



# The effect of fluid overload on sleep apnoea severity in haemodialysis patients

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**Fluid overload plays a key role in the pathogenesis of OSA and CSA in end-stage renal disease**

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**ABSTRACT** As in heart failure, obstructive and central sleep apnoea (OSA and CSA, respectively) are common in end-stage renal disease. Fluid overload characterises end-stage renal disease and heart failure, and in heart failure plays a role in the pathogenesis of OSA and CSA. We postulated that in end-stage renal disease patients, those with sleep apnoea would have greater fluid volume overload than those without.

End-stage renal disease patients on thrice-weekly haemodialysis underwent overnight polysomnography on a nondialysis day to determine their apnoea–hypopnoea index (AHI). Extracellular fluid volume of the total body, neck, thorax and right leg were measured using bioelectrical impedance.

28 patients had an AHI  $\geq 15$  (sleep apnoea group; OSA:CSA 21:7) and 12 had an AHI  $< 15$  (no sleep apnoea group). Total body extracellular fluid volume was 2.6 L greater in the sleep apnoea group than in the no sleep apnoea group ( $p=0.006$ ). Neck, thorax, and leg fluid volumes were also greater in the sleep apnoea than the no sleep apnoea group ( $p<0.05$ ), despite no difference in body mass index ( $p=0.165$ ).

These findings support a role for fluid overload in the pathogenesis of both OSA and CSA in end-stage renal disease.

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## Introduction

Obstructive sleep apnoea (OSA) is common in the general population, having a prevalence of 3–17%, while central sleep apnoea (CSA) is rare, with a prevalence of <1% [1, 2]. However, among patients with fluid overload states, such as end-stage renal disease (ESRD), the overall prevalence of sleep apnoea is much higher, at ~50–60% [3–6], similar to that in heart failure [7], another condition characterised by fluid overload. The increased prevalence of sleep apnoea in both these conditions is not explained by age or body mass index (BMI) [8–10], suggesting that fluid overload itself may play a role in the pathogenesis of both OSA and CSA in ESRD and heart failure.

Fluid overload is an independent predictor of increased mortality in ESRD [11]. The presence of sleep apnoea in ESRD is also associated with increased mortality [12]. This raises the possibility that fluid overload may contribute to increased mortality at least partially through its effect on sleep apnoea. Accordingly, a better understanding of the mechanisms that contribute to the pathogenesis of sleep apnoea in ESRD could facilitate the application of therapies other than continuous positive airway pressure, such as more aggressive fluid volume control, with the aim of reducing morbidity and mortality in this at-risk population.

It has been shown that intensification of dialysis, by conversion from thrice weekly conventional haemodialysis to nocturnal haemodialysis 6 nights per week led to attenuation of sleep apnoea. However, the contribution of attenuation of uraemia *versus* reduced fluid volume on this effect was not elucidated [13]. To this end, we recently showed in ESRD patients on conventional haemodialysis with either OSA or CSA that removal of 2.2 L of fluid, in a single session of ultrafiltration, led to a 36% reduction in the frequency of apnoea and hypopnoea events per hour of sleep (apnoea–hypopnoea index (AHI)) [14] in the absence of any change in uraemia or acid–base status. Conversely, we showed that infusion of ~2 L of saline at sleep onset led to a three-fold increase in the AHI in a group of nonobese healthy older males [15]. Taken together, these findings suggest that fluid overload contributes to the pathogenesis of OSA and CSA [16–19]. Accordingly, we hypothesised that in ESRD patients, those with sleep apnoea would have higher total body, leg, thoracic and neck fluid volumes than those without sleep apnoea.

## Methods

### Subjects

Inclusion criteria were patients with ESRD aged  $\geq 18$  years undergoing conventional thrice weekly haemodialysis in the University Health Network (Toronto, ON, Canada), all of whom underwent annual echocardiography. Patients were recruited consecutively irrespective of symptoms of sleep apnoea. Exclusion criteria were patients who were already treated for sleep apnoea, had a BMI  $>35 \text{ kg}\cdot\text{m}^{-2}$ , tonsillar hypertrophy or a left ventricular ejection fraction  $<45\%$  by echocardiography (figure 1). The protocol was approved by the research ethics board of the University Health Network and all subjects provided written informed consent before participation.

### Polysomnography

All subjects underwent overnight polysomnography (PSG). Prior to PSG, demographic characteristics, medical history and prescribed medications were recorded. PSG was performed using standard techniques and scoring criteria for sleep stages, arousals from sleep and periodic leg movements (PLM), by personnel blind to fluid volume measurements [20, 21]. All subjects slept on a single pillow with the bed flat. Body position was determined by video monitoring. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow by nasal pressure cannulae (BiNAPS model 5500; Salter Labs, Arvin, CA, USA). Arterial oxyhaemoglobin saturation was monitored by oximetry. Central apnoea was

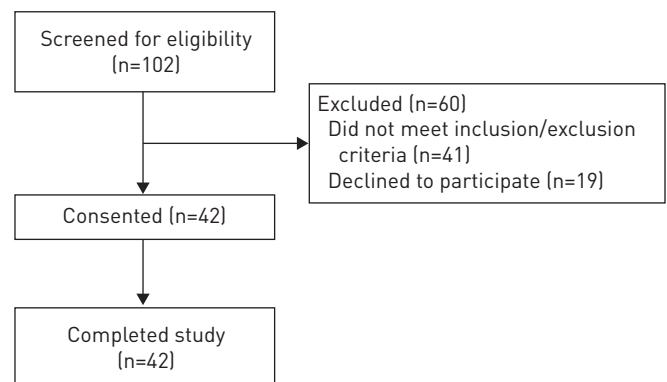


FIGURE 1 Study participant flow-chart.

defined as  $\geq 90\%$  reduction in tidal volume for  $\geq 10$  s in which thoracoabdominal motion was absent, and central hypopnoea as a reduction of  $\geq 30\%$  in tidal volume for  $\geq 10$  s with in-phase thoracoabdominal motion without airflow limitation on nasal pressure accompanied by a  $\geq 3\%$  desaturation or an arousal. Obstructive apnoeas and hypopnoeas were similarly defined, except that they had to be accompanied by out-of-phase thoracoabdominal motion or airflow limitation on nasal pressure, respectively [21]. Subjects were divided into a no sleep apnoea group (AHI <15) and a sleep apnoea group (AHI  $\geq 15$ ). Subjects with sleep apnoea were subdivided into those with OSA, in whom >50% of events were obstructive, and CSA, in whom >50% of events were central. Signals were recorded on a computerised sleep recording system (Sandman; Nellcor Puritan Bennett, Ottawa, ON, Canada) and scored by technicians blind to fluid volume measurements.

### Fluid volumes

Height and body weight were measured before going to bed and on awakening the next morning. With subjects instrumented for PSG, lying awake and supine, total body fluid volume, intracellular fluid volume and extracellular fluid volume (ECFV) were assessed by measuring the impedance to electrical flow between electrodes placed on the right ankle and the right hand using a bioelectrical impedance device (Xitron Hydra, model 4200; Xitron Technologies, San Diego, CA, USA). This well-validated technique uses impedance to electrical current within a body segment to measure fluid content [22]. ECFVs of leg (LECFV), thorax (TECFV) and neck (NECFV) were measured simultaneously using another bioelectrical impedance device (MP150; Biopac Systems Canada, Montreal, QC, Canada). This device uses multifrequency signalling to allow for simultaneous recording of the impedance in multiple body segments [23]. Sensing electrodes were placed on the ankle and upper thigh of the right leg for LECFV; for TECFV, they were positioned on the midline of the posterior aspect of the chest: one at the superior border of the scapula and one at the same level as the xiphoid process; and for NECFV, on the right side of the neck: one below the right ear and one at the base of the neck. Measurements of total body fluid, total body ECFV, LECFV, TECFV and NECFV were repeated the next morning after awakening and before subjects got out of bed and the overnight changes calculated. Measured fluid volumes were adjusted for body surface area (fluid volume index).

### Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables as proportions. Differences in measurements between the two groups were analysed using t-tests or Wilcoxon tests for normally and non-normally distributed variables, respectively. Relationships between independent variables and the presence of sleep apnoea were examined by logistic regression. The independent factors included in the logistic regression were determined by whether they were found to be significantly different between groups. Univariate and multivariate linear regression analyses were performed with AHI as the dependent variable. A two tailed p-value <0.05 was considered significant. Analyses were performed using SPSS (23.0.1; SPSS, Chicago, IL, USA).

## Results

### Subjects

42 patients were recruited and underwent a baseline PSG. Of the 42, 28 had an AHI  $\geq 15$  (21 OSA, seven CSA). The baseline characteristics of all 42 subjects are shown in table 1. The sleep apnoea group was older and had a higher proportion of males than the no sleep apnoea group. There was no difference in

TABLE 1 Baseline characteristics of the subjects

	No sleep apnoea AHI <15	Sleep apnoea AHI $\geq 15$	p-value
<b>Subjects</b>	14	28 <sup>#</sup>	
<b>AHI events-h<sup>-1</sup></b>	5.2 $\pm$ 3.1	43.9 $\pm$ 25.2	<0.0001
<b>Age years</b>	36.4 $\pm$ 11.5	52.9 $\pm$ 11.2	<0.0001
<b>Male:female</b>	6:8	22:6	0.021
<b>BMI kg-m<sup>-2</sup></b>	22.9 $\pm$ 4.1	24.3 $\pm$ 4.4	0.165
<b>Left ventricular ejection fraction %</b>	62.9 $\pm$ 4.2	61.2 $\pm$ 4.0	0.546
<b>Hypertension</b>	12 (85.7)	26 (92.8)	0.590
<b>Ischaemic heart disease</b>	1 (7.1)	2 (7.1)	1.000
<b>Atrial fibrillation</b>	0 (0.0)	1 (3.6)	1.000
<b>Diabetes</b>	2 (14.3)	5 (17.9)	1.000

Data are presented as n, mean $\pm$ SD or n [%], unless otherwise stated. AHI: apnoea-hypopnoea index; BMI: body mass index. <sup>#</sup>: obstructive sleep apnoea n=21, central sleep apnoea n=7.

BMI between the groups. Of the 42 patients, 17 (40.5%) were on an angiotensin converting enzyme inhibitor and/or an angiotensin receptor blocker, 23 (55%) were on a  $\beta$ -blocker, 15 (35.7%) were on a calcium-channel antagonist and three (7.1%) were on a low dose of prednisone. None of the patients was on any sedative medication or diuretic. All were receiving adequate dialysis, as indicated by a percentage reduction of urea >65% post-dialysis (table 2).

### *Sleep structure*

Sleep structure of the two groups is shown in table 3. Compared to the no sleep apnoea group, the sleep apnoea group had significantly less slow wave sleep ( $p=0.001$ ) and a higher arousal index ( $p=0.001$ ). There was no difference in supine sleep time ( $p=0.321$ ) or the PLM index ( $p=0.535$ ) between the groups.

### *Fluid volumes*

As displayed in figure 2, compared to the no sleep apnoea group, the sleep apnoea group had higher total body ECFV ( $p=0.006$ ). In addition, as shown in table 4, the sleep apnoea group had higher evening LECFV ( $p=0.010$ ), evening TECFV ( $p=0.028$ ) and evening NECFV ( $p=0.016$ ). These differences persisted after normalising for body surface area. In the sleep apnoea group there was a greater overnight reduction in LECFV ( $p=0.048$ ), compared to the no sleep apnoea group, and a trend towards a greater overnight change in TECFV that did not reach statistical significance ( $p=0.059$ ). There was no difference in the overnight change in NECFV between the groups ( $p=0.430$ ).

### *Relationships between independent variables and the presence of sleep apnoea*

In a multiple logistic regression analysis, with the presence of sleep apnoea as the dependent variable, and age, sex and total body ECFV index as independent variables, the only variables independently associated with the presence of sleep apnoea were age ( $p=0.005$ ) and total body ECFV index ( $p=0.047$ ) (table 5).

### *Relationships between independent variables and AHI*

In univariate regression analyses, there were significant correlations between AHI and male sex ( $r=0.368$ ,  $p=0.019$ ) and total body ECFV index ( $r=0.468$ ,  $p=0.002$ ). There was no relationship between AHI and age ( $r=0.263$ ,  $p=0.093$ ) or BMI ( $r=0.162$ ,  $p=0.306$ ). In a multivariable linear regression analysis with AHI as the dependent variable and age, BMI, sex and total body ECFV index as independent variables, total body ECFV index was the only independent correlate of the AHI ( $r=0.468$ ,  $p=0.002$ ).

## **Discussion**

The key finding of this study was that ESRD patients with sleep apnoea had a mean total body ECFV 2.6 L greater than those without sleep apnoea. While there was a higher proportion of males and older subjects in the sleep apnoea group compared to the no sleep apnoea group, there was no difference in BMI between the groups. Age and total body ECFV index were the only independent factors associated with the presence of sleep apnoea, and furthermore, total body ECFV index was the only factor that correlated independently with sleep apnoea severity as assessed by the AHI. Another important finding in this study was that the sleep apnoea group had higher LECFV, TECFV and NECFV in the evening, and a greater overnight reduction in LECFV than the no sleep apnoea group. These results are in keeping with evidence that fluid overload is an important factor in the pathogenesis of sleep apnoea in chronic kidney disease and in ESRD.

TABLE 2 Dialysis treatment duration, frequency and adequacy

	No sleep apnoea AHI <15	Sleep apnoea AHI $\geq$ 15	p-value
Subjects	14	28	
Treatment duration h	4 $\pm$ 0	4 $\pm$ 0	1.000
Frequency sessions $\cdot$ week $^{-1}$	3 $\pm$ 0	3 $\pm$ 0	1.000
PRU# %	74.4 $\pm$ 5.9	73.5 $\pm$ 7.1	0.713
Kt/V#	1.6 $\pm$ 0.4	1.6 $\pm$ 0.4	0.725

Data are presented as n or mean $\pm$ sd, unless otherwise stated. AHI: apnoea-hypopnoea index; PRU: percentage reduction in urea; K: dialyser clearance of urea; t: dialysis time; V: volume of distribution of urea. #: PRU and Kt/V are commonly used clinical measures of adequacy of dialysis. PRU is calculated from the pre- and post-dialysis urea levels; a PRU >65% is considered to indicate adequate dialysis. In general, a Kt/V >1.2 is considered to indicate adequate dialysis.

TABLE 3 Sleep structure

	No sleep apnoea AHI<15	Sleep apnoea AHI ≥15	p-value
Subjects	14	28	
TST h	4.7±0.8	4.4±1.4	0.702
Sleep efficiency %	81±12	70±21	0.155
Slow-wave sleep min	59±34	22±23	0.001
Slow-wave sleep % of TST	20±10	8±8	0.001
REM sleep min	53±18	42±27	0.104
REM sleep % of TST	18±7	14±8	0.114
Arousal index events·h <sup>-1</sup>	22±12	49±30	0.001
PLM index events·h <sup>-1</sup>	16±24	25±31	0.535
Minimum S <sub>aO<sub>2</sub></sub> %	92±3	83±16	<0.001
Transcutaneous P <sub>CO<sub>2</sub></sub> mmHg	39.5±4.2 <sup>#</sup>	39.6±3.2 <sup>¶</sup>	0.664
Supine time h	2.6±1.8	2.0±1.9	0.321

Data are presented as n or mean±SD, unless otherwise stated. AHI: apnoea-hypopnoea index; TST: total sleep time; REM: rapid eye movement; PLM: periodic leg movement; S<sub>aO<sub>2</sub></sub>: arterial oxygen saturation; P<sub>CO<sub>2</sub></sub>: carbon dioxide tension. <sup>#</sup>: n=10; <sup>¶</sup>: n=24.

In an observational study of patients with steroid-responsive nephrotic syndrome, in which PSG was performed and total body water was measured prior to and following treatment with steroids, TANG *et al.* [24] demonstrated that total body extracellular water decreased from 20.7±5.9 to 16.1±3.1 L (p<0.001) in association with a 50% reduction in the AHI from 34.8±7.6 to 16.5±4.0 (p<0.05) in 11 subjects with OSA. The same authors showed in 24 ESRD patients that the AHI increased four-fold (from 3.4 to 14.0 events·h<sup>-1</sup>; p<0.001) after conversion from nocturnal to continuous ambulatory peritoneal dialysis, in association with 1.47 L less fluid removal during the latter at night, but without any significant difference in blood urea or creatinine levels [25]. In another study, conversion from conventional to nocturnal haemodialysis led to a reduction in the mean AHI from 25±25 to 8±8 events·h<sup>-1</sup> [13], in association with improved control of both uraemia and total body fluid volume. However, the relative roles of improved uraemic status *versus* reduced fluid volumes in attenuating sleep apnoea were not determined. To address this, we demonstrated, in 15 subjects with sleep apnoea, that removal of 2.2 L of fluid during a single ultrafiltration session led to a 36% reduction in AHI, in the absence of any changes in uraemic or metabolic status [14]. Furthermore, the degree of reduction in AHI correlated with the degree of reduction in total body ECFV (r<sup>2</sup>=0.322, p=0.027). The results of the current study complement these findings in that the total body ECFV was much higher in the sleep apnoea than in the no sleep apnoea group, and total body ECFV was the only independent correlate of the AHI. Furthermore, while elevated BMI is an important risk factor for OSA in the general population [26], in the present study, BMI was within the normal range for the majority of subjects, did not differ between the groups and did not correlate with the AHI. Taken together, these results indicate that fluid overload

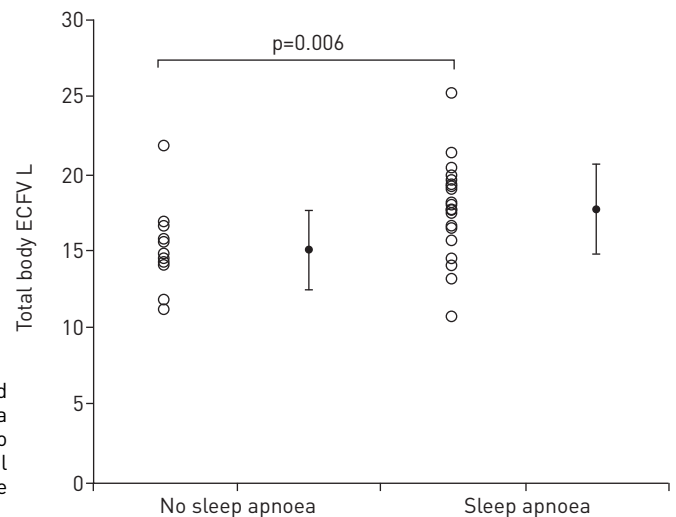


FIGURE 2 Total body extracellular fluid volume (ECFV) in the no sleep apnoea and sleep apnoea groups. In the no sleep apnoea group the mean±SD total body ECFV was 15.1±2.6 L and in the sleep apnoea group it was 17.7±2.9 L.

TABLE 4 Fluid volume measurements

	No sleep apnoea AHI <15	Sleep apnoea AHI ≥15	p-value
<b>Subjects</b>	14	28	
<b>Total body fluid volume L</b>	34.6±5.8	39.7±7.7	0.027
<b>Total body ICFV L</b>	19.5±3.8	21.9±5.4	0.177
<b>Total body ECFV index L·m<sup>-2</sup></b>	8.8±1.0	9.7±1.1	0.004
<b>Evening LECFV mL</b>	1882±332	2240±441	0.010
<b>Evening LECFV index mL·m<sup>-2</sup></b>	1086±178	1234±185	0.020
<b>Overnight change in LECFV mL</b>	-210±75	-272±117	0.048
<b>Evening TECFV mL</b>	2229±576	2817±1017	0.028
<b>Evening TECFV index mL·m<sup>-2</sup></b>	1184±465	1554±524	0.033
<b>Overnight change in TECFV mL</b>	157±179	276±177	0.059
<b>Evening NECFV mL</b>	383±94	467±102	0.016
<b>Evening NECFV index mL·m<sup>-2</sup></b>	222±48	261±51	0.031
<b>Overnight change in NECFV mL</b>	24±49	38±53	0.430

Data are presented as n or mean±SD, unless otherwise stated. AHI: apnoea-hypopnoea index; ICFV: intracellular fluid volume; ECFV: extracellular fluid volume; LECFV: leg extracellular fluid volume; TECFV: thoracic extracellular fluid volume; NECFV: neck extracellular fluid volume.

contributes to the pathogenesis of both OSA and CSA in ESRD patients, and that fluid removal is a mechanism by which sleep apnoea can be improved in this population.

The exact mechanisms by which fluid overload contributes to the pathogenesis of sleep apnoea have yet to be fully elucidated. YUMINO *et al.* [16] showed that the degree of overnight change in leg fluid volume correlated with the AHI in heart failure patients with either OSA or CSA, suggesting that nocturnal rostral fluid shift is a unifying mechanism in the pathogenesis of both OSA and CSA in patients with heart failure. At that time, technical limitations did not allow for measurement of NECFV and TECFV. However, in the OSA subjects, there was an increase in neck circumference overnight that correlated with the AHI, suggesting that fluid shift from the leg was redistributed to the neck. Conversely, in the CSA subjects, the overnight change in LECFV correlated inversely with the mean transcutaneous carbon dioxide tension ( $PCO_2$ ) during sleep, which in turn was inversely related to the AHI. These observations suggested that some of the fluid shifting from the legs redistributed to the chest, leading to increased pulmonary congestion with subsequent stimulation of pulmonary irritant receptors, leading to hyperventilation and subsequent lowering of  $PCO_2$  [27]. This could lead to CSA if the  $PCO_2$  during sleep fell below the apnoea threshold [27]. Given that ESRD patients are fluid overloaded, it is plausible that increases in TECFV could also contribute to the pathogenesis of CSA in ESRD patients by the same mechanisms.

With regards to the pathogenesis of OSA in ESRD, in a study of 26 ESRD patients, 12 of whom had OSA, the degree of overnight fluid shift from the legs did not correlate with the AHI, but did correlate with the apnoea-hypopnoea time, an alternative marker of sleep apnoea severity [15]. ELIAS *et al.* [28] subsequently showed, in 20 ESRD patients, that the only significant independent correlates of OSA severity, as characterised by the AHI, were internal jugular vein volume and upper airway mucosal water content, measured by magnetic resonance imaging. These observations suggested that increased intravascular and interstitial fluid accumulation in the neck tissues surrounding the upper airway could lead to increased collapsibility of the upper airway. In the current study, the finding of a higher mean baseline NECFV in the sleep apnoea compared to the no sleep apnoea group is consistent with those previous finding [28]. Consistent with those results, we also found no significant difference in the overnight change in NECFV between the groups. This suggests the possibility that in ESRD patients the magnitude of fluid overload is

TABLE 5 Multiple logistic regression analysis, with presence of sleep apnoea as dependent factor

	Odds ratio (95% CI)	p-value
<b>Age</b>	1.161 (1.046–1.288)	0.005
<b>Total body ECFV index</b>	3.043 (1.016–9.113)	0.047

ECFV: extracellular fluid volume.

such that it leads to increased NECFV regardless of body position, and therefore NECFV does not subsequently increase overnight any more in those with sleep apnoea than in those without it.

Studies in subjects with normal renal function and in patients with ESRD suggest that ventilatory control system instability and increased chemosensitivity may play a role in the pathogenesis of CSA and OSA [29, 30]. In this context, the finding of a significantly higher TECFV in the sleep apnoea compared to the no sleep apnoea group is of particular interest. As described above, hypocapnia, secondary to pulmonary congestion, may predispose to ventilatory instability and CSA through mechanisms described previously in heart failure patients [27, 31]. With respect to OSA, the subsequent periodic breathing, with waxing and waning of the respiratory drive, could lead to reductions in the neural drive to upper airway dilator muscles and, in susceptible individuals, lead to recurrent upper airway collapse and OSA. While there was no difference in the mean transcutaneous  $PCO_2$  between the groups in our study, this does not necessarily exclude the possibility that the relatively low mean  $PCO_2$  of 39.5 mmHg in the sleep apnoea group could have led to ventilatory instability, at least in some patients. Indeed, we have previously shown that following ultrafiltration there was a mean reduction in TECFV of 450 mL that was accompanied by an increase in the overnight transcutaneous  $PCO_2$  from  $39.2 \pm 1.9$  to  $42.3 \pm 5.1$  mmHg ( $p=0.042$ ) and by attenuation of sleep apnoea [14]. These findings suggested that fluid removal and the subsequent reduction in TECFV led to a reduction in respiratory drive, increased ventilatory stability and attenuation of both OSA and CSA. In this regard, further research is needed to investigate the relative contributions of increased neck, chest and leg fluid volumes as well as to determine the relative roles of upper airway mechanics and respiratory control system stability in the pathogenesis of both OSA and CSA in ESRD patients.

One of the limitations of this study is that the sleep apnoea group was older and had a higher proportion of males than the no sleep apnoea group, characteristics that would increase the risk for OSA [2, 32]. However, we showed in both multiple logistic regression and linear regression analyses, that included age, sex and BMI, that total body ECFV index remained independently associated with both the presence of sleep apnoea and the AHI, which supports an important role for fluid in the pathogenesis of sleep apnoea in ESRD. Another limitation is that, in presenting the results of fluid volume measurements, we did not divide the sleep apnoea group into those with OSA and those with CSA. This was due in part to the small number of patients with CSA ( $n=7$ ), but also because we did not see any difference in total body or segmental fluid volumes between those patients with OSA or CSA. Accordingly, and given the lack of any intervention in this study, it was not possible to determine a cause-effect relationship regarding the role of NECFV and TECFV in the pathogenesis of sleep apnoea in ESRD.

In conclusion, among patients with ESRD, we showed that subjects with sleep apnoea had significantly higher total body ECF volume and segmental fluid volumes than those with no sleep apnoea. These results complement our previous findings that fluid removal by ultrafiltration reduces the AHI of ESRD patients with either OSA or CSA in proportion to the reduction in total body ECFV. Taken together, these results support the role of fluid overload as an important mechanism in the pathogenesis of sleep apnoea in ESRD. They indicate the need for further research to determine the relationship between increased neck and thoracic fluid volumes, and upper airway mechanics and respiratory control system stability, respectively. Ultimately, studies will be required to assess the effects of more aggressive fluid removal on a chronic basis on sleep apnoea severity in ESRD patients.

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