Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients

Olaf Oldenburg1*, Birgit Wellmann1, Anika Buchholz2, Thomas Bitter1, Henrik Fox1, Ulrich Thiem3, Dieter Horstkotte1, and Karl Wegscheider2

1Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr-University Bochum, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany; 2Department of Medical Biometry and Epidemiology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; and 3Department of Medical Informatics, Biometry and Epidemiology, Ruhr-University Bochum, Bochum, Germany

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Aim
This study investigated the prognostic value of sleep-disordered breathing (SDB) in a large cohort of patients with heart failure with reduced left ventricular function (HF-REF), with focus on the role of nocturnal hypoxaemia.

Methods
This single-centre prospective cohort study enrolled patients with chronic stable HF-REF (NYHA ≥ II) receiving guideline-based treatment. Unattended in-hospital polygraphy was performed to determine the apnoea–hypopnoea index (AHI). Pulse oximetry was used to determine hypoxaemic burden [time with oxygen saturation <90% (T90)], and all-cause mortality was recorded.

Results
Complete data were available for 963 of 1249 patients. At baseline, 58% of patients had moderate-to-severe SDB. The median follow-up was 7.35 years; 480 of 963 (49.8%) patients died. Mortality rate (per 100 person-years) was 8.1 [95% confidence interval (CI) 7.0–9.4] in patients with no or mild SDB, but 12.2 (95% CI 10.9–13.7) in moderate-to-severe SDB. Apnoea–hypopnoea index was significantly associated with time to death from any cause in a simple Cox model [hazard ratio (HR) 1.011, P = 0.001], but was no longer significant after adjustment for confounding factors (HR 1.005, P = 0.085). T90 was significantly (P < 0.001) associated with time to death from any cause even after adjustment for confounding factors. The risk of death increased by 16.1% (95% CI 8.6–24.2) per hour of T90. Five-year survival probabilities for patients in T90 quartiles 1, 2, 3, and 4 were 70, 63, 60, and 50%, respectively.

Conclusion
Hypoxaemic burden was a robust and independent predictor of all-cause mortality in chronic stable HF-REF patients. Whether or not targeting nocturnal hypoxaemia is associated with beneficial effects on mortality in HF-REF patients remains to be determined.

Keywords
Sleep-disordered breathing • Hypoxaemia • Heart failure • Mortality

Introduction
Sleep-disordered breathing (SDB) is a highly prevalent but under-recognized co-morbidity in patients with cardiovascular diseases. Sleep-disordered breathing is typically categorized as predominantly obstructive (OSA) or central (CSA) in nature, but many patients experience both types of apnoea events, depending on their individual anatomy and underlying diseases.

Obstructive apnoeas and hypopnoeas result from complete or partial collapse within the upper airways, accompanied by continued or increased efforts to maintain an adequate airflow. In contrast, central respiratory events occur as a consequence of reduced central respiratory drive, and rib cage or abdominal excursions are absent or markedly reduced. Despite these and other differences in the pathophysiology of OSA and CSA, the consequences of both types of sleep apnoea are largely the same: hypoxia and hypoxaemia, hypercapnia, increased sympathetic tone, and chronic inflammation with endothelial dysfunction and apoptosis. These processes might contribute to or accelerate the atherosclerotic process, vascular and cardiac remodelling, and cardiac arrhythmias. Indeed, OSA has been shown to be an independent risk factor for the development of heart failure (HF) and arrhythmic events.

* Corresponding author. Tel: +49 573 197 1258, Fax: +49 573 197 2194, Email: akkleemeyer@hdz-nrw.de

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including sudden cardiac death.\textsuperscript{3–5} In contrast, CSA is rare in subjects without any cardiovascular disease but its prevalence in HF patients increases in parallel with the degree of cardiac dysfunction and, therefore, appears to be a marker of cardiac function.\textsuperscript{6–8}

The severity of OSA and CSA is often determined using the apnoea–hypopnoea index (AHI), which represents the number of apnoeas and hypopnoeas per hour of sleep. An AHI of ≥5/h is generally required to indicate the presence of sleep apnoea, with mild, moderate, and severe disease defined as an AHI of 5–14, 15–29, and ≥30/h, respectively.\textsuperscript{9}

The prevalence of moderate-to-severe SDB (AHI ≥15/h) in patients with HF and reduced left ventricular ejection fraction (HF-REF) is ~50%. Most of these patients will present with predominant CSA, depending on the underlying degree of cardiac dysfunction, gender, and age.\textsuperscript{10,11} Moderate-to-severe sleep apnoea has been identified as an independent predictor of mortality in stable HF-REF patients.\textsuperscript{12–14} However, there is still some doubt about the role of SDB as an independent prognostic factor, particularly for CSA.\textsuperscript{15–17} The results of these studies are based on using AHI as a metric of SDB severity. However, apnoea and hypopnoea lengths increase with advanced HF, meaning that the total number of events may not be as high as in severe HF patients.\textsuperscript{18,19} Another problem is the use of different apnoea and hypopnoea definitions in different studies, which might lead to a different graduation in SDB severity.\textsuperscript{20}

This study investigated the prognostic value of AHI and moderate-to-severe OSA and CSA, in particular, in a large cohort of HF-REF patients using current guideline definitions for apnoea and hypopnoea scoring.\textsuperscript{8} In addition, because AHI may be reduced in severe HF due to prolonged apnoea and hypopnoea lengths, the total time a patient had nocturnal oxygen saturation below 90% (T90) was evaluated as a predictor of all-cause mortality.

**Methods**

**Patients**

Screening SDB for HF patients at the Heart and Diabetes Center North Rhine-Westphalia (Bad Oeynhausen, Germany) was initiated at the end of 2002. Initially, simple screening tools were used (ApneaLink\textsuperscript{TM}, microMESAM\textsuperscript{TM}), then multi-channel polygraphy (PG) was added (Embletta\textsuperscript{TM}, NOX T3\textsuperscript{TM}, SOMNOScreen\textsuperscript{TM}), progressing to full polysomnography (PSG) from early 2008 onwards. A total of 11,792 diagnostic investigations were performed from 4 December 2002 to 31 July 2013. This study includes all PG studies in HF patients who met the following inclusion criteria: stable HF-REF for ≥6 months; New York Heart Association (NYHA) functional class II, III, or IV; left ventricular ejection fraction (LVEF) <45% as measured by echocardiography at baseline or within the previous 3 months; receiving stable HF medication for ≥4 weeks. Patients were excluded if they had acute myocarditis, acute decompensated HF, acute coronary events [including any percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)] at the time of enrolment or within the previous 3 months, stroke, or transient ischaemic attack within the previous 6 months, initiation of cardiac resynchronization therapy (CRT) within the last 6 months, chronic obstructive pulmonary disease (GOLD II), or other structural lung disease, primary haemodynamically significant uncorrected valvular heart disease (obstructive or regurgitant) with planned intervention within 6 months of PG, scheduled CRT initiation within 3 months after PG, or were using or had previously used home oxygen therapy or any positive airway pressure (PAP) therapy [including continuous positive airway pressure, bilevel PAP, and adaptive servo-ventilation (ASV)].

The study protocol was approved by local ethical committee, and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All patients gave informed consent to participate in the study.

**Cardiorespiratory polygraphy**

All sleep studies were undertaken using in-hospital unattended overnight cardiorespiratory PG (Embletta\textsuperscript{TM}, NOX T3\textsuperscript{TM}, SOMNOScreen\textsuperscript{TM}). We reviewed each individual’s first diagnostic PG. Nasal air flow measured by nasal pressure, chest and abdominal effort, pulse oximetry, snoring and body position were recorded continuously and analysed as described previously.\textsuperscript{10} At least two independent sleep specialists scored these recordings according to recent guideline recommendations.\textsuperscript{9,20} Briefly, an apnoea was scored if breathing amplitude decreased by ≥90% for ≥10 s, with (OSA) or without (CSA) any visible ribcage and abdominal respiratory impedance signals. Hypopnoea was defined as a decrease in breathing amplitude of ≥30% for ≥10 s accompanied by a ≥3% drop in oxygen saturation. Patients were classified as having either predominantly CSA or OSA, according to the classification of the majority of apnoea events. Apnoea–hypopnoea index and T90 were calculated. According to recent guidelines,\textsuperscript{3} SDB was defined as absent when AHI was <5/h, mild if AHI was 5–14/h, moderate if AHI was 15–29/h, and severe if AHI was ≥30/h, independent of pulse oximetry results.

**Outcomes**

All-cause mortality was defined as death from any cause, determined by hospital records, or phone calls to patients, their relatives or referring primary physicians or cardiologists. For cases where the cause of death was not determined in this manner, state authorities were involved. Patients were followed up from the time of their PG study until 31 July 2013.

**Statistical methods**

Incidence rates (per 100 person-years) were calculated to determine the association between AHI and T90 and all-cause mortality. The impact of these parameters on the time to death was assessed using Kaplan–Meier analysis, where AHI, SDB type, and T90 were categorized into groups based on the established cut-off values or quartiles, respectively. Multivariable Cox regression models were calculated, adjusting for important predictors, to investigate the influence of AHI, SDB type (no or mild SDB, moderate-to-severe OSA, moderate-to-severe CSA), and T90; some combinations and interactions of these predictors were also investigated. Adjustment factors were selected based on stepwise backward selection, using a likelihood ratio test with significance level 0.05 for exclusion and 0.01 for re-entry. Candidate predictors were NYHA class, ischaemic cardiomyopathy (ICM), diabetes, body mass index (BMI), heart rhythm, implanted cardioverter defibrillator (ICD), or CRT devices, and the use of diuretics, β-blockers and digitals glycosides as part of baseline HF therapy. In cases where CRT or any kind of PAP therapy was initiated during follow-up, these parameters were handled as time-dependent covariates. In addition, clinically important and established predictors age and gender were included in all multivariable models, irrespective of their statistical significance.

To consider potential confounding, the effect estimate obtained for AHI and T90 in the selected model was compared with that obtained for the corresponding starting model. Results are given as hazard ratio.
(HR) with corresponding 95% confidence intervals (CI) and two-sided Wald P-value. A P-value of <0.05 was defined as statistically significant. The linearity and proportional hazards assumptions of the selected model were assessed based on the martingale and Schoenfeld residuals, respectively.

To identify an optimal cut-off value for T90 that distinguishes patients who died from those who survived, a receiver operating characteristic (ROC) curve analysis was performed. A cut-off point was chosen based on the Youden index, i.e. as the point that optimises the differentiating ability when sensitivity and specificity are considered equally important. To visualize relations between AHI and T90, a bivariate kernel density estimate (Epanechnikov kernel, bandwidth 0.5) was used. Descriptive statistics are presented as mean ± standard deviation (SD) or relative frequencies (in %). Analyses were performed using Stata SE 13.1.

**Results**

A total of 1249 patients met the study inclusion and exclusion criteria (Figure 1). After exclusion of 286 patients who had PG recordings in which <90% of the recording time had pulse oximetry data, the final analysis included 963 patients (Table 1). The median follow-up was 7.35 years (95% CI 6.57–7.81) and median survival was 6.5 years (95% CI 6.07–7.52); a total of 49.8% (480/963) of patients died within the follow-up time.

**Apnoea–hypopnoea index as a predictor of all-cause mortality**

The mortality rate per 100 person-years (with 95% CI) in HF-REF patients with no, mild, moderate, or severe SDB was 6.79 (5.43, 8.49), 9.43 (7.79, 11.42), 11.08 (9.36, 13.11), and 13.37 (11.47, 15.59), respectively. The Kaplan–Meier survival curve is shown in Figure 2. As AHI increased, so did the probability of death from any cause. Patients with no SDB had a 5-year survival probability of 71%, whereas survival probabilities in those with mild, moderate, and severe SDB were lower (63, 58, and 54%, respectively).

Apnoea–hypopnoea index (as a continuous predictor) was significantly associated with time to death from any cause (HR 1.011, P < 0.001) in a simple Cox model. However, the effect size was reduced after adjustment for age and gender (HR 1.007, P = 0.015) and was no longer statistically significant after adjustment for age, gender, BMI, NYHA class, LVEF, CRT, ICM, diabetes, and HF medication (β-blocker, digitalis glycosides) at baseline (HR 1.005, P = 0.085).

**Moderate-to-severe central sleep apnoea and obstructive sleep apnoea as predictors of all-cause mortality**

Mortality rates per 100 person-years (with 95% CI values) were higher in HF-REF patients with moderate-to-severe CSA (13.11; 11.48, 14.98) or moderate-to-severe OSA (10.31; 8.28, 12.83) compared with those who had no or mild SDB (8.09; 7.00, 9.36). Kaplan–Meier curves for this comparison are shown in Figure 3. Cox analysis comparing moderate-to-severe OSA and CSA patients with those with no or mild SDB, respectively, showed that only moderate-to-severe CSA was associated with a significantly higher risk of death (final model in Table 2).

**Hypoxaemic burden as a predictor of all-cause mortality**

As hypoxaemic burden increased, the probability of death increased. The 5-year survival probabilities of patients in quartiles 1, 2, 3, and 4 of T90 were 70, 63, 60, and 50%, respectively. Corresponding values for the mortality rate per 100 patient-years (with 95% CI) were 6.93 (5.69, 8.43), 9.40 (7.80, 11.33), 9.40 (7.80, 11.33), 11.50 (9.69, 13.37), and 13.37 (11.47, 15.59), respectively.

**Figure 1** Study flow chart: from 4 December 2002 to 31 July 2013 a total of 11 782 patients were tested for the presence of sleep-disordered breathing. Cardiorespiratory polygraphy (PG) was performed in 1249 patients with stable heart failure with reduced ejection fraction (HF-REF) who fulfilled strict inclusion and exclusion criteria. Of these, 286 patients had to be withdrawn from final analysis because pulse oximetry signals were not sufficient for ≥90% of recording time. Asterisk denotes no relevant differences in baseline characteristics seen between the 286 excluded patients and the remaining 963.
Kaplan–Meier survival curves are shown in Figure 4.

Table 3 shows results of an adjusted model of the relationship between T90 and time to death from any cause. Hypoxaemic burden (T90) was significantly associated with time to death ($P_{0.001}$), independent of other relevant prognostic factors. The risk of death increased by 16.1% (95% CI 1.086, 1.242) for every 1-h increase in T90.

Comparison between apnoea–hypopnoea index, moderate-to-severe central and obstructive sleep apnoeas, and hypoxaemia

In a multivariable Cox model, including both AHI and T90, T90 was the dominant predictor of all-cause mortality with an HR of 1.154 (1.08, 1.24). Kaplan–Meier survival curves are shown in Figure 4.

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Effect of nocturnal hypoxaemia on mortality in stable HF patients

The HR for AHI was 1.002 (95% CI 0.997, 1.008; P = 0.444).

T90 values of zero or close to zero were often seen in combination with a wide range of AHI values (0 to \(\approx 50\) short episodes per hour, Figure 4). Apnoea–hypopnoea index showed the highest density between 10/h and 50/h with a wide range of T90 values (0–8 h, Figure 5). Simple correlation analysis showed a moderate
correlation between T90 and AHI (Spearman correlation: \(r = 0.54; P < 0.001\)).

To explore the relationship between the type of SDB (no or mild SDB, moderate-to-severe CSA, moderate-to-severe OSA) and T90, the former predictor and its interaction with T90 were added to the model shown in Table 3. Again, T90 was the dominant predictor (\(P < 0.001\); type of SDB \(P = 0.153\)) and its effect did not change significantly between patients with no or mild SDB, moderate to severe CSA, and moderate to severe OSA (\(P = 0.980\)).

T90 threshold

Receiver operating characteristic analysis of a potential T90 threshold suggested that a cut-off value of 22 min (0.37 h) was useful for identifying HF-REF patients with higher all-cause mortality. Thus, patients who had nocturnal oxygen saturation <90% for \(\geq 22\) min per night were at higher risk of dying than those with a T90 duration of \(\leq 22\) min.

Discussion

This study is the largest to investigate the effects of SDB-associated nocturnal hypoxaemia on survival in a well-defined cohort of HF-REF patients treated to current HF guidelines. Heart failure with reduced left ventricular function patients with SDB, especially moderate-to-severe CSA, had reduced survival. Hypoxaemic burden (time spent with oxygen saturation <90%, T90) was the most robust independent predictor of all-cause mortality in HF-REF patients, probably because the total AHI is limited in HF-REF patients who often have long apnoea/hypopnoea episodes. A T90 of 22 min was identified as the cut-off value for best predicting mortality in HF-REF patients.

Table 2 Results of an adjusted model of moderate-to-severe CSA with respect to time to death (observations: 963; adjusted \(R^2\) : 0.260).

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe CSA (yes vs. no)</td>
<td>1.233</td>
<td>1.012, 1.502</td>
<td>0.038</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.038</td>
<td>1.026, 1.049</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.232</td>
<td>0.960, 1.583</td>
<td>0.102</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.970</td>
<td>0.946, 0.995</td>
<td>0.020</td>
</tr>
</tbody>
</table>
| NYHA class
  III vs. II | 1.662 | 1.331, 2.074 | <0.001 |
  IV vs. II | 1.986 | 1.411, 2.796 | <0.001 |
| LVEF (%) | 0.981 | 0.969, 0.993 | 0.003 |
| CRT (yes vs. no) | 1.594 | 1.264, 2.011 | <0.001 |
| ICM (yes vs. no) | 1.626 | 1.343, 1.968 | <0.001 |
| Diabetes (yes vs. no) | 1.386 | 1.141, 1.684 | 0.001 |
| β-Blockers (yes vs. no) | 0.529 | 0.411, 0.681 | <0.001 |
| Digitalis (yes vs. no) | 1.277 | 1.049, 1.556 | 0.015 |

BMI, body mass index; CI, confidence interval; CRT, cardiac resynchronization therapy; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 3 Results of an adjusted model of time spent with oxygen saturation <90% (T90) with respect to time to death (observations: 963; adjusted \(R^2\) : 0.276).

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T90 (h)</td>
<td>1.161</td>
<td>1.086, 1.242</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.037</td>
<td>1.026, 1.048</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.307</td>
<td>1.024, 1.670</td>
<td>0.032</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.960</td>
<td>0.935, 0.985</td>
<td>0.002</td>
</tr>
</tbody>
</table>
| NYHA class
  III vs. II | 1.612 | 1.290, 2.013 | <0.001 |
  IV vs. II | 1.976 | 1.410, 2.771 | <0.001 |
| LVEF (%) | 0.980 | 0.968, 0.992 | 0.001 |
| CRT (yes vs. no) | 1.598 | 1.268, 2.014 | <0.001 |
| ICM (yes vs. no) | 1.664 | 1.376, 2.012 | <0.001 |
| Diabetes (yes vs. no) | 1.375 | 1.131, 1.672 | 0.001 |
| β-Blockers (yes vs. no) | 0.553 | 0.431, 0.710 | <0.001 |
| Digitalis (yes vs. no) | 1.289 | 1.058, 1.570 | 0.012 |

BMI, body mass index; CI, confidence interval; CRT, cardiac resynchronization therapy; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 4 Kaplan–Meier survival curves by quartile of time with nocturnal oxygen saturation below 90% (T90). T90 quartile 1: \(\leq 0.02\) h (1.4 min); T90 quartile 2: \(>0.02\) h (1.4 min) to \(< 0.20\) h (12.1 min); T90 quartile 3: \(0.20\) h (12.1 min) to \(< 0.87\) h (52.2 min); T90 quartile 4: \(\geq 0.87\) h (52.2 min).
Obstructive sleep apnoea has been associated with worse outcome in newly-diagnosed HF patients, and moderate-to-severe OSA and CSA were independently associated with increased mortality in acute decompensated HF patients. In contrast, another study in HF-REF patients was unable to confirm the negative effect of SDB on all-cause mortality or a combined endpoint of death and transplantation. However, that trial had a short follow-up duration (median 52 months) and mild cases of SDB (AHI ≥ 5/h) were included. The only measure of hypoxaemia studied was minimum oxygen saturation, which does not accurately reflect hypoxaemic burden.

The present study used strict inclusion and exclusion criteria to enrol 963 patients with stable and well-treated HF-REF and information on T90. The prevalence of SDB was 80%, comparable with the 76% previously reported in a sample of 700 HF-REF patients. The link between moderate-to-severe CSA and worse outcome identified in this study is in agreement with previous findings from France. Damy et al. investigated the influence of SDB on a combined endpoint of left ventricular assist device implantation, heart transplantation, and death. Although having a much smaller sample size, less strict inclusion criteria, a shorter follow-up period, and a composite endpoint, they showed that severe SDB was an independent predictor of prognosis. In addition, as in the current study, severe CSA was particularly associated with worse outcome.

Another prospective study compared mortality rates in HF-REF patients with none or mild SDB (nmSDB, AHI <15/h) or untreated moderate-to-severe OSA (AHI ≥ 15/h). During a mean follow-up of 2.9 years, mortality rates per 100 person-years were 4.2 in the nmSDB group and 8.7 in the OSA group. In the current study, mortality was even higher, at 8.09 per 100 person-years in nmSDB and 10.31 in OSA. This may have been due to the longer follow-up, or the inclusion of a higher proportion of males and patients with ischaemic HF aetiology. Different results were obtained from multivariate models, with the study by Wang et al. reporting an increased risk of death in HF-REF patients with OSA after adjustment for LVEF, NYHA class, and age. Javaheri et al. investigated whether CSA directly influenced prognosis in male HF-REF patients. The authors followed up 88 HF-REF patients (56 with CSA, 32 without SDB) over a median follow-up of 51 months. Cox multiple regression analysis identified CSA as one of the three independent risk factors for reduced survival. T90 was a significant predictor of survival in univariate analysis (HR 1.007 per min of T90, P = 0.03). Data from the current study showed that moderate-to-severe CSA and, in particular, T90 were associated with increased risk of death. Other parameters associated with reduced survival were age, male gender, higher NYHA class, ICM, diabetes, the presence of CRT, and treatment with digoxis glycosides. The latter of these factors are markers of advanced
HF, hence their association with increased mortality. Markers of improved survival were better LVEF and the use of β-blockers. All of these match well with known predictors of survival in HF-REF.24

Apnoea—hypopnoea index on its own might not be the best metric to determine the severity of OSA or CSA in HF-REF patients. It does not consider the duration of episodes and cannot differentiate between patients with a number of short episodes and those with the same number of longer episodes. In addition, our findings show that short AHI episodes do not seem to be long enough to cause oxygen desaturation to <90%. The length of respiratory events (including apnoeas and hypopnoeas) and also their associated ventilation lengths in patients with HF-REF are all dependent on cardiac function.18,19,23 The greater the extent of cardiac dysfunction, the longer these events will be. As a result, the potential number of apnoeas and hypopnoeas within an hour (the AHI) is limited. Therefore, T90 might be a better measure by which to characterize moderate-to-severe SDB. In addition, and irrespective of normal oxygen saturations during the day, nocturnal rostral fluid shift to the lung and neck might aggravate obstruction of the upper airways and pulmonary congestion, and therefore also promote oxygen desaturation.26

In this study, Cox analyses showed that T90 was the best predictor of time to death from any cause (HR 1.154; P < 0.001 vs. HR 1.0002 for AHI; P = 0.444). These findings are consistent with the results of a survival analysis in non-HF patients with suspected OSA admitted for full PSG, which showed that T90 was the strongest OSA-related predictor of cardiovascular events.27 Apnoea—hypopnoea index was significantly associated with a composite cardiovascular outcome on univariate analyses, but was no longer significant after adjustment for potential confounders.27

Overall, hypoxaemia and hypoaxemic burden as a consequence of apnoeas and hypopnoeas might better represent the adverse effects of nocturnal respiratory events and arousals from sleep, explaining why it is a more robust predictor of survival in HF-REF. Other data also support this concept: in a study of 64 HF-REF patients, an increase in nocturnal brain natriuretic peptide concentrations was associated with hypoaxemic burden (T90), but not with the frequency or type of SDB episodes.28

It appears that a certain threshold of hypoxaemia needs to be exceeded to cause adverse cardiovascular outcomes.27 In a longitudinal study of 10 701 adults, oxygen saturation parameters during sleep were some of the most predictive parameters for sudden cardiac death.6 In detail, mean nocturnal oxygen saturation <93% and lowest oxygen saturation <78% were associated with a hazard ratios for death of 2.93 and 2.60, respectively. T90 was not determined in that study, but the findings are supportive of hypoxaemia being associated with worse outcomes, and an increased cardiovascular death rate in particular.

Although this study reports robust data, showing that nocturnal hypoxaemia is associated with increased mortality in stable HF-REF patients, this does not necessarily mean that treatments aimed at reducing nocturnal hypoxaemia will improve survival. In fact, the results of one study showed that nocturnal oxygen therapy has little benefit in HF-REF patients,30 and oxygen supplementation may have deleterious effects, as has been documented in patients with acute myocardial infarction.31 However, current data also suggest that the intermittent hypoxaemia and associated ischemia—reperfusion—re-oxygenation sequence might be one mechanism contributing to reported associations between intermittent hypoxaemia and adverse outcomes in patients with OSA.32

Simple lowering of the AHI does not necessarily translate into improved quality of life and/or survival, as clearly demonstrated by the first results of the SERVE-HF study.31 In fact, effective suppression of respiratory events by treatment with ASV therapy may even be associated with increased mortality in patients with severe systolic heart failure and predominant central sleep apnoea.33 Additional SERVE-HF study results, and especially the findings of a mechanistic substudy,34 are eagerly awaited to shed more light on what is clearly a very complex situation. However, it is interesting to note that, in the SERVE-HF study, ASV therapy was associated with a significant decrease in the AHI but T90 remained close to, or even above, 20 min.33

Limitations
This is the largest study looking at the prognostic impact of SDB and nocturnal oxygen saturation in a well-characterized cohort of HF-REF patients. It is also probably the first study in which HF was treated according to current HF guidelines24 and a uniform and a recommended definition of apnoeas and hypopnoeas used.9 The main weakness of the trial is the use of multi-channel PG rather than full PSG to identify SDB and determine its severity. Theoretically, this might lead to an underestimation of the AHI because actual sleep time (recorded only during full PSG) might be shorter than the estimated sleep time during PG. The moderate-to-severe CSA-to-OSA ratio in this study was 2.6:1, which is higher than that reported by Yumino et al.,35 but less than that documented in other studies, even those using full PSG.6,37 However, central respiratory events occur physiologically when sleep stage changes and may even occur during awake periods in patients with severe HF-REF. Therefore, an overestimation of central respiratory events cannot fully excluded and full PSG might be more appropriate for the determination of the exact number of sleep-related respiratory events and to distinguish central from obstructive events. This study used both abdominal and thoracic impedance effort belts to maximize the reliability of PG data. The fact that the study was conducted at a tertiary referral centre that sees a higher proportion of older patients and/or those with more advanced heart failure may have contributed to a greater proportion of central respiratory events and Cheyne–Stokes respiration.

A current definition of hypopnea was used in this study: ≥30% reduction in airflow amplitude accompanied by a desaturation of ≥3%.9,20 Previous studies mostly used a desaturation criterion of ≥4%, meaning that they are likely to report an even higher hypoaxemic burden in patients classified having SDB, with even greater differentiation of T90 from AHI as a predictor of survival than was seen in this study.

Conclusions
Sleep-disordered breathing and nocturnal hypoxaemia are highly prevalent in stable HF-REF patients. Moderate-to-severe CSA and, in particular, hypoaxemic burden (T90) were identified as independent predictors of time to death from any cause in these patients. Screening for SDB and determination of the hypoaxemic burden should be included in the management of HF-REF patients and...
treatment of SDB should not only target apnoeas and hypopnoeas, but also nocturnal oxygen saturation.

Authors’ contributions

A.B., U.T., and K.W. performed statistical analysis. O.O. and D.H. conceived and designed the research, and handled funding and supervision. B.W., T.B., H.F., and O.O. acquired the data. B.W., A.B., and O.O. drafted the manuscript. All authors made critical revision of the manuscript for key intellectual content.

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References


Danon disease: a rare cause of left ventricular hypertrophy with cardiac magnetic resonance followup

Hajnalka Vago1, Miklos Somloi2, Attila Toth1, and Bela Merkely1

1Heart and Vascular Center, Semmelweis University, 68 Városmajor Street, Budapest H-1122, Hungary; and 2Budai Irgalmasrendi Kórház, Budapest, Hungary

*Corresponding author. Tel: +36 20 825 8036, fax: +36 1 458 6842, Email: merkely.bela@kardio.sote.hu

The first cardiac examination of a 15-year-old female patient was due to palpitation. The ECG morphology was typical of Wolff–Parkinson–White syndrome (Panel A). Three years later the patient’s echocardiography, which was performed after her mother’s sudden death during sport activity, suggested hypertrophic cardiomyopathy (Panel B), thus a cardiac magnetic resonance (CMR) examination was performed. Cardiac magnetic resonance revealed normal ventricular volumes and ejection fractions but demonstrated expressed concentric left ventricular hypertrophy (LVH) (Panel C; Supplementary material online, Movie S1). The delayed contrast enhancement images showed patchy midmyocardial accumulation involving different left ventricular regions (Panel D). In the meantime, a genetic test proved Danon disease. Cardiodefibrillator (ICD) implantation was indicated, but the patient did not give an informed consent to the procedure. A follow-up CMR 4 years later revealed a mild progression of LVH and a marked progression of fibrotic degeneration (40 vs. 24% of left ventricular mass) (Panel E). These unfavourable changes convinced the patient to give an informed consent to ICD implantation.

Danon disease is an X-linked disorder due to deficiency of LAMP2 gene. It is a rare multisystemic glycogen storage disease, resulting often in WPW syndrome, LVH, and structural left ventricular abnormalities such as fibrotic replacement. The structural changes cause electrical inhomogeneity leading to life-threatening ventricular arrhythmias. To our knowledge, our study is the first reported case of Danon disease with long-term CMR follow-up. Cardiac magnetic resonance proved a marked progression of fibrosis, which may contribute to heart failure, ventricular arrhythmias and the poor outcome of Danon disease patients.

Supplementary material is available at European Heart Journal online.