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Pharyngeal narrowing in end-stage renal disease: Implications for obstructive sleep apnea

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Running head: Sleep Apnea in ESRD

Abstract

Background: Sleep apnea is common in patients with end-stage renal disease (ESRD). We hypothesized this is related to a narrower upper airway. **Methods:** We compared upper airway dimensions in patients with and without ESRD and sleep apnea to determine whether upper airway changes associated with ESRD could contribute to the development of sleep apnea. An acoustic reflection technique was used to estimate pharyngeal cross-sectional area. Sleep apnea was assessed by overnight polysomnography. **Results:** Forty-four patients with ESRD receiving conventional hemodialysis and 41 subjects with normal renal function were studied. ESRD and control groups were further categorized by the presence or absence of sleep apnea (apnea-hypopnea index $\geq$ 10 events/hr). Pharyngeal area was smaller in patients with ESRD compared to those with normal renal function (functional residual capacity: 3.04±0.84 cm^2 vs. 3.46±0.80 cm^2; residual volume: 1.99±0.51 cm^2 vs. 2.14±0.58 cm^2). **Conclusions:** The pharynx is narrower in patients with ESRD than those with normal renal function. Since a narrower upper airway predisposes to upper airway occlusion during sleep, we suggest that this contributes to the pathogenesis of sleep apnea in dialysis-dependant patients.

Key words: sleep apnea, pharyngometry, upper airway, kidney failure, dialysis

Introduction

Sleep apnea has been reported in up to 50% to 70% of patients with end-stage renal disease (ESRD) [1], which is at least ten times higher than the prevalence reported in the general population [2]. The pathogenesis of sleep apnea in patients with ESRD remains unclear. Although sleep apnea is not corrected by conventional hemodialysis (CHD) or peritoneal dialysis [3,4], it has been reversed both by nocturnal hemodialysis and kidney transplantation [5-7], indicating that its pathophysiology is uniquely associated with the development of chronic renal failure. Previous investigators have observed features of both central and obstructive sleep apnea (OSA) in patients with ESRD [3-7], which suggests that its pathogenesis is related both to destabilization of central respiratory control and upper airway occlusion.

In patients without renal failure, the pathogenesis of OSA is associated with anatomic or dynamic narrowing of the upper airway [8,9]. Individuals with a narrower pharynx are predisposed to upper airway occlusion during sleep and the development of chronic renal failure may create or enhance this in several ways. Firstly, reduced lung volume, associated with respiratory muscle weakness or pulmonary edema, can decrease upper airway size [10]. Secondly, both fluid overload and systemic inflammation could cause upper airway edema and thereby narrow the airway. Thirdly, uremic myopathy or neuropathy involving the upper airway dilator muscles may reduce airway size. Although there is evidence of both sensory and motor neuropathy in the upper airway in patients with OSA and normal renal function [11,12], this has not been assessed in patients with ESRD.

The objective of this study was to compare the dimensions of the pharynx in a large group of patients with and without ESRD, further subdivided into those with and without sleep apnea, in

order to determine whether ESRD is associated with a narrowed upper airway, which could contribute to the development of sleep apnea.

Methods and Materials

Patient Recruitment: All patients receiving conventional hemodialysis (in-centre, 4 hours, 3 days/week) at the Humber River Regional Hospital, St. Michael's Hospital and the Toronto General Hospital who were referred to the Sleep Laboratory at St. Michael's Hospital for suspected sleep apnea were invited to participate in this study. A detailed medical history was obtained from each patient, including the cause of renal failure, duration of dialysis treatment, dialysis schedule and medications. A control group, matched for BMI with the ESRD group, was recruited from subjects referred for polysomnography who had no history of kidney disease, cardiovascular dysfunction or upper airway surgery and from healthy volunteers (departmental staff and university students) who had no history of snoring or clinical features of sleep apnea and were not taking medications that might influence sleep apnea. The study protocol was reviewed and approved by the research ethics board at St. Michael's Hospital, and all patients gave written informed consent to participate in the study.

Polysomnography: All patients referred to the sleep laboratory underwent diagnostic polysomnography, which was performed in a standardized fashion in the Sleep Laboratory at St. Michael's Hospital. Healthy volunteers who did not have a history of snoring or clinical features of sleep apnea did not have polysomnography (n=8). Patients with ESRD underwent polysomnography within 24 hours of their last hemodialysis session. Recordings were performed

by continuous monitoring of the electroencephalogram (EEG), electrooculogram, and sub-mental electromyogram (EMG), electrocardiogram, nasal airflow (Ultima Dual Airflow Pressure Sensor, Braebon Medical Corporation, Kanata, ON), chest and abdominal respiratory movements (Respitrace, Ambulatory Monitoring; Ardsley, NY), oximetry (Mallinckrodt/Nellcor Puritan Bennett, Hazelwood, MO), and body position. The recordings were performed and scored by registered polysomnographic technologists according to published criteria [13]. Apnea was defined as absence of airflow for more than 10 seconds and hypopnea was defined as any reduction in airflow for 10 seconds or more associated with an arousal and/or reduction in oxygen saturation >3%. Apneas and hypopneas were further classified as central if abdominal and ribcage movements were synchronous, as obstructive if the movements were paradoxical, and mixed if a central event had terminal obstructive features. An arousal was defined as a simultaneous increase in alpha activity on the EEG, EMG activation and eye movements, which lasted for 3 to 15 seconds.

Dialysis adequacy: A venous blood sample (3-5 ml) was drawn immediately prior to polysomnography to determine blood urea nitrogen (BUN) and serum creatinine. The percent reduction in urea per dialysis session (PRU) was used to estimate the adequacy of hemodialysis therapy [14]. The calculation, where pre- and post-BUN represent pre and post dialysis blood urea nitrogen is as follows:

PRU = (pre-BUN – post-BUN) / (pre-BUN) x 100

These measurements were obtained from the dialysis clinics at the time of polysomnography.

Pharyngometry: On the evening that polysomnography was performed, an acoustic pharyngometer (Eccovision, Hood Laboratories, Washington, MA) was used to measure pharyngeal cross-sectional area. The acoustic reflection technique is a non-invasive method for measuring pharyngeal area. It is based on the assumption that the respiratory tract can be modeled as a series of branched tubes of varying cross-sectional area. When a sound wave is sent along such a tract, the wave is partially reflected back every time there is a change in the cross-sectional area of the tract. Measuring the arrival time of these reflections and assuming the speed of sound in the airway, it is possible to calculate the distance traveled by the sound. Knowing the amplitude of the reflected waves, one can calculate the cross-sectional area of the tube. Theoretical considerations and limitations of this method have been described previously [15,16].

Measurements were obtained at the end of a normal tidal breath (functional residual capacity - FRC) and at the end of a forced expiration (residual volume - RV). These measurements were performed during oral breathing and nasal breathing was prevented by using noseclips. We estimated pharyngeal cross-sectional area between the oropharyngeal junction and the glottis (Figure 1). These anatomic landmarks were identified by instructing patients to breathe through the nose, which causes airway narrowing at the oropharyngeal junction, and by performing a Valsalva maneuver, which causes airway narrowing at the glottis. The same landmarks were also used to estimate pharyngeal length. Expiratory reserve volume (ERV) was measured using spirometry (Vmax Series 2130 Spirometer, SensorMedics, Yorba Linda, CA). All patients were studied during wakefulness while seated in the upright position with the pharyngometer held in a horizontal position and connected to the patient through a mouthpiece. Subjects were instructed to

fix their gaze straight ahead at eye level with their head and shoulders aligned in order to avoid excessive head movement. Measurements were taken during four trials at each lung volume (FRC and RV) and the average of these four trials and the coefficient of variation were calculated for each subject. Known sources of artifact, including head extension or flexion and uncontrolled tongue position were avoided.

Analysis: Mean data and standard deviations were analyzed using analysis of variance, regression analysis and unpaired t-test. Nominal data was analyzed using chi-square analysis. All statistical analysis was performed using computer software (SPSS 12.0, SPSS Inc., Chicago, IL). All p values <0.05 were considered statistically significant.

Results

Patient demographics and dialysis adequacy: Eighty-five patients were recruited, 51 males and 34 females, aged 18 to 77 years (Table 1). Patients were divided into ESRD and control groups (normal renal function). Within each group, patients were further classified as apneic and non-apneic, with sleep apnea defined as an apnea-hypopnea index (AHI) ≥ 10. There were 44 patients with ESRD and 41 controls. Gender distribution was similar between the groups. Although there were no differences in age between ESRD and control groups, apneic patients were significantly older than non-apneic patients. By study design, the groups were matched for BMI in order to control for the potential impact of obesity on the upper airway.

The most common cause of ESRD was chronic glomerulonephritis, followed by diabetes mellitus, hypertension, polycystic kidney disease, hemolytic uremic syndrome and

pyelonephritis. In eight patients, the cause of ESRD was unknown. The duration of conventional hemodialysis treatment as well as the effectiveness of dialysis, reflected by PRU, BUN and serum creatinine were similar between apneic and non-apneic patients. Five patients with ESRD were taking benzodiazepines and were instructed to use their medication as usual.

Polysomnography: The proportion of patients who had sleep apnea was 71% and 39% in the ESRD and control groups respectively. By definition, AHI was significantly higher among apneic patients within both ESRD and control groups (Table 2), and apneas and hypopneas were predominantly obstructive, with a smaller proportion classified as central or mixed (Table 3). In all patients, the majority (>65%) of respiratory events had obstructive features. The frequency of obstructive, central or mixed apneas and hypopneas did not differ significantly between ESRD and control groups. Mean oxygen saturation (SaO_2) was not significantly different between the groups (Table 2).

Total sleep time and sleep efficiency were greater in non-apneic than apneic patients within the ESRD group in contrast to the control group wherein both total sleep time and sleep efficiency were greater in apneic than non-apneic patients (Table 2). The percentage of non-rapid eye movement, rapid eye movement and slow wave sleep were similar between groups. Apneic patients had a significantly greater number of arousals from sleep, which were predominantly arousals associated with apneas and hypopneas. There were no significant differences in the number of arousals and awakenings between ESRD and control groups. The number of awakenings was not significantly different between groups.

Pharyngometry: Within all groups, pharyngeal cross-sectional area was significantly greater at FRC than RV (Table 4). Pharyngeal cross-sectional area was significantly smaller both at FRC and RV in patients with ESRD compared to controls (FRC: 3.04±0.84 cm^2 vs. 3.46±0.80 cm^2; RV: 1.99±0.51 cm^2 vs. 2.14±0.58 cm^2; mean difference = 0.28±0.13, 95% confidence intervals, 0.02-0.54, p=0.033). This difference remained significant when data from patients receiving benzodiazepines were excluded. However, pharyngeal cross-sectional area was not different between apneic and non-apneic patients (FRC: 3.15±0.88 cm^2 vs. 3.36±0.79 cm^2; RV: 2.05±0.59 cm^2 vs. 2.07±0.50 cm^2; mean difference = 0.03±0.13, 95% confidence intervals, -0.23-0.29). Mean intra-subject coefficient of variation, measured at FRC, was acceptably low (all subjects: 5±4%) and was similar between ESRD and control groups (ESRD: 5±4%; control: 5±5%). There were no significant inter-group differences in pharyngeal length. ERV was similar between patients with and without sleep apnea, but significantly smaller in patients with ESRD compared to controls (0.96±0.53 L vs. 1.33±0.52 L, p=0.014). Within the ESRD group, there was a significant positive correlation between ERV and pharyngeal cross-sectional area at FRC (r=0.492, p=0.001) and RV (r=0.363, p=0.019).

Discussion

Previous studies in the non-renal failure population have found a narrower upper airway in patients with OSA compared to healthy subjects [8,9,17,18]. Narrowing of the upper airway increases the likelihood of upper airway occlusion during sleep when diminished dilator muscle tone and gravitational forces associated with the supine position combine to narrow the airway further. Previous investigators, using the acoustic reflection technique, reported that pharyngeal

cross-sectional area was 26% smaller in patients with OSA compared to those without OSA [17]. We found that pharyngeal cross-sectional area in patients with ESRD was 12% smaller than in non-ESRD control subjects. Recent work using the same methodology as ours, has shown that increasing pharyngeal cross-sectional area as little as 6%, concurrent with weight loss, was sufficient to reduce the severity of sleep apnea, reflected by the apnea-hypopnea index, by 73% [19]. Consequently, we believe that the difference in cross-sectional area we found between patients with ESRD and subjects with normal renal function is clinically significant and may contribute to the development of sleep apnea in this patient population. Pharyngeal narrowing in non-renal failure patients with OSA may be associated with increased parapharyngeal fat due to obesity and thickened lateral pharyngeal walls possibly due to genetic inheritance or trauma associated with recurrent intraluminal negative pressure swings and snoring vibration. Upper airway caliber is also influenced by gender and age [20,21]. However, these mechanisms do not explain our findings since there were no significant differences in body mass index, age, gender distribution or severity of sleep apnea between patients with ESRD and those with normal renal function (Tables 1, 2 and 4). Consequently, we are left to speculate on potential reasons for upper airway narrowing that are unique to hemodialysis patients.

Upper airway size is significantly altered by changes in lung volume, widening as lung volume increases and narrowing as lung volume falls [10]. Consequently, pharyngeal narrowing in ESRD patients may be related to reduced lung volume as reflected by the smaller ERV we observed (Table 4). Respiratory muscle weakness has been described in patients with ESRD [22] which could decrease FRC by reducing chest wall expansion. Alternatively, FRC may be reduced by pulmonary edema associated with fluid overload, which is common in ESRD. Decreased lung volume associated with respiratory muscle weakness and/or fluid overload can

increase upper airway collapsibility and thereby reduce upper airway calibre by reducing caudal tracheal traction [23,24]. These possibilities are supported by the positive correlation we found between ERV and pharyngeal cross-sectional area in patients with ESRD. However, the change in ERV accounted for less than 25% of the variability in pharyngeal cross-sectional area which indicates that other potential mechanisms for reduced pharyngeal size must be considered.

Increased vascular distension in the upper airway due to fluid overload could contribute to pharyngeal narrowing in ESRD. In healthy subjects, decreasing central venous pressure by impeding venous return to the heart using leg cuff inflation increased upper airway dimensions [25]. Fluid overload could also lead to interstitial edema of the pharyngeal wall or para-pharyngeal tissues, which can narrow the airway. This suggestion is supported by the recent report that fluid displaced rostrally from the legs increases pharyngeal resistance in healthy subjects [26]. Alternatively, upper airway edema and pharyngeal narrowing could be caused by systemic inflammation. Pharyngeal narrowing has been noted in pre-eclampsia [27] which may be related to widespread systemic inflammation and edema. End stage renal disease is a chronic inflammatory state and similar mechanisms may contribute to pharyngeal narrowing in this patient population. Another possibility is upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia or to the underlying cause of ESRD, such as diabetes mellitus. Sensory neuropathy has been demonstrated in the upper airway in OSA patients with normal renal function [12] and may exacerbate the disease process: topical anesthesia of the upper airway increases apnea duration in patients with OSA [28]. Muscle denervation has been described in non-renal failure patients with OSA [11], and may contribute to upper airway narrowing.

Although we found that pharyngeal cross-sectional area was smaller in patients with ESRD than control subjects, it was not significantly different between those with and without OSA. These findings are not unique. Stauffer and colleagues [29] measured pharyngeal cross-sectional area using computerized tomography and found no difference between men with and without OSA matched for age and body mass index. Similar to our study, these authors included both snoring and non-snoring subjects in their control group. Inclusion of snorers in our control group may account for the similarities we observed in pharyngeal size between apneic and non-apneic patients as there is evidence that pharyngeal cross-sectional area is similar between non-apneic snorers and patients with OSA [17]. Conflicting results between studies may also be related to differences in the measurement technique. Acoustic reflection measures the cross-sectional area from the oropharyngeal junction to the glottis, but does not measure dimensions of the velopharynx or the shape or configuration of pharyngeal structures. More recent studies have noted differences in velopharyngeal cross-sectional area between patients with and with OSA, but have failed to find differences in the size of the oropharynx [9,18]. Differences in the configuration of the velopharynx (lateral narrowing) but not the oropharynx also distinguished apneic from non-apneic patients [18]. The relevance of these findings to our results are highlighted by the observation that the velopharynx has been identified as the primary site of occlusion in patients with OSA [9].

Notwithstanding these potential explanations for the absence of significant differences between apneic and non-apneic patients, our findings do suggest that pharyngeal narrowing *alone* does not account for the development of sleep apnea in patients with ESRD and that interaction with another pathogenic factor is required. We do not believe that the presence of sleep apnea in our ESRD patients was due to the timing of dialysis since polysomnographic and

respiratory assessment in ESRD patients were done in a standardized fashion (within 24 hours of the last hemodialysis session). Furthermore, the development of sleep apnea was not related to variability in the efficiency of hemodialysis since we found no difference between PRU, BUN or serum creatinine between ESRD patients with and without sleep apnea. It is possible that the development of sleep apnea in this patient population depends on the interaction between upper airway narrowing and the stability of ventilatory control [30]. There is evidence that instability in central control of respiration can be associated with upper airway occlusion during sleep. In an experimental model of central control instability induced by transient hypoxia during sleep [31], the likelihood that central instability was accompanied by upper airway closure was greater if the airway was narrow. More recently, it has been reported that increased loop gain, which reflects ventilatory instability, is associated with the development of OSA in patients whose upper airway closes during sleep at a luminal pressure that is close to zero [32]. We have previously observed increased respiratory chemoreflex responsiveness in patients with ESRD and OSA [33], which is known to destabilize central respiratory control. It is possible that the combination of central destabilization and upper airway narrowing contributes to the development of OSA in patients with ESRD.

The study does have some limitations. Firstly, upper airway measurements were done during wakefulness while other respiratory measurements were performed during sleep. We acknowledge that sleep onset induces changes in the upper airway that are pivotal to the development of OSA. However, we believe that the pharyngeal narrowing we observed during wakefulness continued during sleep and contributed to the pathogenesis of sleep apnea in patients with ESRD. Secondly, acoustic reflection measurements in the upper airway vary significantly between individuals, which can make it difficult to find significant differences

between groups of subjects. Our comparison between groups may be limited by a lack of overall power, attributed in part to this inherent variability and also to our small sample size. Nevertheless, the fact that we were able to find significant differences between patients with and without ESRD, despite the inherent variability in the measurement, makes our findings more robust. Finally, our study design was cross-sectional and consequently cannot infer causality between pharyngeal changes and sleep apnea in patients with ESRD. Nevertheless, we believe that pharyngeal narrowing likely contributes to upper airway occlusion during sleep, particularly when it is combined with other factors such as instability in central respiratory motor output.

In summary, pharyngeal cross-sectional area is reduced in patients with ESRD. Since a narrower upper airway predisposes patients to upper airway occlusion during sleep, we suggest this contributes to the pathogenesis of sleep apnea in ESRD. Further studies are required to understand how upper airway narrowing develops and to determine what additional mechanisms contribute to the development of sleep apnea in this patient population.

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Figure Legend

Figure 1. Example of a typical pharyngogram. The vertical axis is cross-sectional area and the horizontal axis is the distance into the airway, with 0.0 cm corresponding to the position of the incisor teeth. Pharyngeal cross-sectional area (P_{area}) is calculated as the average cross-sectional area between the oro-pharyngeal junction (OPJ) and the glottis.

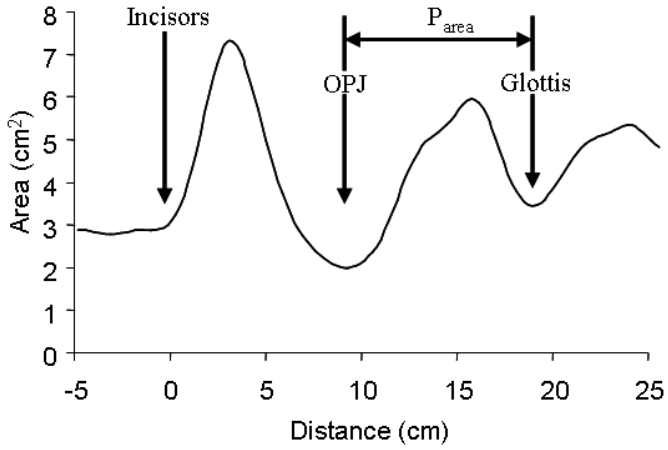

Table 1 – *Patient Demographics and Effectiveness of Dialysis in ESRD and Control groups*

	ESRD		**Control**	
	Apneic	**Non-Apneic**	**Apneic**	**Non-Apneic**
# of Patients	31	13	16	25
Males/Females	20/11	8/5	7/9	16/9
Age (years)*	51.6±12.3	45.5±14.5	50.0±14.4	41.4±13.0
BMI (kg/m^2)	27.2±4.9	26.4±3.5	27.1±4.4	27.1±4.9
Neck (cm)	38.5±3.2	36.9±3.3	37.1±3.1	37.0±3.7
Neck/Height	0.23±0.02	0.22±0.02	0.22±0.02	0.22±0.01
Etiology of ESRD				
Glomerulonephritis	10	5	-	-
Diabetes	8	3	-	-
Hypertension	4	0	-	-
PCKD	2	2	-	-
HUS	0	1	-	-
Pyelonephritis	1	0	-	-
Cyrptogenic	6	2	-	-
Months on Dialysis	12.9±14.0	12.4±19.3	-	-
PRU (%)	74.6±9.6	69.7±13.2	-	-
Creatinine (µmol/L)	629±232	559±177	-	-
Urea (mmol/L)	13.1±5.7	12.5±4.3	-	-

ESRD = end-stage renal disease; BMI = body mass index; Neck = neck circumference; Neck/Height = neck circumference indexed to height; PCKD = polycystic kidney disease; HUS = haemolytic uremic syndrome; PRU = percent reduction in urea per dialysis session. Data presented as mean ± standard deviation.

* Apneic vs non-apneic, p=0.019

Table 2 – *Polysomnography in ESRD and Control groups*

	ESRD		**Control**	
	Apneic	**Non-Apneic**	**Apneic**	**Non-Apneic***
AHI (events/hr)[†]	33.6±22.7	4.5±3.3	33.1±16.9	4.7±3.0
Mean SaO_2 (%)	94.3±1.9	94.8±2.2	94.3±1.5	94.9±1.4
Total sleep time (hr)	5.3±1.1	6.0±1.2	5.8±1.3	5.1±1.4
Sleep efficiency (%)	77.1±13.7	87.0±15.0	79.6±17.3	74.2±17.0
Stage 1 (% total sleep time)	10.5±8.7	7.1±3.7	8.6±7.9	8.4±5.1
Stage 2 (% total sleep time)	53.2±13.5	52.7±9.2	56.9±12.6	55.8±12.1
Slow Wave Sleep (% total sleep time)	17.6±8.7	21.0±10.2	20.0±9.1	19.2±14.2
REM (% total sleep time)	18.7±8.2	19.2±10.4	14.6±6.2	16.6±5.6
Total arousals (events/hr)[†]	44.0±27.9	15.5±11.6	40.2±13.4	19.1±9.7
Awakenings (events/hr)	7.1±7.0	3.7±1.8	6.0±5.0	4.7±1.7

ESRD = end-stage renal disease; Sleep efficiency = total sleep time expressed as a proportion of total study duration; REM = rapid eye movement sleep; AHI = apnea-hypopnea index; SaO_2 = oxyhemoglobin saturation. Data presented as mean ± standard deviation. *Only data for patients who underwent overnight polysomnography are shown.

[†] Apneic vs non-apneic, $p<0.001$

Table 3 – *Respiratory Events during Sleep in Patients with Sleep Apnea*

	ESRD	**Control**
Obstructive		
Events (/hr)	29.4±20.7	31.0±14.9
Events occurring in REM (/hr)	39.2±29.0	43.4±20.6
Events occurring in NREM (/hr)	27.4±21.1	28.7±15.2
% of total events	90.4±17.9	94.8±7.0
Central		
Events (/hr)	2.4±4.6	0.8±1.5
Events occurring in REM (/hr)	0.4±0.8	0.4±1.6
Events occurring in NREM (/hr)	2.8±5.4	0.9±1.6
% of total events	6.4±10.1	2.6±4.6
Mixed		
Events (/hr)	1.8±7.2	1.3±2.8
Events occurring in REM (/hr)	1.1±5.5	0.8±2.4
Events occurring in NREM (/hr)	1.9±7.4	1.3±3.0
% of total events	3.1±10.4	2.6±5.5
Total		
Events (/hr)	33.6±22.7	33.1±16.9
Events occurring in REM (/hr)	40.8±28.1	44.6±19.7
Events occurring in NREM (/hr)	32.1±23.9	30.9±17.9

Obstructive = obstructive apneas and hypopneas; Central = central apneas and hypopneas; Mixed = mixed apneas and hypopneas, as defined in the methods section; REM = rapid eye movement sleep; NREM = non-rapid eye movement sleep. Data presented as mean ± standard deviation.

Table 4 – *Pharyngometry in ESRD and Control groups*

	ESRD		**Control**	
	Apneic	**Non-Apneic**	**Apneic**	**Non-Apneic**
Pharyngeal Area (cm^2)*†				
FRC	3.10±0.92	2.91±0.63	3.23±0.82	3.60±0.77
RV	2.00±0.55	1.98±0.41	2.16±0.67	2.12±0.54
Pharyngeal Length (cm)	9.28±1.49	8.90±1.47	9.37±1.77	9.52±1.65
ERV (L)‡	0.94±0.55	1.02±0.52	1.15±0.49	1.45±0.51

ESRD = end-stage renal disease; FRC = functional residual capacity; RV = residual volume; ERV = expiratory reserve volume. Data presented as mean ± SD

* FRC vs RV, $p<0.001$

† ESRD vs control, $p=0.033$

‡ ESRD vs control, $p=0.014$