Lung (2006) 184:43–49
DOI 10.1007/s00408-005-2563-2

Sleep-Disordered Breathing in Nondialyzed Patients with Chronic Renal Failure

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Accepted: 3 August 2005

Abstract The prevalence and significance of sleep-disordered breathing (SDB) in dialysis-independent chronic renal failure (CRF) remains unknown. We studied the presence of SDB in nondialyzed CRF patients. Diagnostic polysomnography was performed in consecutive stable nondialyzed CRF patients. Inclusion criteria were age ≤70 years, absence of systolic dysfunction or history of pulmonary edema, $FEV_1 > 70\%$ pr, absence of neurologic disease or hypothyroidism, and calculated creatinine clearance <40 ml/min. Thirty-five patients (19 male, 16 female) were studied. An apnea–hypopnea index (AHI) ≥5/h was present in 54.3% (almost exclusively obstructive events). AHI correlated with urea ($r = 0.35$, $p = 0.037$), age ($r = 0.379$, $p = 0.025$), and body mass index (BMI) ($r = 0.351$, $p = 0.038$), but not with creatinine clearance. AHI or SDB were unrelated to gender. In nondiabetics ($n = 25$), AHI correlated with urea ($r = 0.608$, $p = 0.001$) and creatinine clearance ($r = -0.50$, $p = 0.012$). Nondiabetics with severe CRF (calculated GFR < 15 ml/min/1.73 m^2) had a significantly higher AHI compared with less severe CRF. Restless legs syndrome (RLS) was present in 37.1% and periodic limb movements in 28.6%. Daytime sleepiness was not associated with respiratory events, but was more common in patients with RLS. The prevalence of SDB and RLS is high in dialysis-independent CRF. SDB weakly correlates with indices of kidney function and this association becomes stronger in nondiabetics.

Keywords Chronic renal failure · Dialysis · Sleep-disordered breathing · Restless legs syndrome · Periodic limb movements

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Introduction

Patients with chronic renal failure (CRF) undergoing renal replacement therapy have a high prevalence of sleep-disordered breathing (SDB) [13, 15, 21, 22, 24–26, 33, 37, 38]. There are reasons to believe that SDB may contribute to cardiovascular and renal morbidity in these patients. A link between SDB, hypertension, and cardiovascular morbidity has been clearly established in the general population and possibly exists in asymptomatic sleep apneics as well [17, 41]. The finding that nocturnal hypoxemia (probably related with apneas) is associated with the ''nondipping'' arterial pressure profile in dialysis patients [45] makes SDB a probable contributing factor to hypertension in CRF as well. The demonstration that nocturnal hypoxemia predisposes to left ventricular hypertrophy [46] and to cardiovascular complications [48] in end-stage renal disease (ESRD) is further indirect evidence of possible deleterious consequences of SDB in this group. Nocturnal hypoxemia in dialyzed patients has also been shown to

dampen autonomic cardiovascular reflexes, compromising parasympathetic function [47]. Reversal of SDB is a probable explanation for the observed improvement of cardiovascular autonomic control during sleep in patients undergoing nocturnal hemodialysis [7].

SDB through its associations with cardiovascular disease, which is known to be the leading cause of death in the dialysis population [36], may be indirectly contributing to mortality in CRF. Admittedly, Benz et al. [6] could not confirm an association between SDB and mortality in ESRD, but their study was probably inadequately powered. It should also be noted that in their study patients had a greatly shortened survival time regardless of SDB. Perhaps an effect of SDB on mortality can be more obvious at an earlier CRF stage, e.g., before initiation of dialysis, and with patients with higher overall life expectancy.

Through the aggravation of hypertension, SDB may also be contributing to the deterioration of renal function in CRF [31, 34]. This assumption is strengthened by the finding that patients with obstructive sleep apnea (OSA) can develop proteinuria that responds to treatment with continuous positive airway pressure (CPAP) [32]. A confirmation of this hypothesis could make screening and treatment for SDB a possible intervention in slowing the progression to ESRD in nondialyzed patients.

Surprisingly, although SDB may also be present before initiation of dialysis [22], very little is known about SDB or indeed about other sleep problems in these patients. Iliescu et al. [20] report poor quality of sleep in nondialyzed CRF patients, but their study did not use polysomnography, nor did it address the question of SDB in CRF. There are virtually no data available on SDB prevalence in dialysis-independent CRF. It is also unknown whether the degree of renal dysfunction is associated with SDB in these patients.

Clearly, data on SDB in ESRD cannot be automatically extrapolated in patients not yet on renal replacement therapy. Serious differences may exist in severity of renal failure, volume overload, metabolic derangements, and nervous system complications between dialyzed and nondialyzed patients [2] and such differences may have an impact on SDB. Dialysis itself may also be expected to have a modifying influence on SDB, for example, through modifications in the control and pattern of breathing [8, 14, 18, 42] or through changes in volume overload and upper airway patency [30]. In isolated case reports the start of dialysis has been associated with both improvement and aggravation of SDB [10, 21].

We investigated with polysomnography (PSG) the presence of SDB and other sleep disorders like restless legs syndrome (RLS) or periodic limb movements (PLMs) in consecutive nondialyzed CRF patients and searched for associations of SDB with the severity of kidney dysfunction. Because diabetes mellitus predisposes to both SDB and RLS through diabetic neuropathy [11, 27], we also performed a separate analysis of nondiabetics with CRF because it was felt that the presence of diabetes can probably confound possible associations between renal dysfunction and SDB.

Methods

Study Subjects

A prospective observational study was undertaken between September 2002 and January 2004 in consecutive stable CRF patients not on dialysis who visited the Nephrology Department of ''A Fleming'' Hospital. Inclusion criteria were age ≤ 70 years, absence of systolic dysfunction on echocardiography (ejection fraction > 40% in the previous 12 months), lack of history of cardiogenic pulmonary edema, FEV_1 > 70% pr, absence of neurologic disease, absence of clinical hypothyroidism, calculated creatinine clearance (Cockroft–Gault equation) < 40 ml/min, clinical and laboratory stability two months before inclusion in the study (no history of hospitalization and changes in serum creatinine of less than 0.5 mgr/dl), and no treatment with sedatives or hypnotics in the previous month.

A total of 40 patients were found eligible for the study. Thirty-five patients (19 male, 16 female) participated in the study after written informed consent. The causes of CRF were diabetes mellitus (10 patients), glomerulonephritis (7), systemic lupus erythematosus/vasculitis (4), polycystic kidneys (3), renovascular disease (4), other nephropathies (7). The study was approved by the Hospital Bioethics Committee.

Study Design

All patients had an interview with a pulmonary medicine physician with experience in sleep disorders. The interview was focused on medical problems and sleep history. Patients were specifically questioned about daytime sleepiness, presence of snoring at least five times a week, RLS, and presence of chronic insomnia (defined as a perceived sleep latency > 30 min and/or perceived sleep efficiency <80% most days of the week for more than 6 months, with consequences for daytime functioning). Evaluation of snoring was based on both patients' and bedpartners' accounts. Each subject also completed the Epworth Sleepiness Scale (ESS). The patients' medical records were reviewed and hemoglobin, urea, and creatinine levels were measured. Patients were stratified on the basis of CRF severity into two groups. Group A consisted of patients with calculated glomerular filtration rate (GFR) ≥ 15 ml/min/1.73 m^2 and Group B of patients with

GFR < 15 ml/min/1.73 m^2 and who were not yet on dialysis. GFR was calculated on the basis of the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation [2].

All patients were offered an all-night, in-hospital, attended polysomnography (PSG) regardless of symptoms. The following parameters were monitored on a P Series Plus Sleep System (Compumedics, Abbotsford, Victoria): (a) EEG (C3/A2, C4/A1, O2/A1, O1/A2) based on the 10–20 international electrode placement system, (b) right and left electro-oculogram, (c) chin and leg EMG, (d) ECG, (e) respiration (thoracic and abdominal wall motion with strain gauges and measurement of oronasal airflow with a thermistor), (f) pulse oximetry, and (g) snoring (with a neck microphone). Sleep was staged using the Rechtshaffen and Kales criteria [28] with arousals scored using the American Sleep Disorders Association (ASDA) criteria [3]. Respiratory events were scored using the American Academy of Sleep Medicine recommendations [1] and periodic limb movements (PLMs) were scored on the basis of the International Classification of Sleep Disorders [9].

We studied the prevalence of sleep symptoms, SDB (defined as AHI ≥ 5/h), and PLMs in our patients. Associations of apnea–hypopnea index (AHI) with parameters of sleep architecture were sought. The relationship of AHI to demographics, body mass index (BMI), renal function indices, and hemoglobin level was investigated and differences in AHI, demographics, laboratory parameters, and sleep parameters between groups A and B were assessed. We also performed a separate analysis of nondiabetics, because it is known that the presence of diabetes mellitus is a risk factor for both SDB and RLS and, thus, diabetes can probably confound possible associations between renal dysfunction and SDB [11, 27].

Statistics

Statistical analysis was performed with the statistical programs NCSS 2004 and GraphPad Prism v4. Normality of distributions was tested with Shapiro–Wilk *W* and Kolmogorov–Smirnov tests and with visual inspection of histograms and normal probability plots. Data are presented as mean ± SD (standard deviation). Comparisons were made with the unpaired-sample *t*-test for normally distributed variables and with the Mann–Whitney *U* test when normality was absent. For normally distributed variables, equality of variances was tested with the modified Levene equal-variance test. In cases of unequal variance, the Aspin–Welch unequal variance test was performed. Differences in categorical data were compared with the chi-square test. Relationships between variables were analyzed with Pearson correlation when both variables were numerical and normal, or with Spearman's rank correlation when numerical variables were not normally distributed.

Table 1 Demographic data and laboratory findings (mean ± SD)

Demographic data	
Age (yr)	57.3 ± 12
Male/Female	19/16
BMI (kg/m^2)	26.47 ± 3.22
Laboratory findings	
Urea (mg/dl)	147.1 ± 57.6
Creatinine clearance (ml/min)	26.8 ± 9.2
Hb (g/dl)	12.11 ± 1.41
Prevalence of sleep symptoms	
Daytime sleepiness	12 (34.8%)
ESS > 10	4 (11.4%)
Chronic insomnia	6 (17.14%)
RLS	13 (37.1%)
Snoring (at least 5 nights a week)	14 (40%)
Snoring and daytime sleepiness	6 (17.14%)
Sleep architecture	
Sleep efficiency (% TST)	70.8 ± 16.1
Stage 1 (% TST)	7.3 ± 4.7
Stage 2 (% TST)	48 ± 10.1
SWS (% TST)	28.8 ± 10.8
REM (% TST)	15.6 ± 6.4
Arousal index (arousals/h)	20.8 ± 10.8

Results

Demographic data, laboratory findings, sleep-related symptoms, and data on sleep architecture are presented in Table 1. Males and females did not differ in age, BMI, creatinine clearance, and hemoglobin concentration.

Mean AHI was 9.9 ± 1.65/h and SDB was present in 54.3% of our patients. Respiratory events were almost exclusively obstructive. Increased AHI accompanied by daytime sleepiness was present in 20%. SDB of at least medium severity (AHI > 15/h) was present in 11 patients (31.4%), while severe SDB (AHI > 30/h) was present in 2 (5.7%).

PLMs were present in 28.6% of patients.

No difference was found in AHI or the presence of SDB in patients reporting daytime sleepiness; this finding persisted when a threshold of AHI > 15/h was used for SDB. On the other hand, daytime sleepiness was more frequent in patients with RLS (χ^2, $p = 0.0090$, RR = 3.39 with 95% CI = 1.26–9.07).

With the exception of arousal index, which was moderately associated with AHI ($r = 0.41$, $p = 0.012$) as well as with PLMSI ($r = 0.40$, $p = 0.016$), no association was found between parameters of sleep architecture and SDB.

AHI significantly correlated with BMI ($r = 0.351$, $p = 0.038$), age ($r = 0.379$, $p = 0.025$), and urea ($r = 0.35$, $p = 0.037$) (Fig. 1), but not with creatinine clearance ($r = -0.12$, $p = 0.506$) and hemoglobin. No significant

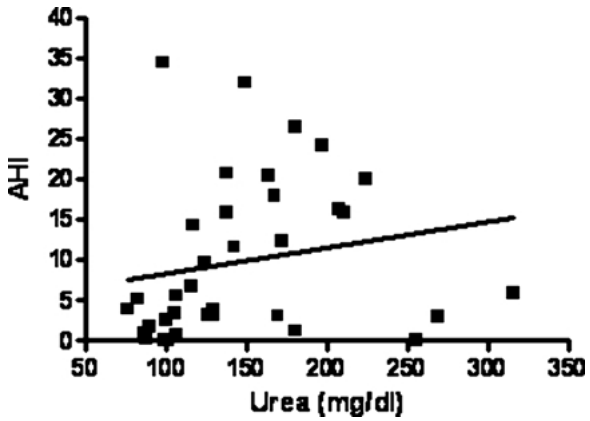

Fig. 1 AHI vs. urea (all patients), Spearman $r = 0.35$, $p = 0.0037$

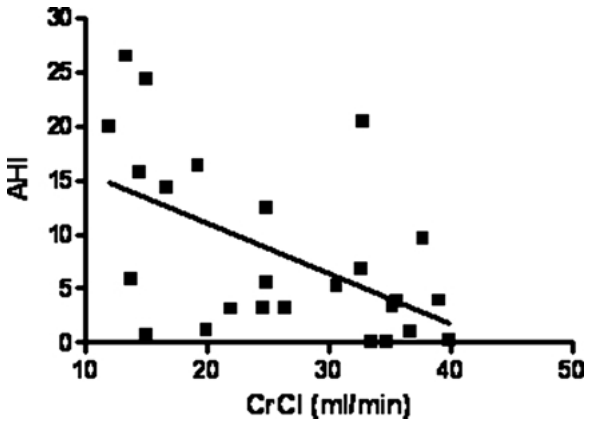

Fig. 2 AHI vs. creatinine clearance (nondiabetics), Spearman $r = -0.50$, $p = 0.001$

Table 2 Demographic, laboratory, polysomnographic parameters, and presence of sleep disorders in CRF patients, grouped according to severity of renal failure (mean ± SD)

	Group A ($n = 24$)	Group B ($n = 11$)
Age	56.2 ± 13.1	59.9 ± 9.2
Sex (male/female)	14/10	5/6
BMI	26.08 ± 3.19	27.31 ± 3.27
Hb (gr/dl)	12.4 ± 1.4	11.4 ± 1.2
AHI	9.10 ± 9.91	11.67 ± 9.61
ESS	6.46 ± 3.27	7.55 ± 2.11
PLMSI	11.04 ± 20.24	19.71 ± 29.05
SDB	12 (50%)	7 (63.6%)
OSA	4 (16.66%)	3 (27.27%)
RLS	6 (25%)	5 (45.45%)
Sleep efficiency (%TST)	74.29 ± 14.91	63.44 ± 16.58
Arousal index	20.93 ± 10.70	20.36 ± 11.44
REM (%TST)	14.72 ± 6.02	17.61 ± 6.91
SWS (%TST)	31.51 ± 10.27	22.86 ± 9.69*
SpO_2 awake	95.7 ± 1.5	95.1 ± 1.3
Mean SpO_2 at sleep	94 ± 1.6	92.9 ± 2.1

*$p \leq 0.05$

difference between males and females was observed in AHI or the presence of SDB.

Data on groups A and B are presented in Table 2. No significant difference was observed in AHI, but patients in group B had significantly less slow-wave sleep (SWS).

Sleep-Disordered Breathing in Nondiabetics

No significant difference was observed between diabetics ($n = 10$) and nondiabetics ($n = 25$) in AHI or prevalence of SDB, but the prevalence of RLS was higher in diabetics. The two groups did not differ significantly in age, BMI, gender, hemoglobin, urea, and creatinine clearance. No association was observed in diabetics between AHI and indices of renal function.

When diabetics were excluded, a significant correlation was found in the remaining patients ($n = 25$) between AHI and creatinine clearance ($r = -0.50$, $p = 0.012$) (Fig. 2), while the correlation of AHI with urea became stronger ($r = 0.608$, $p = 0.001$). No association was observed between AHI and age, gender, BMI, or hemoglobin concentration. In addition, in nondiabetics AHI was significantly higher in group B (14.2 ± 9.7 events/h vs. 5.5 ± 5.6 events/h, $p = 0.04$). The two groups differed only in indices of renal function.

Discussion

We have found that both SDB and RLS are common problems in CRF patients, even before initiation of dialysis. The prevalence of SDB in our study was much higher than that reported for the general middle-aged population (24% for males and 9% for females), while the prevalence of SDB associated with daytime sleepiness was similarly increased [43]. Comparisons with dialyzed patients are not easy because reported prevalence of SDB in this group varies widely, depending on the study, from 30% to 71% [13, 15, 21, 22, 24–26, 33, 37, 38]. If only the few studies using full PSG on consecutive ESRD patients without preselection by symptoms are considered, the prevalence of SDB seems to be in the area of 50%–71% [15, 26, 37]. Possible presence of comorbidities (like heart failure) may have contributed to the very high prevalence (71%) reported for SDB by Hanly and Pierratos [15]. Nevertheless, even with careful exclusion of patients with symptoms suggestive obstructive sleep apnea or with comorbidities predisposing to SDB, the prevalence of SDB was still 50% in dialyzed patients [26]. Thus, we conclude that SDB is probably observed with more or less similar frequency in dialyzed and in dialysis–independent CRF.

As diabetes mellitus is known to predispose to SDB (through the development of autonomic neuropathy) [11],

the inclusion of diabetics might have contributed to the high prevalence of SDB in our study. Nevertheless, we found no significant difference in AHI or prevalence of SDB between diabetics and nondiabetics.

In striking contrast with some previous studies in dialyzed patients [15, 21, 24], we found that respiratory events in predialysis CRF are almost exclusively obstructive. The absence of central or mixed apneas in our series may be attributed in part to the exclusion of comorbidities like heart failure that can predispose to periodic breathing and central apneas. An additional explanation may be that our patients were not dialyzed, thus avoiding a possible detrimental effect of renal replacement therapy on sleep (through promotion of instability in central control of ventilation) [29].

Similar to some previous investigators [24, 33, 38], we have found that in CRF, AHI or presence of SDB are unrelated to gender. This could probably be attributed to an increased prevalence of amenorrhea, a factor known to predispose to SDB [44], in females with CRF, or to the fact that many of our female patients could be expected to be past menopause because of their more advanced age. Interestingly, we observed only a weak correlation of AHI to BMI, which did not persist when nondiabetics were analyzed separately. The lack of association between AHI and hemoglobin levels in our study confirms previous findings in ESRD [5]. Regarding the association of SDB with indices of renal dysfunction, we found that AHI correlated weakly but significantly with urea but not with creatinine clearance. When diabetics were excluded, the correlation of AHI with urea became stronger and a fair correlation with creatinine clearance was also observed. Moreover, nondiabetics with stage 5 CRF had a significantly higher AHI and a trend to higher prevalence of SDB compared with patients with less severe renal disease. A possible explanation for the finding that association of AHI with creatinine clearance was limited to nondiabetics is that in diabetics the overriding factor for the development of SDB may be not renal dysfunction *per se* but other complications like diabetic autonomic neuropathy. Thus, inclusion of diabetics may have confounded associations between SDB and renal dysfunction.

It should be noted that no association between AHI and biochemical variables (urea, creatinine) has been demonstrated in CRF patients on dialysis [13, 15, 21, 22, 24–26, 33, 37, 38]. Nevertheless, reports of SDB reversal after renal transplantation [4, 23] or with daily nocturnal hemodialysis [15, 16] confirm that factors related to renal failure precipitate SDB in ESRD and offer indirect support to our finding that the degree of CRF severity is associated with SDB. The wider range of urea and creatinine values in our patients probably allowed the demonstration of such an association.

CRF can lead to SDB either through a destabilization of chemical control of breathing or through a compromised upper airway patency [8, 14, 18, 29, 30, 42]. As renal function deteriorates, these problems can be expected to become more prominent, thus precipitating or worsening SDB. For example, uremic autonomic neuropathy, abnormalities in neurotransmitter synthesis, and subclinical uremic encephalopathy may influence chemosensitivity and reduce muscle tone of the upper airway muscles, while fluid retention may further compromise the upper airway [12, 15]. In addition, the respiratory adaptation to chronic metabolic acidosis in CRF promotes the development of hypocapnia with lowering of the PCO_2-apnea threshold, which may favor an unstable breathing pattern [15, 30]. Coexistence of other disorders like congestive heart failure may also contribute to SDB [30], but such comorbidities were excluded in our study.

The prevalence of RLS was also increased in our nondialyzed patients compared with the general population [27]. Again, comparisons with dialyzed patients are not easy because of a widely varying prevalence (20%–80%) from study to study [19, 38–40]. Prevalence of RLS was not increased in stage 5 CRF in our series but was higher in patients with diabetes mellitus, confirming a previously reported association of RLS with diabetes [27].

Changes in sleep architecture in our study were more or less similar to findings reported in dialyzed patients [15, 33, 37, 38]. Interestingly, we found less slow-wave sleep in more severe CRF. Daytime sleepiness was not associated with SDB but was associated with RLS. It should be noted that in dialyzed patients associations of daytime sleepiness with SDB are also far from clear-cut [16, 26, 33]. Daytime sleepiness in CRF is probably multifactorial. A review of the literature suggests that PLMs, RLS, or the direct effects of even mild elevations of uremic toxins on the central neural system are important contributors that may increase susceptibility to daytime sleepiness, even without interference with SDB [12, 16, 26, 33, 35, 38, 40].

In conclusion we have found that in dialysis–independent CRF the prevalence of SDB is much higher than that reported for middle–aged adults in the general population. Respiratory events during sleep are almost exclusively obstructive and are moderately associated with indices of renal function. The finding that SDB is not associated with sex and is unrelated to symptoms of daytime sleepiness, suggests that nondialyzed patients with uremia and SDB represent a clinical population different from patients with primary airway obstruction during sleep.

The likelihood of selection bias in our study is low given the low nonparticipation rate and the enrollment of all patients with CRF, without preselection on the basis of symptoms of SDB. Admittedly our study suffers from a relatively small number of patients and lack of suitable

control groups (patients on dialysis and normal controls). In addition, the time of follow up was short and did not allow insight into the possible relationship of SDB with cardiovascular complications, progression of renal disease, and mortality in CRF. Given the high prevalence of SDB in nondialyzed patients with CRF, further study is warranted in order to clarify these questions.

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