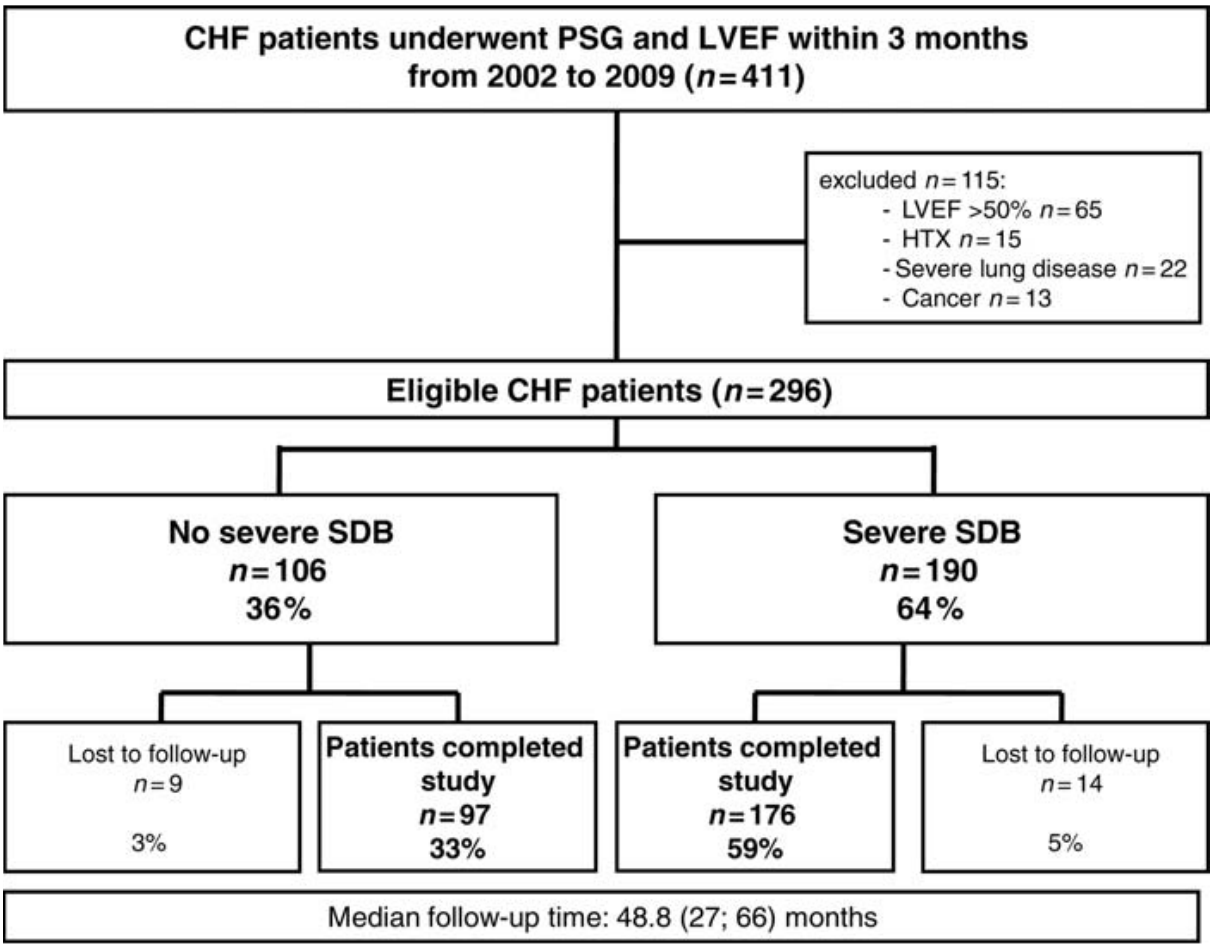
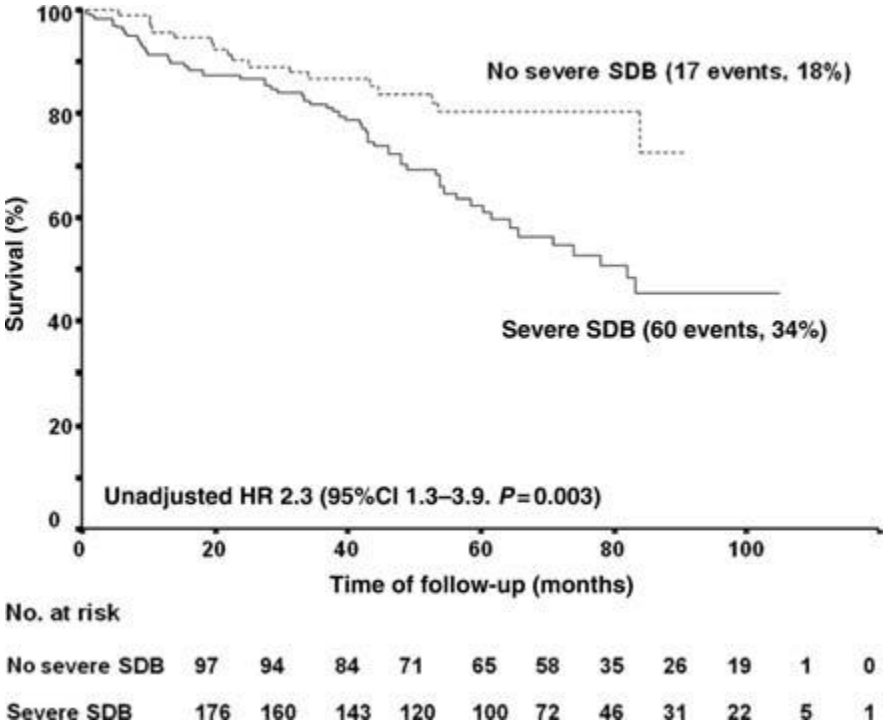


Figure 1 Progress of the cohort through the study. CHF, chronic heart failure; PSG, polysomnography; mo, months; LVEF, left ventricular ejection fraction; no severe SDB, sleep-disordered breathing defined as apnoea–hypopnoea index < 22.5 h^{-1}; severe SDB, severe sleep disordered breathing defined as apnoea–hypopnoea index ≥ 22.5 h^{-1}.



No. at risk

No severe SDB	97	94	84	71	65	58	35	26	19	1	0
Severe SDB	176	160	143	120	100	72	46	31	22	5	1

Figure 2 Kaplan–Meier plots for patients without severe sleep-disordered breathing (SDB, defined as apnoea–hypopnoea index < 22.5 h^{-1}) and severe sleep-disordered breathing (apnoea–hypopnoea index ≥ 22.5 h^{-1}). Survival was computed using unadjusted Cox proportional hazard analysis. HR, hazard ratio; CI, confidence interval.

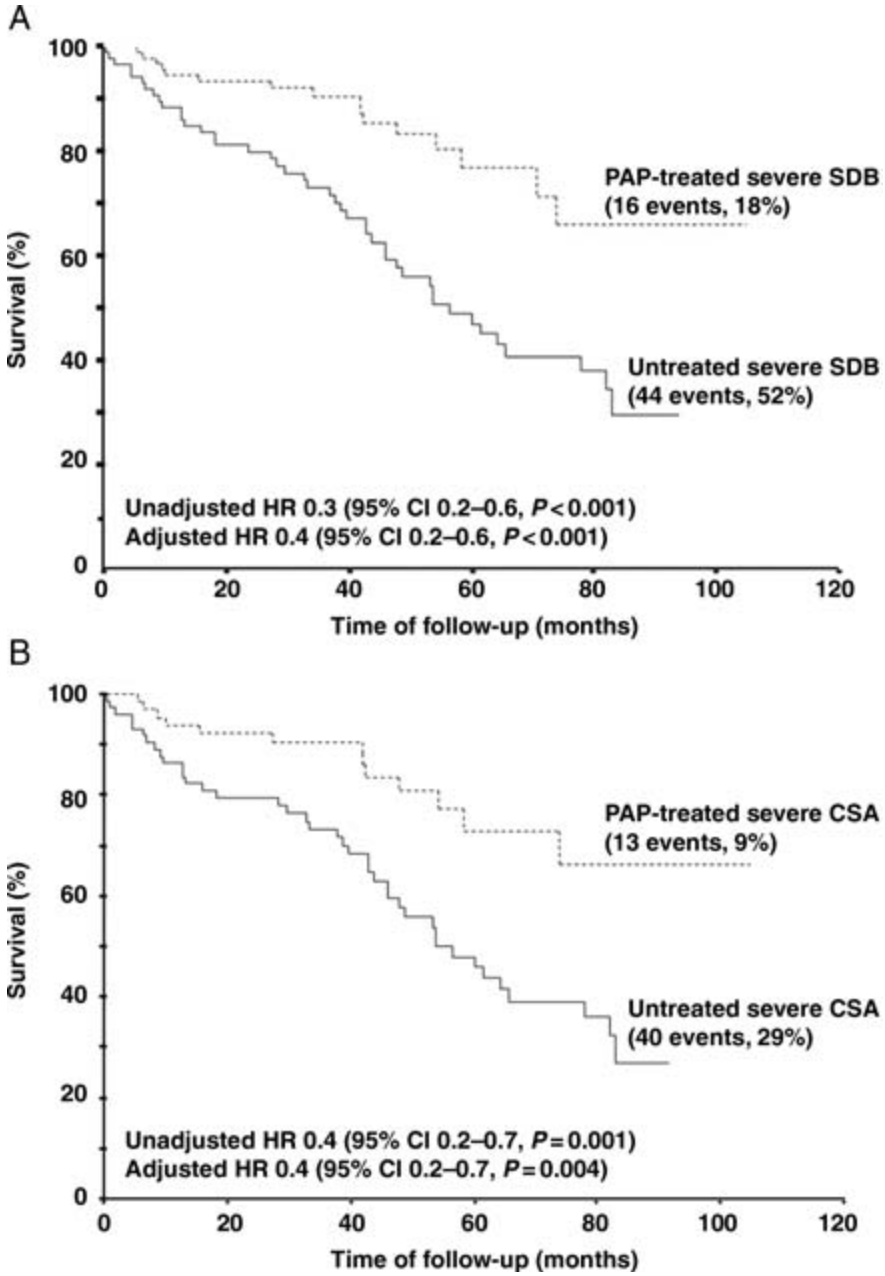


Figure 3 (A and B) Kaplan–Meier plots for patients with severe sleep-disordered breathing (SDB, apnoea–hypopnoea index ≥ 22.5 h^{-1}, A) and the subgroup of patients with severe central sleep apnoea (CSA, B) with and without positive airway pressure (PAP, defined as treatment .6 months or until a primary event). The unadjusted and adjusted Cox proportional hazard model is shown. The adjusted Cox proportional hazard model accounts for the significant confounders age, NYHA-class, cause of CHF, and diabetes through a propensity score. HR, hazard ratio; CI, confidence interval.

Tabellenverzeichnis:

Table 1 Possible confounders for death

Age, gender, body-mass index (BMI)
LVEF, **NYHA class, cause of CHF (ischaemic/non-ischaemic),** Atrial fibrillation
History of hypertension, **diabetes**, and hyperlipidaemia
Biventricular pacemaker, defibrillator
ACE-inhibitors/AT1-receptor antagonists, spironolactone, ß-receptor-blockers,
digitalis, diuretics, lipid reducers
Positive airway pressure treatment

Significant confounders (> 10% change in hazard ratio for death according to category of sleep-disordered breathing) are marked in bold.

Table 2 Baseline characteristics of patients without severe sleep disordered breathing (AHI < 22.5 h^{-1}) and severe sleep disordered breathing (AHI ≥ 22.5 h^{-1})

	AHI< 22.5 h^{-1}	AHI ≥ 22.5 h^{-1}	*P*-value
n	97	176	
Age (years)	59 ± 11	65 ± 9	0.028
Female (%)	16	11	< 0.001
BMI (kg/m^2)	27.9 ± 4.4	30.3 ± 5.6	0.002
LVEF (%)[a]	30 (25; 38)	34 (25; 44)	0.349
NYHA class	2.2 ± 0.5	2.4 ± 0.5	< 0.001
Ischaemic cardiomyopathy (%)	39	59	0.569
Atrial fibrillation (%)	21	25	0.322
Cardiovascular risk factors			
Hypertension (%)	45	57	0.645
Diabetes (%)	26	39	< 0.001
Hyperlipidaemia (%)	57	66	0.011
Rhythm devices			
Pacemaker (%)	19	30	< 0.001
Biventricular pacemaker (%)	8	5	0.042
Defibrillator (%)	26	27	0.59
Medications			
ACE-inhibitors/ AT1-antagonists (%)	94	93	0.688
Diuretics (%)	88	90	0.169
ß-blockers (%)	91	88	0.105
Spironolactone (%)	62	49	0.001
Digitalis (%)	29	25	0.178
Lipid lowering agents (%)	46	63	0.017

[a]LVEF is not normally distributed, reported as median (interquartile range), and differences between groups were compared with the Mann–Whitney U-test.

Table 3 Polysomnographic data of patients

	AHI< 22.5 h^{-1}	**AHI ≥ 22.5 h^{-1}**	***P*-value**
AHI (h^{-1})	12 ± 7	45 ± 17	< 0.001
Obstructive events (%)	30 ± 34	25 ± 30	0.078
Mean O_2 saturation (%)	93 ± 2	92 ± 3	0.122
Minimum O_2 saturation (%)	85 ± 6	76 ± 10	< 0.001
Total sleep time (min)	343 ± 49	320 ± 70	0.006
Sleep latency (min)	36 ± 29	38 ± 28	0.504
Sleep efficiency (%)	85 ± 10	81 ± 14	0.007
Arousals (h^{-1})	21 ± 14	33 ± 19	< 0.001
Slow and REM sleep (%)	35 ± 4	26 ± 2	0.008
Nocturnal heart rate (min^{-1})	61 ± 3	60 ± 2	0.616
Daytime sleepiness (ESS)	6.5 ± 4.3	7.9 ± 4.4	0.757
PAP treatment, n (%)	21 (22)	91 (52)	0.001

Table 4 Baseline characteristics of patients with use of positive airway pressure therapy vs. untreated sleep disordered breathing

	PAP-treated severe SDB	**Untreated severe SDB**	***P*-value**
n	91	85	
Age (years)	65 ± 10	65 ± 9	0.68
Female (%)	7	6	0.699
BMI (kg/m^2)	30.6 ± 6.2	29.9 ± 4.9	0.006
LVEF (%)[a]	35 (28; 45)	30 (25; 36)	< 0.001
NYHA class	2.3 ± 0.5	2.5 ± 0.5	0.009
Ischaemic cardiomyopathy (%)	55	64	0.033
Atrial fibrillation	20	29	0.04
Cardiovascular risk factors			
Hypertension (%)	57	57	0.893
Diabetes (%)	36	41	0.196
Hyperlipidaemia (%)	64	68	0.212
Rhythm devices			
Biventricular pacemaker (%)	3	7	0.032
Defibrillator (%)	25	29	0.223
Medications			
ACE-inhibitors/ AT1-antag. (%)	94	92	0.343
Diuretics (%)	89	92	0.218
Spironolactone (%)	55	44	0.843
ß-Blocker (%)	85	91	0.016
Digoxin (%)	23	27	0.227
Lipid lowering agents (%)	64	62	0.707

[a]LVEF is not normally distributed, reported as median (interquartile range), and differences between groups were compared with the Mann–Whitney U-test.

Table 5 Polysomnographic data of patients with use of positive airway pressure therapy vs. untreated sleep disordered breathing

	PAP-treated severe SDB	**Untreated severe SDB**	***P*-value**
AHI (h^{-1})	48.9 ± 19	41.9 ±13	0.017
Obstructive events (%)	31 ±32	18 ±27	0.011
Mean O_2 saturation (%)	92 ±3	92 ±2	0.076
Minimum O_2 saturation (%)	75 ±11	78 ±7	0.001
Total sleep time (min)	323 ±72	317 ±69	0.791
Sleep latency (min)	36 ±27	40 ±29	0.793
Sleep efficiency (%)	81 ±16	80 ±16	0.085
Arousals (h^{-1})	38 ±21	29 ±16	0.063
Slow and REM sleep (%)	26 ±3	25 ±2	0.741
Nocturnal heart rate (min^{-1})	60 ±4	59 ±3	0.554
Daytime sleepiness (ESS)	7.9 ±4.5	7.8 ±4.1	0.591

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