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Original Article

Prognostic impact of sleep duration and sleep efficiency on mortality in patients with chronic heart failure

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ABSTRACT

Background: Both short and long self-reported sleep duration (SD_{SR}) has been linked to increased mortality. Our analysis tested the hypothesis that long SD_{SR} is paralleled by impaired objective sleep efficiency (SE_{PSG}) measured by polysomnography (PSG) and that impaired SE_{PSG} is a risk factor for death in patients with chronic heart failure (CHF).

Methods: SD_{SR} and SE_{PSG} were assessed by standardized questionnaire and PSG in 188 consecutive CHF patients (age range, 63 ± 10 year; left ventricular ejection fraction, 34 ± 10%) admitted to the Sleep Center of the University Hospital Regensburg between 1/2002 and 12/2009. The mean follow-up period was 44 ± 26 months.

Results: SE_{PSG} in CHF patients from the highest quintile of SD_{SR} ($\geqslant$9 h) was significantly lower compared with the middle quintile (7.25–8 h; 71 ± 15% vs 77% ± 11%; $p = 0.032$) and similar to the lowest quintile ($\leqslant$5.75 h; 71 ± 15% vs 71 ± 16%, $p = 0.950$). SE_{PSG} is an independent predictor for death in the multivariable model after accounting for the significant confounders age, left ventricular ejection fraction, cause of CHF, and NYHA class (hazard ratio [HR] per 5% increase, 0.85; 95% confidence interval [CI], 0.77–0.93; $p < 0.001$).

Conclusions: Data indicate that subjective long sleepers with CHF have poor sleep efficiency. Objectively measured SE_{PSG} strongly predicts mortality in CHF patients, underscoring the importance of objective assessment of sleep.

1. Introduction

Modern lifestyle contributed to an increasing restriction of sleep in the past half century. Currently, approximately 45% of American adults report sleep durations of less than seven hours on a regular weekday, and roughly one-third denies that their sleep needs required to function at their best are being met [1]. The vast majority of a representative sample of Americans believes that sufficient and undisturbed sleep is an integral part of a healthy lifestyle [1].

In agreement with this notion, there is compelling evidence from large cohort studies linking chronic exposure to short sleep duration with cardiovascular events and mortality [2–6]. In addition, sleep restriction experiments demonstrate a causal relationship between short sleep duration and acute sympathetic activation, increase of blood pressure, and impairment of glucose metabolism [7,8]. Interestingly, long self-reported sleep duration (SD_{SR}) also is associated with increased mortality in large cohort studies [3,4,6]. Thus, according to the current knowledge a U-shaped relationship between nightly sleep duration and mortality has been observed. The highest mortality risk is reported in individuals with the shortest and longest SD_{SR}, whereas those who report sleep durations of seven to eight hours carry the lowest risk [4–6,9].

However, previous epidemiological studies fall short to explain why long sleepers carry similar mortality risk as short sleepers. Proposed mechanisms include that individuals with long SD_{SR} have poor sleep efficiency due to sleep disorders (eg, sleep-disordered breathing, [SDB]), or that long SD_{SR} simply reflects terminal disease (eg, advanced heart failure) [10–13]. In addition, it is unknown if the common phenomenon of the misperception of SD_{SR} may even

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have weakened the observed relationship between sleep duration and mortality [14–16].

Therefore, the aim of our study was to test if (1) longer SD_{SR} is paralleled by impaired polysomnographically assessed sleep efficiency (SE_{PSG}), which provides an objective measurement of sleep efficiency; and (2) if SE_{PSG} is, in contrast to SD_{SR}, an independent risk factor for death. These hypotheses were studied in a sample of chronic heart failure (CHF) patients with well-defined disease severity in the absence of other known life-threatening diseases.

2. Methods

2.1. Subjects

We examined 411 CHF patients who were referred for polysomnography (PSG) to the sleep laboratory of the University Hospital Regensburg between 01/2002 and 12/2009. Inclusion criteria for this analysis were: (1) CHF due to ischemic or nonischemic cardiomyopathy with objective evidence of systolic dysfunction (left ventricular ejection fraction [LVEF], $\leqslant 50\%$) measured by echocardiography within 3 months prior to enrollment ($n = 346$); and (2) stable clinical status and stable optimal medical therapy for at least 4 weeks. Patients were included regardless of symptoms of sleep disordered breathing (SDB). Exclusion criteria were (1) CHF due to valvular heart disease ($n = 0$), (2) listing for heart transplantation ($n = 15$), (3) known life-threatening illnesses (eg, severe pulmonary disease or cancer, $n = 35$), (4) oxygen or current treatment with positive airway pressure ($n = 0$), and (5) unavailability of health questionnaires ($n = 85$). This retrospective analysis was approved by the local ethics committee.

2.2. Polysomnography

PSG was performed in all subjects using standard polysomnographic techniques [17]. During PSG, body position, eye and leg movements, cardiotachography, nasobuccal airflow, chest and abdominal effort, electroencephalogram (EEG) monitoring, and arterial oxyhemoglobin saturation (SaO_2) assessed by pulse oximetry were recorded (Alice 3.5, Respironics, Pittsburgh, USA). Sleep stages were determined according to Rechtschaffen and Kales [18]. Apnea was defined as a cessation of inspiratory airflow ($\geqslant 10$ s) and hypopnea was defined as a reduction of airflow (>50%) or thoracoabdominal effort lasting $\geqslant 10$ seconds resulting in a $\geqslant 4\%$ drop in SaO_2 [19]. The apnea–hypopnea index (AHI) was defined as the number of apneas or hypopneas per hours of sleep. The oxygen desaturation index was defined as the number of $\geqslant 4\%$ oxygen desaturations per hour of sleep. Periodic limb movements of sleep were scored only if they were part of a series of $\geqslant 4$ successive movements lasting at least 0.5 to 5 seconds, separated by intervals between four and 90 seconds and occurring during regular breathing [20,21]. Secondary periodic limb movements after an arousal or leg movement were not scored [21]. Time in bed (TIB_{PSG}) was defined as the time span between lights off and lights on recorded by PSG laboratory staff, and total sleep time (TST_{PSG}), was defined as the total time subjects spent in sleep stages 1 to 4 and REM recorded by EEG monitoring. SE_{PSG}, an important indicator of sleep quality, is the proportion of sleep in the recorded period and was calculated as the ratio of TST_{PSG} divided by TIB_{PSG} in percent.

2.3. Interviews and other measurements

At the time of the diagnostic PSG, all subjects underwent a baseline clinical examination with measurements of vital signs and anthropometry as well as routine laboratory analyses. Subjects were asked to complete the detailed standardized health questionnaire of the sleep center, including the assessment of prevalent medical conditions and risk factors, CHF symptoms, and prescription medication use. Furthermore, specific questions concerning sleep habits, such as self-reported habitual sleep duration (eg, TIB_{SR}, average numbers of nightly awakenings, initial and nightly sleep onset latency), snoring, or daytime sleepiness were recorded. SD_{SR} was calculated as follows: TIB_{SR} – (initial self-reported sleep onset latency plus number of nightly awakenings $\times$ nightly sleep onset latency). Self-reported sleep efficiency (SE_{SR}) was determined by dividing SD_{SR} by TIB_{SR} in percent. Delta sleep efficiency (ΔSE, %) was defined as SE_{SR}–SE_{PSG}, as a metric of potential misperception of sleep quality.

2.4. Outcome

The primary outcome was the all-cause mortality during follow-up. Outcome and causes of death were ascertained by medical documents in the case of in-hospital death or family physicians in the case of out-of-hospital death. Follow-up was performed between 12/2009 and 01/2010.

2.5. Statistical analysis

Continuous data are expressed as means ± standard deviation, unless otherwise indicated. Baseline characteristics of patients were compared by analysis of variance. Differences between groups were assessed by 2-sided t tests for continuous variables, and by χ^2 tests for nominal variables, except where expected counts were <5, in which the Fisher exact test was used.

To determine the impact of SE_{PSG} on mortality risk independently of other risk factors, a multivariable adjusted Cox proportional hazards model over the course of the study was used. Known risk factors for death and potential confounders were introduced into the model using a forward stepwise regression analysis by selecting variables according to the likelihood ratio test. The relationship between single variables was assessed in a correlation matrix using Pearson product moment correlation above and Spearman nonparametric below the diagonal to avoid excess collinearity in the multivariable Cox proportional hazard model. Variables included age, gender, LVEF, New York Heart Association (NYHA) functional class, causes of CHF, body mass index (BMI), diabetes, arrhythmia, nocturia, AHI, treatment of SDB with positive airway pressure on follow-up, and periodic limb movement index, while age was included as a fixed factor due to its known high prognostic value for death. In addition to avoiding multicollinearity between predictor variables in the multivariable model, the variance inflation factor for each variable was calculated. A variance inflation factor of >2.5 was considered as an indicator for multicollinearity concerns. In all models, proportional hazards' assumptions were verified using the Grambsch–Therneau residual-based test. It was applied by the R procedure called cox.zph (library: survival), while a p value of <0.05 was considered a violation. To perform an exploratory graphical analysis of the nonlinear relationship of self reported sleep duration and self-reported time in bed to mortality, restricted cubic splines (RCS) with 3 knots were used in a multivariable Cox proportional hazards regression model analysis. For simplicity, we designated the knots at the fifth, 50th, and 95th percentiles. The results were adjusted for the same potential confounding factors as in the main Cox proportional hazards regression model analysis. This method was applied by use of a SAS macro written by Heinzl and Kaider [22].

A 2-sided p value of <0.05 was considered as statistically significant. All analyses were performed using IBM SPSS Statistics 20.0, *R* (version 2.14.2) and using the package *survival* and *SAS 9.3* (*Institute, Cary, NC, USA*).