Sleep-disordered breathing predicts cardiovascular events and mortality in hemodialysis patients

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Abstract

Background. Sleep-disordered breathing (SDB), characterized by repetitive apnea and hypopnea during sleep, is a risk factor for cardiovascular disease. However, the links between SDB and cardiovascular events in hemodialysis (HD) patients have not been clearly evaluated.

Methods. We followed the clinical outcome of 94 HD patients, who underwent overnight pulse oximetry on dialysis day. The SDB group was defined as 3% oxygen desaturation index (ODI) over five events per hour, and the others were the normal group. The primary outcome was cardiovascular events and death. We used Kaplan–Meier curve and Cox proportional hazard model for survival analyses.

Results. Forty-four patients (46.8%) were classified into the SDB group. Body mass index, diabetes mellitus, 3% ODI and Epworth sleepiness scale were significantly higher, and duration of dialysis, Kt/V, normalized protein catabolism rate and hemoglobin were lower in the SDB group than in the normal group. During a median 55 months of follow-up, Kaplan–Meier analysis revealed that the SDB group had a significantly higher rate of cardiovascular events and all-cause mortality than the normal group. Age, cardiothoracic ratio, serum albumin and 3% ODI were predictors of cardiovascular events and all-cause mortality at univariate Cox regression analysis. In the adjusted analysis, SDB is an independent predictor of increased cardiovascular events (hazard ratio 3.10; 95% confidence interval (CI), 1.35–7.12; P = 0.008) and all-cause mortality (hazard ratio 2.81; 95% CI, 1.07–7.41; P = 0.037).

Conclusions. SDB is an independent risk factor for cardiovascular events and mortality in HD patients. Effective and
earlier treatment for these patients is needed to improve clinical outcome.

Keywords: cardiovascular events; hemodialysis; mortality; oxygen desaturation index; sleep-disordered breathing

Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive nocturnal hypoxia and sleep disturbances, such as snoring, frequent waking and daytime sleepiness. Hemodialysis (HD) patients have a higher prevalence (30–70%) and more severe SDB than the general population [1–7]. Although the SDB type in the general population is mostly the obstructive type, SDB in dialysis patients includes features of both central and obstructive types [1,3,8]. While obesity is closely associated with SDB severity in the general population, obesity itself might not be associated with SDB severity in dialysis patients [4,9]. These unique characteristics of SDB in dialysis patients seem to be linked to a reduction in airway muscle tone due to uremic toxins [10,11], metabolic acidosis and fluid overload resulting in upper airway closure [11,12] and increased chemoreflex sensitivity to carbon dioxide pressure (PCO$_2$), which leads to ventilatory instability and oscillations in respiratory output by lowering PCO$_2$ [3,9,13].

SDB has been reported to be associated with hypertension [14,15], coronary artery disease, stroke and all-cause death [16–19] in the general population. Several cross-sectional studies in dialysis patients reported that SDB is associated with severe coronary artery disease and elevated oxidative stress and hypertension [7,20]. In addition, in dialysis patients, nocturnal hypoxia due to SDB is linked to important cardiovascular risk factors, such as a nondipping arterial pressure profile, sympathetic hyperactivity and left ventricular hypertrophy [21–24]. We also reported that nocturnal hypoxia assessed by pulse oximetry is associated with elevated plasma C-reactive protein (CRP), an independent risk factor for cardiovascular disease in HD patients [25]. In several prospective outcome studies, poor sleep quality in dialysis patients predicts increased mortality [26,27].

However, it is still unknown whether repetitive nocturnal hypoxia due to SDB directly predicts future cardiovascular events and mortality in HD patients. We therefore prospectively followed the maintained HD patients who underwent overnight pulse oximetry to evaluate the clinical outcome of SDB.

Subjects and methods

Patients

We studied 94 HD patients (50 males and 44 females) in Japanese Red Cross Koga Hospital, Ibaraki prefecture, Japan. From April 2004 to March 2005, 108 dialysis patients were treated in our hospital. Among these patients, seven patients were excluded according to the following criteria: active malignancy, pulmonary disease, peritoneal dialysis, patients died within 3 month after pulse oximetry and those unable to cooperate or give consent. Among 108 patients, 1 was excluded because of hepatocellular carcinoma, 1 because of pulmonary hemorrhage, 1 because of fatal pneumonia, 2 because of peritoneal dialysis and 2 because of death within 3 months after pulse oximetry (1 sudden death and 1 malnutrition). Seven patients were unable to cooperate or give consent. Thus, a total of 94 patients were included in the final analysis. Dry weight was targeted in each case to achieve a normotensive edema-free state. This study followed the Declaration of Helsinki and was approved by the local ethics committee of Japanese Red Cross Koga Hospital, Japan. Informed consent was obtained from all patients.

Pulse oximetry

The presence and severity of SDB were determined by wristwatch-type pulse oximetry (PULSOX-MZ4; Teijin Pharma Ltd, Tokyo, Japan) [29–31]. Overnight home pulse oximetry was performed on dialysis day. When patients went to bed, a pulse oximeter was attached to the contralateral arm to the vascular access. It was removed when they awoke in the morning. The sensor probe was fitted to the second finger and secured with tape to prevent it from detaching. The internal memory of this device stores the values of arterial blood oxygen saturation by performing a moving average for the last 5 seconds with updates every second. Data were analyzed using the software supplied with the equipment (DS-M version 3.02; Konika Minolta, Tokyo, Japan) as previously described [32]. We used the value of oxygen desaturation index (ODI), as the indicator of SDB severity. The 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of the recording time in which the patient's blood oxygen level fell by 3%. The recording time was the time that the patient was in bed. However, this time is often longer than the correct sleep time. Therefore, the patients kept a sleep log in order to exclude the waking time from the analysis and minimize potential overestimation of the sleep time, as described previously [28–31]. SDB was defined as 3% ODI over five events per hour, as previously described [28–31]. Using pulse oximetry, we also recorded average oxygen saturation (SaO$_2$), minimum SaO$_2$, cumulative time when SaO$_2$ was <95% (expressed as a percentage of total sleep time) and the total pulse oximetry measurement time. The Epworth sleepiness scale (ESS) was used to investigate daytime sleepiness.

Other measurements

Blood samples were obtained on the first dialysis day of the week after the patients had been in the supine position for at least 10 min. Hemoglobin, serum albumin, total cholesterol, serum calcium, serum phosphate and intact parathyroid hormone (iPTH) were determined by an autoanalyzer. Kt/V and normalized protein catabolism rate (nPCR) were calculated using the formulas, as described previously [33]. Blood pressure was measured before HD with a calibrated digital scale. Body mass index (BMI) was calculated from weight and height measurements as weight (kg) divided by the square of height (m$^2$). Smoking and history of cardiovascular events were ascertained by questionnaire. Cardiovascular events were defined in the following section.

Outcome measurements

The primary outcomes were the first episode of fatal and nonfatal cardiovascular events and all-cause mortality. Cardiovascular events were defined as follows: angina or myocardial infarction (MI) documented by
electrocardiogram (ECG), congestive heart failure and symptomatic arrhythmia requiring hospitalization, stroke, peripheral vascular disease, major arterial/venous thrombotic episode and sudden death. For patients with multiple cardiovascular events, the time to the first episode was taken for survival analysis. Cardiovascular events and cause of death were assessed by the attending physician who was unaware of the ODI findings. The information in the patient medical chart was also included in the analysis. During the follow-up period, 47 patients were transferred to seven other dialysis clinics. The prognostic information about these patients was obtained from interviews with each attending doctor.

Statistical analysis
A statistical analysis was performed using StatView for Windows version 5.0 (SAS Institute Inc., Chicago, IL). Data were expressed as the mean ± SEM. We used the Student’s t-test to evaluate the differences in means and the χ² test to evaluate the differences in proportion. Cumulative patient and cardiovascular event-free survival was calculated with the Kaplan–Meier method, and comparisons between groups were made with the log-rank test. For evaluation of the effect of significant SDB in predicting the time to cardiovascular events and all-cause mortality, factors predictive of cardiovascular events and mortality were identified with Cox regression analysis to reduce the hazard ratios and 95% confidence interval (CI). Next, the predictors for SDB at baseline and the risk factors for cardiovascular events and mortality were entered into the multivariate Cox regression model. Log-transformed 3% ODI was used for Student’s t-test and Cox regression analysis because 3% ODI has a skewed distribution (Figure 1). A value of P <0.05 was considered to be significant.

Results

General characteristics
From April 2004 to March 2005, 94 maintenance HD patients (age 64.4 ± 1.3 years, male 53.2%, BMI 22.1 ± 0.5 kg/m², diabetes mellitus 40.4%, duration of dialysis 5.2 ± 0.5 years) in Japanese Red Cross Koga Hospital underwent overnight pulse oximetry. Informed consent was obtained from all patients.

The baseline clinical characteristics (demographic, clinical and biochemical parameters) were summarized in Table 1. The median 3% ODI of the total patients was

![Fig. 2. Cardiovascular event-free survival (A) and overall survival (B) calculated by the Kaplan–Meier method, base on the 3% ODI. SDB, 5 ≤ 3% ODI.](https://academic.oup.com/ndt/article-abstract/26/7/2289/1895824)
6.8 ± 0.8 (range 0.15–55.12) events per hour. Forty-four patients (46.8%) were classified into the SDB group. At baseline, BMI, diabetes mellitus and sleep parameters (3% ODI, average SaO₂, lowest SaO₂, SaO₂ <95% and ESS) were significantly higher in the SDB group than in the normal group, while duration of dialysis, Kt/V, nPCR and hemoglobin were significantly lower in the SDB group than in the normal group.

Distribution of SDB according to 3% ODI is presented in Figure 1. Forty-four SDB patients (46.8%) were classified into the SDB group. At univariate Cox regression analysis, 3% ODI as well as age, nPCR, cardiothoracic ratio and serum albumin predict incident cardiovascular events. However, male gender, BMI, diabetes mellitus, duration of dialysis, Kt/V, systolic blood pressure, hemoglobin, total cholesterol, calcium phosphate product, iPTH, average SaO₂, lowest SaO₂ and ESS failed to significantly predict cardiovascular events.

Univariate Cox regression analysis for cardiovascular events is presented in Table 2. At univariate Cox regression analysis, 3% ODI as well as age, nPCR, cardiothoracic ratio and serum albumin predict incident cardiovascular events. However, male gender, BMI, diabetes mellitus, duration of dialysis, Kt/V, systolic blood pressure, hemoglobin, total cholesterol, calcium phosphate product, iPTH, average SaO₂, lowest SaO₂ and ESS failed to significantly predict cardiovascular events.

Univariate Cox regression analysis for all-cause mortality is presented in Table 2. At univariate Cox regression analysis, 3% ODI as well as age, nPCR, cardiothoracic ratio and serum albumin predict incident cardiovascular events. However, male gender, BMI, diabetes mellitus, duration of dialysis, Kt/V, systolic blood pressure, hemoglobin, total cholesterol, calcium phosphate product, iPTH, average SaO₂, lowest SaO₂ and ESS failed to significantly predict cardiovascular events.

Multivariate Cox regression analysis for cardiovascular events and all-cause mortality by the SDB group as the referent normal group is shown in Table 3. The SDB group was significantly associated with cardiovascular events (hazard ratio 3.09; 95% CI, 1.48–6.46; P = 0.003) and all-cause mortality (hazard ratio 3.90; 95% CI, 1.64–9.30; P = 0.002) compared with the normal group. Subsequent

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiovascular events</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>1.05 (1.02–1.09)</td>
<td>1.05 (1.01–1.10)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.68 (0.82–3.43)</td>
<td>2.78 (1.17–6.61)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.03 (0.96–1.11)</td>
<td>1.03 (0.95–1.12)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.93 (0.96–3.86)</td>
<td>3.25 (1.45–7.29)</td>
</tr>
<tr>
<td>Duration of dialysis (year)</td>
<td>0.96 (0.88–1.04)</td>
<td>0.90 (0.79–1.01)</td>
</tr>
<tr>
<td>Kt/V (per week)</td>
<td>0.47 (0.17–1.33)</td>
<td>0.29 (0.10–0.91)</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>0.08 (0.01–0.72)</td>
<td>0.30 (0.03–3.37)</td>
</tr>
<tr>
<td>Cardiothoracic ratio (%)</td>
<td>1.10 (1.03–1.16)</td>
<td>1.10 (1.03–1.18)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.01 (0.99–1.02)</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>1.04 (0.81–1.35)</td>
<td>0.92 (0.70–1.21)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>0.45 (0.21–0.99)</td>
<td>0.38 (0.16–0.91)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>1.00 (0.99–1.01)</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>Ca × P</td>
<td>0.98 (0.95–1.00)</td>
<td>0.98 (0.95–1.01)</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>1.00 (0.997–1.001)</td>
<td>1.00 (0.998–1.002)</td>
</tr>
<tr>
<td>3% ODI (events/h)</td>
<td>2.73 (1.31–5.69)</td>
<td>4.99 (2.00–12.44)</td>
</tr>
<tr>
<td>Average SaO₂ (%)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.86 (0.70–1.05)</td>
</tr>
<tr>
<td>Minimum SaO₂ (%)</td>
<td>1.00 (0.98–1.02)</td>
<td>0.99 (0.97–1.00)</td>
</tr>
<tr>
<td>ESS</td>
<td>1.07 (0.99–1.15)</td>
<td>1.01 (0.91–1.11)</td>
</tr>
</tbody>
</table>

*Log-transformed values were used for the analysis. CI, confidence interval. Values expressed as mean ± SE or percent. BMI, body mass index; nPCR, normalized protein catabolism rate; iPTH, intact parathyroid hormone; ODI, oxygen desaturation index; SaO₂, oxygen saturation; ESS, Epworth sleepiness scale.
SDB predicts cardiovascular events

1 SDB group 3.09 (1.48–6.46) 0.003 3.90 (1.64–9.30) 0.002
2 1 + age 2.79 (1.33–5.82) 0.007 3.47 (1.45–8.29) 0.025
3 2 + gender 2.69 (1.28–5.65) 0.009 3.11 (1.29–7.48) 0.012
4 3 + diabetes mellitus 2.57 (1.18–5.62) 0.018 2.53 (1.02–6.28) 0.045
5 4 + history of cardiovascular events 2.66 (1.20–5.87) 0.016 2.53 (1.02–6.28) 0.045
6 5 + serum albumin 2.92 (1.29–6.59) 0.010 2.83 (1.11–7.26) 0.030
7 6 + cardiothoracic ratio 3.10 (1.35–7.12) 0.008 2.81 (1.07–7.41) 0.037

*p CI, confidence interval.

Table 3. Multivariate Cox regression analysis for cardiovascular events and all-cause mortality by the sleep-disordered (SDB) group as the referent normal group

Discussion

This cohort study suggests that SDB is a risk factor for cardiovascular events and mortality in HD patients. In addition, 3% ODI assessed by pulse oximetry is a novel prognostic marker, although other prospective outcome studies used apnea–hypopnea index (AHI) by polysomnography (PSG) as a prognostic parameter [16,19,34–36]. Repetitive apnea and hypopnea due to SDB cause intermittent hypoxia, hypercapnia, microarousal, pulmonary stretch receptor stimulation and chemoreceptor stimulation [37,38]. Repetitive nocturnal hypoxemia is also associated with increased oxidative stress, which induces the activation of inflammatory pathway and endothelium damage [39–41]. In addition, increased sympathetic activation caused by frequent awakening in SDB leads to hypertension, elevation of heart rate and platelet activation, which in turn contribute to coronary atherosclerosis [38,42,43]. Furthermore, intermittent negative intrathoracic pressure causes mechanical stress on the ventricular and atrial walls, which contribute to the development of left ventricular hypertrophy, heart failure and atrial fibrillation [38,42].

In this study, 3% ODI assessed by pulse oximetry is a prognostic parameter for cardiovascular events and mortality. In many SDB studies, AHI assessed by PSG is used as a diagnostic and prognostic parameter for SDB [18,19,44]. Standard PSG includes electroencephalogram, electrooculogram, submental electromyogram, ECG, chest wall movement by inductance plethysmography, airflow by a nasal pressure transducer and finger pulse oximetry [5,39]. Therefore, PSG could provide detailed sleep information including correct sleep time, AHI (average number of episodes of apnea and hypopnea per hour of sleep), apnea type (obstructive, central or mix), nocturnal average SaO2, sleep type [rapid eye movement (REM) or non-REM] and periodic leg movement [17–19,45]. However, PSG may not be practical in places where a sleep laboratory is not readily available. There is no sleep laboratory in most HD hospitals, although SDB is common in HD patients (30–70%) [1–7]. For this reason, PSG is not always useful for diagnosing SDB in HD patients. On the other hand, pulse oximetry, which could measure ODI, average SaO2, lowest SaO2 and heart rate, is easy to perform [32]. Therefore, pulse oximetry has been widely used to screen obstructive sleep apnea in the general population [46,47]. In addition, we recently reported that pulse oximetry is useful for screening sleep apnea in dialysis patients [48]. In this report, 3% ODI assessed by pulse oximetry was significantly correlated with AHI assessed by PSG (r = 0.657, P < 0.0001) [48], and using a cutoff of AHI ≥15 and 3% ODI (4% ODI) ≥15, the sensitivity and specificity were 100% (76.0%) and 55.2% (93.1%), respectively [48]. Several cross-sectional studies have shown that ODI assessed by pulse oximetry is associated with cardiovascular risk factors, such as coronary artery atherosclerosis [28] and silent cerebrovascular disease [29]. However, there has been no prospective outcome study that reveals the efficacy of ODI as a prognostic parameter. Our results suggest that ODI assessed by pulse oximetry is not only a screening marker for sleep apnea but also a prognostic parameter for cardiovascular events and mortality.

Zoccali et al. [49] reported that nocturnal low average SaO2 in dialysis patients (40 HD patients and 10 continuous ambulatory peritoneal dialysis patients) predicts cardiovascular complications. We also reported that nocturnal low average SaO2 in HD patients is associated with elevated plasma CRP, an independent risk factor for cardiovascular disease [25]. From these results, we expected that nocturnal average SaO2 would predict cardiovascular events and all-cause mortality in this study. Unexpectedly, however, average SaO2 did not predict these clinical outcomes (Table 2). AHI/ODI, the number of apnea and hypopnea events per hour, is thought to be closely associated with average SaO2. Actually, 3% ODI is inversely correlated with average SaO2 in our study (r = –0.457, P < 0.001). However, there are several differences between AHI/ODI and nocturnal average SaO2. In several cases, sustained hypoxia disease,
such as chronic obstructive pulmonary disease and lung congestion, results in nocturnal low average SaO₂, even if AHI/ODI is very small. In addition, the pathological differences between intermittent hypoxia and sustained hypoxia have been described in some experimental studies. A rat model study from Hui et al. [50] revealed that attenuation of catecholamine biosynthesis and release in carotid bodies during intermittent hypoxia as compared with sustained hypoxia may contribute to augmented chemoreceptor input and increased sympathetic output leading to the development of hypertension. In an in vitro model, Hela cells exposed to intermittent hypoxia demonstrated activation of the proinflammatory transcription factor nuclear factor-κB, although the exposure to sustained hypoxia did not activate this pathway [39]. Furthermore, intermittent hypoxia induced more extensive neuronal damage than sustained hypoxia in dopaminergic neoplastic cells [51]. These mechanisms suggest that the ‘repetitive’ apnea and hypopnea events might be the stronger cardiac and peripheral adrenergic drive compared with nocturnal low average SaO₂. In addition, our study subjects, which included diabetes patients (40.4%), might also influence the results, while the subjects by Zoccali et al. [49] excluded diabetes patients.

Our results suggest that effective and earlier treatment for SDB in HD patients is needed to prevent cardiovascular events and all-cause death. Continuous positive airway pressure is a standard treatment for obstructive sleep apnea, which improves hypertension, left ventricular systolic function and cardiovascular prognosis [35,38,52]. In addition, recent reports showed that adaptive servo-ventilation improves AHI, cardiac function and sleep quality in patients with chronic heart failure and Cheyne-Stokes breathing [34,53,54]. However, the effects of these devices for SDB in dialysis patients have not been clearly evaluated. As a specific treatment for dialysis patients, it has been reported that nocturnal HD and nocturnal cycler-assisted peritoneal dialysis improve AHI, control of blood pressure and higher heart rate [24,55–57]. Possible mechanisms for these observations are thought to be a better fluid clearance and attenuation of sympathetic activation during sleep [24,55–57].

There are several limitations to this study. First, this study includes a relatively small sample size and a small number of events. Thus, it might lead to the wide CI, although over-adjustment of covariates at multivariate Cox regression analysis was avoided. Second, pulse oximetry is inferior to PSG in diagnostic accuracy for SDB. Third, this is a group of HD patients that may not be applicable to patients starting dialysis. Fourth, the severity of SDB in this study is rather mild, which may be due to the longer dialysis duration compared with other cohort studies [20,58]. Finally, this observational nature study precludes the causal links between SDB and the prognosis. Interventional treatments for normalization of ODI are needed to evaluate whether elevated ODI itself causes cardiovascular events and all-cause death.

In conclusion, we demonstrated that SDB is an independent risk factor for cardiovascular events and all-cause mortality in HD patients. ODI assessed by pulse oximetry is not only a screening marker for sleep apnea but also a prognostic parameter. Effective and earlier treatments for SDB in HD patients are needed to improve clinical outcome.

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Conflict of interest statement. None declared.

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