Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea

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Abstract

Background. In both healthy male subjects and men with heart failure, the severity of obstructive sleep apnea (OSA) is related to the amount of fluid displaced from their legs into the neck overnight. Whether overnight rostral fluid shift contributes to the pathogenesis of OSA in patients with end-stage renal disease (ESRD) is unknown. We hypothesized that the change in neck circumference (NC) and severity of OSA are related to the extent of overnight change in leg fluid volume (LFV) in patients with ESRD.

Methods. We studied 26 patients with ESRD (14 men) on conventional hemodialysis. All subjects underwent polysomnography. LFV was measured by bioelectric impedance at bedtime and repeated in the next morning on awakening.

Results. Our cohort’s overall apnea–hypopnea index was 22.8 ± 26.8 episodes/h of sleep. Their overnight change in LFV was −243 ± 278 mL. The change in LFV correlated with apnea–hypopnea time (AHT) (P = 0.001) and NC (P = 0.0016). Other independent factors associated with AHT included age (P = 0.005), baseline neck (P = 0.0002), sitting time (P = 0.008) and male gender. Stepwise multiple regression analysis revealed that age, change in LFV and male gender remained independent related to AHT.

Conclusions. Nocturnal rostral fluid shift is associated with the severity of OSA in ESRD. Prospective evaluation of the effect of reducing fluid overload and severity of OSA in ESRD patients warrants further examination.

Keywords: fluid shift; end-stage renal disease; obstructive sleep apnea

Introduction

Obstructive sleep apnea (OSA) is a common disorder causing significant morbidity and affects ~9% of men and 4% of women [1]. OSA is more prevalent in end-stage renal disease (ESRD) than in the general population and is associated with elevated blood pressure, left ventricular (LV) hypertrophy and increased mortality [2–4]. Although OSA is due to repetitive collapse of the upper airway (UA) during sleep, the cause of UA collapse is not completely understood. In addition, given that ESRD patients generally do not comply well with continuous positive airway pressure therapy [5], a better understanding of the pathogenesis of OSA in ESRD might lead to better treatments.

The observation that OSA is more prevalent in patients with edematous states, such as heart failure (HF) and ESRD, than in the general population [1, 6, 7], raises the possibility that fluid retention may increase the risk of developing OSA. For example, fluid that has accumulated in the lower extremities while upright during the day could shift rostrally into the neck on assuming the recumbent position during sleep. Such fluid displacement might cause distension of the great veins of the neck and/or edema of the peripharyngeal soft tissue and predispose to UA obstruction. Indeed, it was recently demonstrated in 23 non-obese healthy men that the amount of fluid displaced from the legs overnight (i.e. overnight fluid shift) was associated with an increase in neck circumference (NC) and the severity of OSA despite having no detectable edema [8]. The amount of fluid shifting out of the legs in these subjects was related to the amount of time spent sitting in the daytime. Thus, in these individuals, physical inactivity led to fluid retention in the legs. Similar findings were reported in patients with hypertension and in those with HF [9, 10]. Taken together, these observations suggest that patients with other fluid overloaded states, such as ESRD, will behave in a similar fashion. If so, this would support a common pathogenetic mechanism that could explain, at least in part, the higher prevalence of OSA in patients with fluid overloaded and edematous states.

We therefore hypothesized that patients with ESRD would experience increases in NC and severity of OSA in association to overnight fluid shifts. To test this hypothesis, we examined the relationships between overnight fluid
displacements, changes in NC and indices of OSA severity in ESRD.

Materials and methods

Subjects

Consecutive ESRD patients receiving conventional thrice-weekly hemodialysis, age ≥18 years, who agreed to undergo overnight polysomnography in the Sleep Research Laboratory at Toronto Rehabilitation Institute, were enrolled in the study. ESRD patients were recruited from the hemodialysis unit of the University Health Network’s Toronto General Hospital, irrespective of symptoms of sleep apnea. The patients were studied in the day before dialysis, 48 h after their last dialysis.

We excluded anyone who was treated for sleep apnea or had a LV ejection fraction <45% on echocardiogram. Demographic characteristics, medical history and prescribed medications were recorded. Charlson comorbidity index was calculated for all patients [11]. Biochemical data and dialysis related index were measured within 2 months of polysomnography.

Subjective sleepiness

Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS) [12]. The ESS is a self-administered questionnaire designed to measure the general level of daytime sleepiness. Patients rate on a scale of 0–3 how likely they are to fall asleep in eight different situations commonly encountered in daily life. Total ESS score ranges from 0 to 24; higher scores indicate more subjective sleepiness.

Physical fitness

Physical fitness was assessed by the Duke Activity Status Index (DASI) [13]. DASI scores range from 0 to 58, with higher scores reflecting greater physical fitness. This questionnaire has been validated in hemodialysis patients [14]. Subjects also completed an hourly diary indicating the amount of time they spent sitting, walking or lying down in the daytime preceding polysomnography, from the time they arose in the morning until bedtime in the sleep laboratory [5].

Weight, leg fluid volume and neck and calf circumferences

Dry weight was informed by the patient, corresponding to the target weight reached post-dialysis. Weight gain was calculated as a difference between dry weight and the weight immediately before the sleep study. Weight was measured just before bedtime and within 30 min of waking the following morning, by the same observer. Subjects’ weights were expressed both as body mass index (BMI) and as a percentage of the ideal body weight (%IBW) based on sex, age and height [15]. IBW is a better way of comparing body habitus between men and women than BMI since it takes into account differences in fat, muscle and bone composition.

Weight was measured just before bedtime and within 30 min of waking the following morning, by the same observer. Subjects’ weights were expressed both as body mass index (BMI) and as a percentage of the ideal body weight (%IBW) based on sex, age and height [15]. IBW is a better way of comparing body habitus between men and women than BMI since it takes into account differences in fat, muscle and bone composition between the sexes [15]. With subjects instrumented for sleep studies, lying awake and supine with the legs straight, right leg fluid volume (LFV) was measured by bioelectrical impedance (Hydra 4200; Xitron Technologies Inc., San Diego, CA). We measured NC above the cricothyroid cartilage and we measured leg circumference of the thickest portion of the right calf by tape measure. Lines were drawn at these levels to ensure that measurements before and after sleep were made at the same level. Subjects then slept during polysomnography. On awakening the next morning measurements made before sleep were repeated without knowledge of the polysomnography results. The differences between LFV, NC and calf circumference, before and after sleep, were considered the overnight changes in these variables.

Polysomnography

All subjects underwent overnight polysomnography with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep [16]. All subjects slept on a single pillow with the bed flat. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow was monitored by nasal pressure cannulae (Binaps model 5500; Salter Labs, Arvin, CA). Arterial oxyhemoglobin saturation (SaO2) was monitored by oximetry. Obstructive apnea was defined as a >90% reduction of tidal volume for ≥10 s with thoracoabdominal motion, and obstructive hypopnea was defined as a 50–90% reduction in tidal volume from baseline for ≥10 s with out-of-phase thoracoabdominal motion or airflow limitation on nasal pressure. Apneas were classified as central in the absence of thoracoabdominal motion, and hypopneas were classified as central in the presence of in-phase thoracoabdominal motion and without airflow limitation on nasal pressure. The apnea–hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of sleep. As another index of OSA severity, we took into account differences in duration of apneas and hypopneas, in addition to their frequency, by calculating apnea–hypopnea time as a percentage of total sleep time (%AHT, mean duration of apneas and hypopneas in seconds × total number of apneas and hypopneas/total sleep time × 100). This index has been shown to be more strongly related to degree of nocturnal desaturation than the AHI [17]. Signals were recorded on a computerized sleep recording system (Sandman; Nellcor Puritan Bennett Ltd, Ottawa, Canada) and scored by a technician blind to measurements of LFV, NC and calf circumference. Sleep apnea was defined as an AHI ≥15 events/h of sleep in the present data. The severity of sleep apnea is classified according to AHI: mild (AHI between 5 and 15), moderate (AHI between 15 and 30) and severe (AHI >30).

The protocol was approved by the Research Ethics Boards of the University Health Network and Toronto Rehabilitation Institute, and all subjects provided written informed consent before participation.

Statistical analysis

Student’s t-test was used for normally distributed continuous variables and Mann–Whitney U-test was used for abnormally distributed variables. The χ² or Fisher exact test was used to compare nominal variables. Relationships between single variables were examined by Pearson correlation coefficient. Multivariable relationships between %AHT and independent variables and between overnight change in LFV and independent variables were also examined by stepwise linear regression, with P < 0.05 to enter and P > 0.1 to remove. Collinear variables were excluded from multiple regression modeling. Data are presented as means ± SD unless indicated otherwise. A P-value <0.05 was considered significant. Analyses were performed with the use of SPSS 17.0.1 (SPSS Inc., Chicago, IL).

Results

We studied 26 consecutive ESRD patients (14 men) from 1 August 2009 to 1 February 2011, whose characteristics are shown in Table 1. In general, our study population was receiving adequate dialysis. The patients were 1.50 ± 1.43 kg above the dry weight in the day of the sleep study. There was no difference in weight gain between men and women (1.76 ± 1.61 versus 1.15 ± 1.15 kg, P = 0.307) and between patients with and without OSA (1.88 ± 1.82 versus 1.19 ± 1.00 kg, P = 0.236). Polysomnographic data are shown in Table 2. Overall, 46.1% or 12/26 patients had AHI ≥15. Table 3 shows that the mean overnight change in right LFV was −242.7 ± 278.2. Figure 1 shows an inverse correlation between the overnight changes in LFV and in NC (r = −0.587, P = 0.0016). There was no significant relationship between overnight change in LFV and total AHI (r = −0.356, P = 0.074). However, there was a significant relationship between overnight change in LFV and apnea–hypopnea time, as percentage of total sleep time (%AHT) (r = −0.607, P = 0.001) (Figure 2). Univariate analysis demonstrated significant associations between change in LFV and age (P = 0.024) and sitting time (P = 0.010) (Table 4). Similarly, %AHT was associated with age (P = 0.005), male gender (P = 0.007), neck baseline (P = 0.0002), weight (P = 0.038) and sitting time (P = 0.008) (Table 5). Stepwise multiple regression analysis revealed that age, change in LFV and male gender remained independently associated with %AHT and accounted for 64% in the variability of %AHT (Table 6).
Our study provides new insights into the pathogenesis of OSA in patients with ESRD. Firstly, the amount of fluid spontaneously displaced from the legs overnight was related to %AHT. Secondly, there was a significant correlation between the overnight change in LFV and the overnight change in NC. Taken together, our findings suggest that overnight redistribution of fluid into the neck and peripharyngeal tissues from the lower extremities during recumbency may play a role in the pathogenesis of OSA in ESRD. However, unlike our previous studies in which we showed that overnight change in LFV was related to the AHI in non-obese men, men with HF and patients with hypertension [8–10]; in the present study, we found that it was related to %AHT, another index of OSA severity [17].

In healthy subjects, application of lower body positive pressure, using medical anti-shock trousers while awake, was accompanied by an increase in NC, an increase in UA resistance and a reduction of UA size [13, 14]. In addition, several studies have demonstrated a consistent association

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (Mean ± SD)</th>
</tr>
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<tbody>
<tr>
<td>Age, year</td>
<td>45.3 ± 15.1</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.8 ± 25.4</td>
</tr>
<tr>
<td>Weight, % of ideal</td>
<td>119.7 ± 30.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.1 ± 7.6</td>
</tr>
</tbody>
</table>

Table 2. Polysomnographic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>303.7 ± 68.6</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>81.0 ± 16.2</td>
</tr>
<tr>
<td>REM sleep, min</td>
<td>44.3 ± 28.0</td>
</tr>
<tr>
<td>Non-REM sleep, min</td>
<td>261.4 ± 61.6</td>
</tr>
<tr>
<td>ArI, events/h of sleep</td>
<td>31.4 ± 28.7</td>
</tr>
<tr>
<td>AHI, events/h of sleep</td>
<td>22.8 ± 26.8</td>
</tr>
<tr>
<td>AHT, min</td>
<td>35.6 ± 43.9</td>
</tr>
<tr>
<td>AHT, %TST</td>
<td>11.9 ± 15.7</td>
</tr>
<tr>
<td>AHI ≥ 15 events/h of sleep, n (%)</td>
<td>12 (46.1)</td>
</tr>
<tr>
<td>Minimal SaO2</td>
<td>86.0 ± 12.3</td>
</tr>
<tr>
<td>Mean SaO2</td>
<td>96.3 ± 1.8</td>
</tr>
</tbody>
</table>

Table 3. Overnight changes in weight, LFV, and neck and calf circumferences

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg edema scale, 0–3</td>
<td>0.96 ± 0.91</td>
</tr>
<tr>
<td>Overnight change in body weight, kg</td>
<td>-0.052 ± 0.754</td>
</tr>
<tr>
<td>Overnight change in body weight, %</td>
<td>-0.004 ± 1.225</td>
</tr>
<tr>
<td>Overnight change in LFV, mL</td>
<td>-242.7 ± 278.2</td>
</tr>
<tr>
<td>Overnight change in calf circumference, cm</td>
<td>-1.38 ± 0.78</td>
</tr>
<tr>
<td>Baseline NC, cm</td>
<td>39.7 ± 6.3</td>
</tr>
<tr>
<td>Overnight change in NC, cm</td>
<td>0.78 ± 0.94</td>
</tr>
</tbody>
</table>

Discussion

Our study provides new insights into the pathogenesis of OSA in patients with ESRD. Firstly, the amount of fluid spontaneously displaced from the legs overnight was related to %AHT. Secondly, there was a significant correlation between the overnight change in LFV and the overnight change in NC. Taken together, our findings suggest that overnight redistribution of fluid into the neck and peripharyngeal tissues from the lower extremities during recumbency may play a role in the pathogenesis of OSA in ESRD. However, unlike our previous studies in which we showed that overnight change in LFV was related to the AHI in non-obese men, men with HF and patients with hypertension [8–10]; in the present study, we found that it was related to %AHT, another index of OSA severity [17].

In healthy subjects, application of lower body positive pressure, using medical anti-shock trousers while awake, was accompanied by an increase in NC, an increase in UA resistance and a reduction of UA size [13, 14]. In addition, several studies have demonstrated a consistent association...
between nocturnal rostral fluid shift and the severity of OSA in otherwise healthy non-obese men [8], in men with HF [10] and in patients with hypertension [9]. The present data therefore adds to the growing body of evidence that spontaneous rostral fluid displacement from the legs into the neck contributes to the pathogenesis of UA collapse and OSA during sleep.

With respect to ESRD, it has been shown that conversion from conventional to nocturnal hemodialysis was accompanied by a significant reduction in the severity of sleep apnea in 14 patients with ESRD [18]. However, the mechanism for this effect was not determined. Similar findings were demonstrated in a cohort of patients who were switched from nocturnal peritoneal dialysis to continuous ambulatory peritoneal dialysis: the severity of OSA was lower while on nocturnal than on continuous peritoneal dialysis in association with a greater amount of fluid removed during the night [19]. Furthermore, in an extension study, Tang et al. [20] showed that conversion from nocturnal peritoneal dialysis to continuous peritoneal dialysis was accompanied by a reduction in UA size and by worsening of sleep apnea.

Although men and women had similar overnight LFV and were receiving comparable dialysis doses, men appeared to have a difference in severity of %AHT. This observation suggests that nocturnal rostral fluid redistribution may be of lesser importance to the pathogenesis of OSA in women than in men with ESRD. On observation, the prevalence of OSA is two to three times higher in men than in women in the general population [21] and in patients with ESRD [22]. It is possible that differences in levels of sex hormones between women and men may contribute to differences in OSA prevalence. Similarly, it is known that men with ESRD have higher mortality during hospital admission due to fluid overload than women [23].

In addition, men on peritoneal dialysis have greater fluid content [24]. A post hoc analysis of the HEMO study also suggests that women and men behave differently to an increase in dialysis dose [25]. Alternatively it is plausible that women may have a greater tendency to sequester fluid in capacitance vessels, such as pelvic veins [26]. Taken together, it is reasonable to hypothesize that gender may be an independent variable that affects the severity of OSA in ESRD, which requires further investigations.

All ESRD patients in our study were either anuric or had low urine output, one would expect little or no overnight weight loss in relation to urine excretion. In this regard, compared to previous studies, the overnight reduction in weight was smaller: −0.05 ± 0.75 kg compared to −0.3 kg in non-obese healthy men [8] and −0.6 kg in men with HF [10]. This infers that the relative degree of overnight fluid retention in our ESRD patients is greater than in subjects without ESRD so that fluid dynamics during sleep in patients with ESRD may differ from other subjects. This might explain in part why we found no correlation between overall AHI and the change in LFV. Instead, we observed an inverse relationship between overnight change in LFV and %AHT, suggesting that changes in LFV had a greater influence on the duration rather than on the frequency of apneas and hypopneas.

We found an inverse correlation between overnight change in LFV and sitting time. In humans, the upright bipedal posture predisposes to gravitational fluid accumulation in the legs that is counteracted by contraction of the calf muscles during physical activity, particularly walking [27–29].

In summary, we report a relationship between spontaneous rostral displacement of fluid from the lower extremities and AHT in ESRD. Although our study is limited by its observational nature, our findings are consistent with a unifying hypothesis that fluid retention in the legs during the day and its rostral displacement during the night contributes to the pathogenesis and severity of OSA. Given the emerging literature of the role of hypervolemia and OSA, it would be important to determine whether extra fluid volume removal would reduce the overall duration of apneas and hypopneas in patients with ESRD and OSA.

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Conflict of interest statement. None declared.

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