Sleep apnea is a novel risk predictor of cardiovascular morbidity and death in patients receiving peritoneal dialysis

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Sleep apnea syndrome is increasingly recognized in peritoneal dialysis patients; however, its prognostic implication in this population is unknown. To study this, we prospectively followed the clinical outcome of 93 peritoneal dialysis patients with baseline polysomnography. Of these, 51 were diagnosed with the syndrome defined by an apnea–hypopnea index (AHI) of at least 15 per hour. During a median follow-up of 41 months, there were 30 deaths, of which 17 were due to cardiovascular causes. Kaplan–Meier analysis for the entire follow-up period indicated that patients with sleep apnea at baseline had significantly higher all-cause and cardiovascular mortality during follow-up than those without. Minimal nocturnal saturation and desaturation indices were predictors of mortality and cardiovascular events at univariate analysis. Multivariable Cox regression analysis identified significant sleep apnea syndrome at baseline as an independent predictor of increased all-cause mortality independent of age, male gender, and diabetic status. Further, an absolute increase in the AHI was associated with an incremental risk of cardiovascular events. Thus, sleep apnea syndrome, detected at the start of peritoneal dialysis, is a novel risk predictor for subsequent mortality and cardiovascular events.

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KEYWORDS: cardiovascular morbidity; peritoneal dialysis; sleep apnea; survival

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Sleep disturbances are highly prevalent among dialysis patients compared with the general population.[1,2] Among the various sleep disturbances, sleep apnea is being increasingly recognized in dialysis patients.[3] Although sleep-disordered breathing occurred in 2–4% of the middle-aged Chinese population,[4,5] its prevalence is uniformly over 50% among Chinese subjects on peritoneal dialysis as gauged by self-reported questionnaires[6,7] or by the more objective method of overnight polysomnographic measurement.[8] Unruh *et al.*[9] recently reported that patients on hemodialysis had a fourfold increase in prevalence of sleep-disordered breathing and nocturnal hypoxemia even after adjusting for cardiovascular morbidity and diabetic status, compared with participants from the Sleep Heart Health Study matched for age, gender, body mass index, and race, indicating that the pathophysiology of sleep apnea is uniquely associated with the development of chronic renal failure. Several studies have addressed the effect and importance of sleep apnea on quality of life of peritoneal dialysis patients and showed that sleep problems severely affect their general health and psychosocial well-being.[10,11] However, it remains unknown whether sleep apnea in peritoneal dialysis patients is a risk factor for mortality and morbidity, in particular cardiovascular events as occurs with the nondialysis population.[12]

We have embarked on the 'Sleep apnea in PD patients' program since 2001 to study sleep apnea in Chinese peritoneal dialysis patients, focusing on the pathogenetic mechanisms of sleep apnea during uremia.[8,13] We prospectively collected baseline polysomnographic data on a cohort of Chinese peritoneal dialysis patients soon after the commencement of peritoneal dialysis and followed their clinical outcome longitudinally. In this study, we hypothesize that the severity of sleep apnea, reflected by the apnea-hypopnea index (AHI) or the number of apneic or hypopneic events per hour of sleep, is a polysomnographic marker that predicts all-cause mortality and cardiovascular events in the chronic peritoneal dialysis population.

RESULTS

From 2001 onward, 93 incident patients were recruited into our 'Sleep apnea in PD patients' program and underwent at least one overnight polysomnography (PSG) measurement at the commencement of PD. The baseline demographic, clinical, and biochemical parameters are summarized in Table 1. The median AHI of the entire study cohort was 21.7/h (interquartile range 3.0–48.2). The prevalence of significant sleep apnea (AHI $\geqslant$15/h) was 55% ($n=51$). The median AHI for patients with AHI $<$15 and $\geqslant$15/h is shown in Figure 1. The key PSG parameters were shown in Table 2. Analysis of the apneic components showed that obstructive pattern was the predominant form of apnea. The median central and obstructive apnea indices were 0.9 and 14.9 episodes/h, respectively (Table 2). Six patients (6.2%) had predominant central apnea, defined as a central apnea index (CAI) of $\geqslant$15/h and CAI/total AHI $>$50%. After a median follow-up of 41 months (interquartile range, 24–49), 53 patients (56.9%) developed one or more cardiovascular events, in whom 20 (21.5%), 9 (9.7%), 11 (11.8%), and 13 (14.0%) patients had 1, 2, 3, and $>$3 episodes, respectively. The first fatal or nonfatal cardiovascular event was ischemic heart disease in 7, congestive heart failure or fluid overload in 29, arrhythmia in 3, poorly controlled blood pressure requiring hospitalization in 8, cerebrovascular event in 4, and peripheral vascular disease in 2 patients.

Thirty (32.2%) patients had died, 13 (13.9%) received kidney transplantation, and 5 (5.3%) were transferred to permanent hemodialysis during follow-up. Among the 30 deaths, 17 (56.6%) were due to cardiovascular events (including ischemic heart disease in six, congestive heart failure in three, arrhythmia in one, peripheral vascular disease in one, cerebrovascular accident in two, and sudden death in four patients), and 13 (43.3%) were due to other causes (including peritonitis in four, pneumonia in two, other infections in five, and termination of dialysis because of ill-health in two patients).

During the follow-up period, 5 in the group with baseline AHI $<$15/h vs 25 patients with baseline AHI $\geqslant$15/h had died, and the all-cause mortality was 5.4 vs 26.9%, respectively ($P=0.015$, Figure 2). The Kaplan–Meier estimates for all cardiovascular event-free survival according to the AHI cutoff of 15/h was shown in Figure 3. Patients with baseline AHI $\geqslant$15/h took significantly shorter time to develop more cardiovascular events than those with AHI $<$15/h ($P=0.001$). When patients were analyzed according to whether they lived or died during follow-up, the baseline AHI was significantly higher in those who died ($P=0.0001$, Figure 4). Similarly, when patients were stratified according to whether they developed a cardiovascular event during follow-up, patients with one or more events had significantly higher baseline AHI ($P=0.006$, Figure 5).

The unadjusted and fully adjusted hazard ratios of AHI $\geqslant$15/h and other factors in relation to all-cause and all fatal and nonfatal cardiovascular events were shown in Tables 3 and 4. For all-cause mortality, both age and AHI $\geqslant$15/h were important predictors in both the univariate and the fully adjusted multivariable Cox regression models. The fully adjusted hazard ratio of AHI $\geqslant$15/h was 1.72 (95% CI, 1.03–2.88; $P=0.037$). Minimal nocturnal oxygen saturation was predictive of mortality in the univariate model, but was removed during multivariate analysis. Also at univariate analysis, both minimal oxygen saturation and desaturation index predicted cardiovascular events. However, both variables were subsequently removed when introduced into the Cox model. For fatal and nonfatal cardiovascular events, age, AHI, and diabetes mellitus stood out in the fully adjusted multivariable Cox regression models to be significant predictors. The hazard ratio for every unit increase in AHI by 1 episode/h was 1.02 (95% CI, 1.01–1.03; $P=0.003$). Other covariates known to affect cardiovascular morbidity including serum albumin, calcium, phosphate, and hemoglobin levels were not predictive of all-cause or cardiovascular mortality in the present cohort.

DISCUSSION

The presence of significant sleep apnea at baseline is associated with vascular risk factors and with substantial cardiovascular morbidity and mortality in epidemiological studies.[14] In addition, it is clearly associated with increased risks for stroke and death in the nondialysis population. Among over 1000 subjects aged 50 or more, the presence of even mild obstructive sleep apnea (AHI $\geqslant$5/h) constituted a nearly twofold increase in risk even after adjustment for demographic and clinical characteristics and smoking habit.[12] In the hemodialysis population, nocturnal hypoxemia, a key indicator of sleep-disordered breathing, is a strong predictor for incident cardiovascular complications.[15] However, data are lacking as to whether the sleep apnea syndrome may constitute equivalent risks in the peritoneal dialysis population.

In this observational cohort study, we reported for the first time that baseline AHI $\geqslant$15/h is an independent predictor of subsequent all-cause mortality and cardiovascular morbidity independent of other cardiovascular risk factors on extended follow-up. We used an AHI cutoff of 15/h, which is in line with previous studies reporting sleep apnea in peritoneal dialysis patients,[8,13] and which reflects moderate sleep apnea in the nondialysis population.[16] In terms of mortality, baseline AHI $\geqslant$15/h constituted a 1.7-fold increase in risk after adjustment for age, sex, and diabetic status. For cardiovascular event-free survival, absolute AHI posed an increased risk and diabetes also stood out as an independent risk factor. This is not surprising given the association between diabetes and cardiovascular morbidity. Apart from AHI, minimal nocturnal oxygen saturations as well as the desaturation index were predictive of cardiovascular events at univariate analysis, which is in keeping with previous report[15] of the importance of oxygen saturation in this regard. However, mean nocturnal oxygen saturation did not predict cardiovascular events. This may be related to the differences in the two cohorts of study subjects: in the study

Table 1 | Baseline demographic and clinical parameters of the study subjects[a]

	Total (*N*=93)	AHI <15/h (*N*=42)	AHI ⩾15/h (*N*=51)	*P*[b]
Demographic and clinical parameters				
Age (years)	55.3 ± 14.5	52.3 ± 16.3	57.9 ± 12.5	0.063
Percentage male (%)	51.6	40.5	60.8	0.062
Dialysis vintage (months)	9.8 ± 10.8	7.6 ± 10.1	11.7 ± 11.2	0.071
Body mass index (kg/m^2)[c]	23.4 ± 3.7	22.8 ± 3.7	24 ± 3.6	0.116
Neck circumference (cm)	35.5 ± 3.7	35.0 ± 5.2	35.9 ± 1.5	0.231
Neck-height ratio	0.224 ± 0.026	0.222 ± 0.035	0.226 ± 0.017	0.466
Underlying renal disease				
Diabetes mellitus	42 (45.2%)	14 (33.3%)	28 (54.9%)	0.060
Unknown	19 (20.4%)	6 (14.3%)	12 (23.5%)	0.302
Chronic glomerulonephritis	18 (19.4%)	13 (31.0%)	5 (9.8%)	0.016
Others	15 (16.1%)	9 (21.4%)	6 (11.8%)	0.262
Cardiovascular risk factors				
Diabetes mellitus (*N*)	42 (45.2%)	14 (33.3%)	28 (54.9%)	0.060
Systolic blood pressure (mm Hg)	136 ± 9	136 ± 10	136 ± 9	0.817
Diastolic blood pressure (mm Hg)	82 ± 7	82 ± 7	81 ± 7	0.906
Hypertension (*N*)	66 (71%)	31 (74%)	35 (69%)	0.828
No. of antihypertensive drugs	2.27 ± 0.71	2.31 ± 0.78	2.24 ± 0.65	0.618
Fasting lipid profile				
Total cholesterol (mmol/l)	5.31 ± 0.44	5.35 ± 0.42	5.27 ± 0.51	0.444
LDL cholesterol (mmol/l)	3.78 ± 0.49	3.78 ± 0.45	3.77 ± 0.53	0.894
HDL cholesterol (mmol/l)	1.05 ± 0.16	1.08 ± 0.15	1.03 ± 0.17	0.107
Triglycerides (mmol/l)	2.40 ± 0.21	2.42 ± 0.22	2.38 ± 0.21	0.389
Hemoglobin (g/dl)	8.5 ± 1.5	8.4 ± 1.5	8.7 ± 1.5	0.322
Serum calcium (mmol/l)	2.32 ± 0.2	2.31 ± 0.18	2.34 ± 0.22	0.441
Serum phosphate (mmol/l)	1.78 ± 0.52	1.85 ± 0.56	1.72 ± 0.47	0.211
Serum Ca × PO_4 product (mmol^2/l^2)	4.12 ± 1.21	4.23 ± 1.16	4.03 ± 1.25	0.440
Smoking habit (history of)	17 (18%)	7 (17%)	10 (19.6%)	0.792
Cardiovascular co-morbidities				
History of cerebrovascular disease	7 (7.5%)	3 (7.1%)	4 (7.8%)	1.0
History of myocardial infarction/CHF	9 (9.6%)	3 (7.1%)	6 (11.7%)	0.506
History of peripheral vascular disease	4 (4.3%)	2 (4.7%)	2 (3.9%)	0.506
Dialysis-related indices				
KT/V_{urea} (per week)				
Peritoneal	1.54 ± 0.60	1.47 ± 0.64	1.60 ± 0.57	0.327
Renal	0.51 ± 0.50	0.52 ± 0.49	0.51 ± 0.52	0.919
Total	2.05 ± 0.66	1.99 ± 0.75	2.11 ± 0.59	0.415
Creatinine clearance (l per week per 1.73 m^2 BSA)				
Peritoneal	35.7 ± 14.3	33.0 ± 14.6	38.0 ± 13.8	0.100
Renal[d]	33.6 ± 34.2	37.0 ± 39.2	30.8 ± 29.4	0.399
Total	69.3 ± 30.8	69.9 ± 36.5	68.8 ± 25.4	0.866
PET (dialysate/plasma Cr conc at 4 h)[e]	0.66 ± 0.11	0.67 ± 0.11	0.66 ± 0.10	0.583
High transporter (0.82–1.03)	7	5	2	
High average transporter (0.66–0.81)	36	15	21	
Low average transporter (0.5–0.64)	46	20	26	
Low transporter (0.34–0.49)	4	2	2	
Body water composition[f]				
Total body water (l)	35.1 ± 6.8	33.9 ± 7.1	36.5 ± 6.3	0.158
Extracellular water (l)	17.4 ± 3.2	16.8 ± 3.4	18.1 ± 3.0	0.134
Intracellular water (l)	17.7 ± 3.8	17.1 ± 3.9	18.4 ± 3.6	0.207
Hydration fraction (%)	63.6 ± 8.0	62.1 ± 7.4	65.4 ± 8.4	0.129
Normalized protein catabolic rate (g/kg per day)[g]	1.09 ± 0.41	1.08 ± 0.44	1.10 ± 0.40	0.798
Serum albumin (g/l)	34.8 ± 5.0	36.2 ± 4.2	34 ± 5.3	0.056
Number on erythropoietin	52 (56%)	22 (52%)	30 (59%)	0.679

Abbreviations: AHI, apnea-hypopnea index; BSA, body surface area; Cr, creatinine; conc, concentration; CHF, congestive heart failure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Plus–minus values are means ± s.d.
[b]For comparisons between patients with AHI < and ⩾15/h.
[c]Abdomen emptied.
[d]Renal creatinine clearance was calculated by averaging urea and creatinine clearance rates estimated from 24-h urine collections.
[e]According to the method of peritoneal equilibration test (PET) and classification of transport status by Twardowski.[27]
[f]Data available from 54 subjects (29 with AHI < 15/h) and computed as previously described.[8]
[g]Derived from the Randerson formula.[29]

by Zoccali *et al.*,[15] the primary dialysis modality was HD instead of PD. Moreover, diabetes was an exclusion criterion in the HD study, whereas diabetes was present in up to 45% of patients here.

In contrast, residual renal function, hemoglobin levels, and serum calcium x phosphate product, which are traditionally viewed as a strong predictor for survival did not have any effect. This is likely due to the narrow spread of the baseline values in these parameters among the two groups. Furthermore, the observation of higher AHI values in patients who subsequently died or developed one or more cardiovascular events are in agreement with the increased health risks observed in hemodialysis and nondialysis populations. The predominance of obstructive over central forms of apnea obviates the argument that baseline presence of central apnea may be a confounder in the subsequent survival analysis.

There are good reasons why obstructive sleep apnea predisposes to cardiovascular complications in dialysis patients. First, sleep apnea is characterized by repetitive cycles of apnea, hypoxia, hypercapnia, and arousal.[17,18] Nocturnal hypoxemia has been linked to elevated oxidative stress, increased coronary calcification, development of sympathetic hyperactivity, and subsequent left ventricular hypertrophy in chronic hemodialysis patients.[19,20] Increased cardiac and peripheral adrenergic drive may explain why sleep apnea and nocturnal hypoxemia have been associated with left ventricular hypertrophy.[21] In addition, sleep apnea is linked to the development of accelerated atherosclerosis, myocardial infarction, hypertension, and heart failure in the general population.[22,23] It is therefore not surprising that over half of the deaths in our cohort were due to cardiovascular events, and that cardiovascular event-free survival was inferior in the group of subjects with significant sleep apnea at baseline.

The main medical therapy for the sleep apnea syndrome is airway pressurization during sleep, and this has been shown

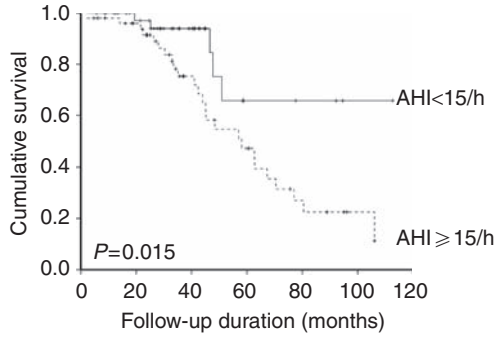

Figure 2 | Kaplan–Meier estimates of patient survival according to baseline presence (apnea-hypopnea index (AHI) ⩾15/h) or absence (AHI <15/h) of significant sleep apnea.

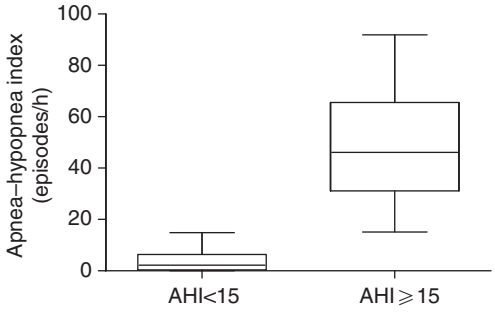

Figure 1 | Median apnea-hypopnea indices (AHIs) for patients with baseline AHI <15/h (*N* = 42) and AHI ⩾15/h (*N* = 51). Box, line across, and whiskers indicate first and third quartiles, median, and range, respectively.

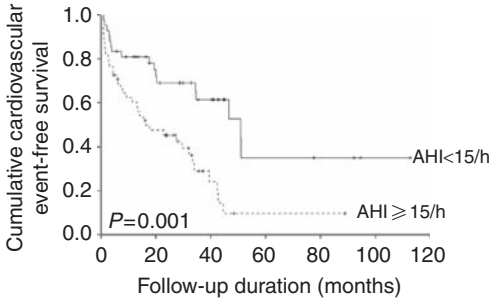

Figure 3 | Kaplan–Meier estimates of cardiovascular event-free survival according to baseline presence (apnea-hypopnea index (AHI) ⩾15/h) or absence (AHI <15/h) of significant sleep apnea.

Table 2 | Sleep apnea components of the study subjects

	Total (*N*=93)	AHI <15/h (*N*=42)	AHI ⩾15/h (*N*=51)	*P*[b]
AHI[a]	21.7 (3, 48.1)	2.2 (0.4, 5.9)	46.1 (31.7, 63.6)	<0.001
Central apnea index[a]	0.9 (0, 6.0)	0 (0, 0.5)	4.8 (1.4, 12.6)	<0.001
Obstructive apnea index[a]	14.9 (2.4, 38.4)	2.2 (0.4, 5.6)	36.7 (22.5, 47.9)	<0.001
Mixed apnea index[a]	3.9 (0.5, 14)	0.8 (0, 2.6)	11.1 (3.5, 23.0)	<0.001
Mean nocturnal SaO_2[c]	96.0 (94, 97)	96.3 (94.8, 97.5)	95.5 (94, 97)	0.195
Minimal nocturnal SaO_2[c]	86.5 (77, 90.5)	90 (86.8, 93)	80 (68, 88)	<0.001
Desaturation index[a]	12.9 (2.9, 38.6)	3 (1.8, 8.8)	32.3 (13.3, 49.2)	<0.001

Abbreviation: AHI, apnea-hypopnea index.
[a]Results are expressed as median number of episodes (interquartile range)/h of total sleep time.
[b]For comparisons between patients with AHI < and ⩾15/h.
[c]Results are expressed as median oxygen saturation in % (interquartile range).

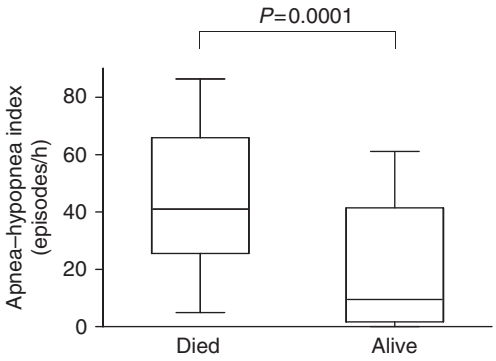

Figure 4 | Box plots showing baseline apnea-hypopnea indices (AHIs) in patients who died ($N = 30$) and those who were alive ($N = 63$) during follow-up. Box, line across, and whiskers indicate first and third quartiles, median, and 10th and 90th percentiles, respectively.

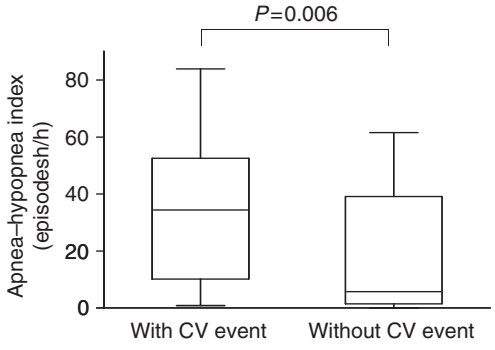

Figure 5 | Box plots showing baseline apnea-hypopnea indices (AHIs) in patients with one or more subsequent cardiovascular events ($N = 53$) and those without ($N = 40$) during follow-up. Box, line across, and whiskers indicate first and third quartiles, median, and 10th and 90th percentiles, respectively.

to reduce the risk of cardiovascular events.[24] This study, however, was not designed or powered to address adherence to treatment or the effect of treatment on outcomes. Indeed, only a minority of subjects have agreed to referral for consideration of nocturnal continuous positive airway pressurization (CPAP). The reluctance stems mainly from the need to perform nocturnal fluid exchange and the perceived additional discomfort of two systems of treatment at bed time. Even among referred subjects, reduced compliance with treatment may have had a role in the failure of therapy to reduce the risk to baseline levels. Furthermore, it is likely that many of our patients had had untreated sleep apnea for years before the commencement of peritoneal dialysis, resulting in a prolonged exposure to cardiovascular risk. The median 41 months of follow-up may not have been a sufficient length of time to derive the potential cardiovascular therapeutic benefits even if the affected subjects had all been provided with and adhered to CPAP.

Several methodologic issues should be considered in the interpretation of our results. First, the ascertainment of cardiovascular outcome was not possible in all patients, as data were tracked over a long period of time. Some patients for whom death was reported as the outcome event may have had a previous unreported cardiovascular event. The consequences of this methodologic limitation are reduced by an analysis that focuses on the combined end point of fatal and nonfatal cardiovascular events, but it is nonetheless possible that uncaptured events occurring much earlier in patients who died would alter the time-dependent character of the findings. A related issue involves possible nonfatal episodes among patients who were alive but were not hospitalized. Second, it is possible that residual confounding factors affected our adjusted hazard ratios, in spite of our attempts to control for major cardiovascular risk factors. Finally, the sample size is not big enough to control for

Table 3 | Multivariable Cox regression analysis for all-cause mortality

Covariate	Unit change	Unadjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio[a] (95% CI)	*P*
Demographic variables					
Age	+1 year	1.05 (1.02–1.09)	0.001	1.03 (1.01–1.05)	0.001
Gender (male)		1.18 (0.57–2.41)	0.659		
Diabetes mellitus		2.53 (1.16–5.46)	0.020		
Dialysis vintage	+ 1 month	1.0 (0.97–1.03)	0.998		
Sleep-related parameters					
AHI $\geqslant$ 15/h		3.13 (1.19–8.20)	0.021	1.72 (1.03–2.88)	0.037
Mean SaO_2	+1%	0.95 (0.85–1.053)	0.312		
Minimal SaO_2	+1%	0.97 (0.95–1.00)	0.036		
Desaturation index	+1 episode/h	1.01 (1.00–1.02)	0.114		
Biochemical parameters					
Residual CrCl	+1 l per week per 1.73 m^2	0.99 (0.98–1.0)	0.403		
Hemoglobin	+1 g/dl	0.97 (0.91–1.04)	0.420		
Serum albumin	+1 g/l	0.96 (0.88–1.04)	0.296		
Ca $\times$ PO_4 product	+1 $mmol^2/l^2$	1.02 (0.74–1.41)	0.886		

Abbreviation: AHI, apnea-hypopnea index.
[a]Adjusted for age, gender, diabetic status, dialysis vintage, residual creatinine clearance (CrCl), and minimum nocturnal oxygen saturation (SaO_2) on recruitment.

Table 4 | Multivariable Cox regression analysis for cardiovascular events

Covariate	Unit change	Unadjusted hazard ratio (95% CI)	P	Adjusted hazard ratio[a] (95% CI)	P
Demographic variables					
Age	+ 1 year	1.04 (1.02–1.06)	<0.001	1.03 (1.00–1.06)	0.04
Gender (male)		1.70 (0.98–2.95)	0.057		
Diabetes mellitus		3.64 (2.05–6.45)	<0.001	2.77 (1.46–5.26)	0.002
Dialysis vintage	+ 1 month	1.0 (0.98–1.03)	0.825		
Sleep-related parameters					
AHI ⩾15/h		2.72 (1.51–4.93)	0.001		
AHI	+1/h	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	0.003
Mean SaO_2	+1%	0.99 (0.94–1.03)	0.531		
Minimal SaO_2	+1%	0.97 (0.95–0.987)	0.001		
Desaturation index	+1 episode/h	1.019 (1.009–1.03)	0.001		
Biochemical parameters					
Residual CrCl	+1 l per week per 1.73 m^2	0.99 (0.98–1.0)	0.144		
Hemoglobin	+1 g/dl	0.84 (0.70–1.01)	0.070		
Serum albumin	+1 g/l	0.95 (0.89–1.01)	0.092		
$Ca \times PO_4$ product	+1 $mmol^2/l^2$	1.11 (0.88–1.39)	0.382		

Abbreviation: AHI, apnea-hypopnea index.
[a]Adjusted for age, gender, diabetic status, and residual creatinine clearance (CrCl) on recruitment.

all possible confounders, although attempts were made to correct for over-fitting. Nevertheless, we believe this is to date the largest peritoneal dialysis cohort with baseline PSG data and long-term longitudinal follow-up of clinical outcome.

In conclusion, sleep apnea syndrome detected at the outset of peritoneal dialysis is significantly associated with the risk of death from any cause and cardiovascular events, and this association is independent of other risk factors, including age and diabetes mellitus. Increased severity of the syndrome is associated with an incremental risk of cardiovascular morbidity. The assessment for the possibility of significant sleep apnea through questionnaire with a view to further PSG measurement should be considered as part of the routine cardiovascular monitoring in chronic peritoneal dialysis patients to identify those who have significant sleep apnea and are at increased risk for subsequent cardiovascular morbidity for timely intervention.

PATIENTS AND METHODS

Patients

The study protocol was fully reviewed and approved by the clinical research ethics committee and Institutional Review Boards of all participating institutions. Since 2001, consenting subjects who participated in the 'Sleep apnea in PD patients' program and had undergone at least one PSG measurement were enrolled for analysis. All subjects must be deemed clinically euvolemic with serum sodium between 135 and 145 mmol/l before undergoing overnight PSG. Exclusion criteria included patients with underlying malignancy, chronic structural heart disease, chronic obstructive pulmonary disease, or bronchiectasis that required more than one hospitalization per year, chronic liver disease, and active autoimmune disorders. In addition, patients with primary or known sleep apnea or pulmonary diseases or other illnesses that may cause sleep apnea independently of chronic renal failure, patients who were unable to cooperate or give consent were also excluded. The recruitment flow diagram is shown in Figure 6.

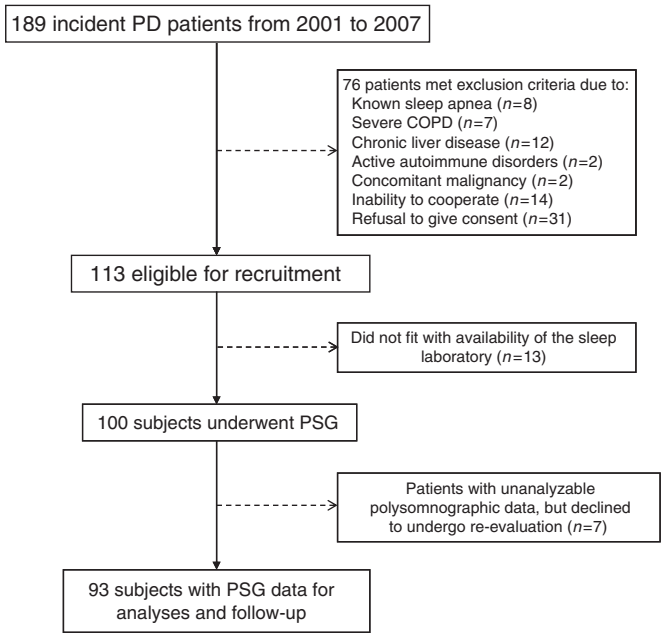

Figure 6 | Flow diagram of patient recruitment process. COPD, chronic obstructive pulmonary disease; PSG, polysomnography.

Dialysis protocol

A 'PD-first' policy is generally adopted in Hong Kong. On initiation of dialysis, the particular PD system used was solely the choice of the patient after they had received detailed information. In general, patients performed 3–4 daily

exchanges of 2 l PDF using either UltraBag (Baxter Healthcare, Guangzhou, People's Republic of China), StaySafe or AndyDisk (Fresenius Medical Care, Bad Homburg, Germany), or Gambrosol Trio (Gambro Lundia AB, Lund, Sweden) system. Dialysis regimens were adjusted to achieve euvolemia and a weekly KT/V_{urea} of 1.8–2.1.

Polysomnography

Comprehensive overnight PSG was performed in hospital using Alice 3 or Alice 5 machine (Healthdyne, Atlanta, GA, USA). Recordings included electroencephalogram, electrooculogram, submental electromyogram (EMG), bilateral anterior tibial EMG, electrocardiogram, chest and abdominal wall movement (respiratory effort) by inductance plethysmography, airflow by a nasal pressure transducer (PTAF 2, Pro-Tech, Woodinville, WA, USA), and finger pulse oximetry. All variables were recorded continuously by a computerized data-acquisition system and stored on an optical disk for subsequent analyses.

All polysomnograms were scored manually by an independent expert in sleep medicine without knowledge of the mode of dialysis according to standard criteria.[16,25,26] Apnea was defined as the cessation of airflow for >10 s, and hypopnea was defined as a reduction of airflow of $\geqslant 50\%$ for >10 s plus an oxygen desaturation of $\geqslant 4\%$. The average number of episodes of apnea and hypopnea per hour of sleep (AHI) was calculated as the summary measurement of sleep-disordered breathing. To assess oxygen saturation during sleep, the following parameters were also manually scored: (1) Mean nocturnal oxygen saturation (SaO_2) while in REM and non-REM sleep; (2) Minimal nocturnal SaO_2; and (3) Desaturation index, defined as the mean number of episodes of SaO_2 drop by $\geqslant 4\%$ per hour of sleep.

Significant sleep apnea was arbitrarily defined as an AHI of $\geqslant 15$ events per hour of sleep as we previously reported among PD subjects.[8] Apnea were classified as central if there was no chest and abdominal movement, or as obstructive if they moved paradoxically, and as mixed if an initial absence of ventilatory effort was followed by an obstructive apnea pattern on resumption of effort. Cheyne–Stokes respiration was defined as an episode of central apnea (or hypopnea) alternating with breathing that had a pattern of cyclical crescendo and decrescendo amplitude for at least three cycles of not <60 s each. Periodic leg movements were defined as four or more involuntary leg movements during sleep, each lasting 0.5–5.0 s, with 5–90 s between movements.

Outcome measurements

The primary clinical outcomes evaluated were all-cause mortality and the first episode of fatal and nonfatal cardiovascular morbidity in patients with and without significant sleep apnea at baseline, defined as AHI $\geqslant 15$/h. Cardiovascular events included angina with electrocardiographic changes of myocardial ischemia or infarction, heart failure, fluid overload, acute pulmonary edema, arrhythmia, poorly controlled blood pressure requiring hospitalization, transient ischemic attack, thromboembolic or hemorrhagic stroke, peripheral vascular disease, or sudden cardiac death. For patients with multiple cardiovascular events, the time to the first episode was taken for survival analysis. Secondary outcomes included hemoglobin levels, nutritional status, and transfer to another mode of renal replacement therapy. Patients who underwent kidney transplantation or transferred to hemodialysis were censored at the time of transfer to alternative renal replacement therapy. If a patient died within 3 months of transfer to hemodialysis, the death was not censored because such mortality was considered to reflect the health status during PD. The nature of cardiovascular event was established by the attending physician, and this information was retrieved from the online Clinical Management System of the Hong Kong Hospital Authority. During the period of follow-up, all deaths were accurately recorded with the exact cause of death provided by the attending physician.

Laboratory measurements and dialysis indices

Complete blood count, standard renal function tests including serum bicarbonate levels were measured on the day of PSG. Adequacy of dialysis was assessed at the steady state using standard urea kinetic studies when patients were established on PD for approximately 2 months. Total body water (TBW) was derived using the Watson formula. Residual renal function was estimated by 24-h urine collection and expressed as renal Kt/V (total weekly urea clearance) and weekly creatinine clearance. Peritoneal membrane transport properties were assessed at the same setting using standard peritoneal equilibration test.[27] Body water composition was measured before PSG in the evening using multifrequency bioelectrical impedance analysis, and TBW, extracellular water, and intracellular water, and hydration fraction (TBW expressed as % body weight) were computed according to previously described methods.[8]

Statistical analysis

Data are presented as means ± s.d. All statistical analyses were performed using SPSS v.16.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) or GraphPad Prism v.5.0 (GraphPad Software Inc., La Jolla, CA, USA) as appropriate. All analyses were performed on an intention-to-treat basis and included all patients who underwent at least one PSG. Continuous characteristics at the start of treatment were compared with Wilcoxon rank-sum tests. Categorical groups were compared by the χ^2 test and Fisher's exact test, as appropriate. 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 sleep apnea (AHI $\geqslant 15$/h) in predicting the time to all-cause mortality and the development of the first episode of fatal or nonfatal cardiovascular event, factors predictive of mortality and fatal and nonfatal cardiovascular morbidities were identified with Cox regression analysis to

deduce the hazard ratios and 95% confidence intervals. Factors with $P<0.25$ on univariate analysis were entered into the multivariable Cox regression model. A backward elimination procedure with $P>0.05$ to remove was performed to identify independent predictors for the development of all-cause mortality and cardiovascular events. To correct for over-fitting as a result of the low total number of deaths ($n=30$), each regression coefficient obtained from the Cox model was multiplied by a shrinkage factor computed according to the method by Van Houwelingen *et al.*[28] All probabilities were two-tailed.

DISCLOSURE

All the authors declared no competing interests.

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