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Original Article

Relationship of left atrial size to obstructive sleep apnea severity in end-stage renal disease

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ABSTRACT

Background: Increased left atrial (LA) size is linked to elevated mortality in end-stage renal disease (ESRD). In addition, the degree of overnight rostral fluid shift from the legs is associated with severity of obstructive sleep apnea (OSA). As rostral fluid shift might distend the left atrium and increase fluid accumulation in the neck, we postulated that LA size would be related to the degree of overnight rostral fluid shift and OSA severity in ESRD patients.
Methods: Patients with ESRD underwent echocardiography and polysomnography. Leg fluid volume (LFV) was measured by bioelectrical impedance before and after the overnight sleep study in a subset of 21 patients.
Results: Forty patients (22 men), with a mean apnea–hypopnea index (AHI) of 25.1 ± 23.4/h of sleep, had echocardiography and polysomnography performed. In men, there was a correlation between the AHI and LA size indexed for body surface area ($r = 0.743$, $p < 0.001$) that was not observed in women. Strong relationships were seen, again in men only, between LA size indexed to body surface area and the overnight change in leg fluid volume (ΔLFV) ($r = -0.739$, $p = 0.02$) and between AHI and ΔLFV ($r = -0.863$, $p = 0.003$).
Conclusions: In ESRD patients, there are relationships between ΔLFV and both LA size and OSA severity. These findings suggest that the relationship between LA size and mortality in ESRD may be related to ΔLFV and severity of OSA.

1. Introduction

Patients with end-stage renal disease (ESRD) have an annual mortality rate between 10% and 20%, mainly due to cardiovascular causes [1–3]. Increased left atrial (LA) size contributes to cardiovascular mortality in both the general population and in patients with ESRD [4,5]. In ESRD, the prevalence of obstructive sleep apnea (OSA), characterized by repetitive upper airway collapse during sleep, is at least 50% and is much higher than in the general population [6,7] with men having a higher prevalence than women [8]. In ESRD patients on peritoneal dialysis, the presence of OSA has been shown to be an independent predictor of cardiovascular morbidity and death [9]. It has also been shown that the severity of OSA is directly related to the degree of overnight fluid shift from the legs in ESRD [10]. Given that ESRD causes fluid retention, that OSA is very common in ESRD, and that OSA increases cardiovascular risk [2,3,11], it is important to examine potential mechanisms through which fluid retention, nocturnal rostral fluid shift, and OSA may contribute to potentially reversible changes in cardiac structure in ESRD patients.

The left atrium plays a crucial role in maintaining optimal cardiac function. It modulates left ventricular (LV) filling by acting as a reservoir during ventricular systole, a conduit during early diastole, and as an active pump in late diastole [12]. Its thin-walled structure means that it is more distensible than the left ventricle in response to increases in pressure or volume of pulmonary venous inflow [13]. The most common causes of an enlarged left atrium are LV dysfunction or hypertrophy, mitral valve disease, and fluid overload [13,14]. The relationship with fluid overload is of particular relevance in ESRD, given that fluid overload is a hallmark of this condition and predicts increased mortality [15].

The high prevalence of OSA in ESRD and in heart failure [16], both pathological states characterized by fluid overload, has led to an interest in the role of fluid retention and fluid shift from the legs in the pathogenesis of OSA in these conditions. In ESRD, the increased prevalence of OSA is not explained solely by comorbidities or increased body mass index (BMI) [17]. Indeed, OSA patients with ESRD tend to have a lower mean BMI than OSA patients with normal

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renal function [2,17,18]. The severity of OSA has been shown to be directly related to the degree of overnight rostral fluid shift from the legs in both heart failure [19] and ESRD patients [10]. In ESRD patients, the volume of fluid accumulating in the legs during the day is likely to be greater than in the general population. Consequently, it is likely that fluid overload and increased overnight fluid shift from the legs play important roles in the pathogenesis of OSA in this population. As fluid overload and rostral fluid shift might distend the LA and increase fluid accumulation in the neck, we postulated that in ESRD patients, LA size would be related to the degree of overnight rostral fluid shift and that, in turn, OSA severity would be related to LA size. To test this hypothesis, we examined LA size determined by echocardiography in relation to OSA severity as determined by polysomnography (PSG) in patients with ESRD.

2. Methods

2.1. Subjects

Inclusion criteria were patients with ESRD at least 18 years of age undergoing thrice-weekly hemodialysis at the University Health Network Toronto General Hospital. Patients were recruited consecutively irrespective of symptoms of sleep apnea. Exclusion criteria were patients who were already treated for OSA or had an LV ejection fraction (LVEF) of <45%.

2.2. Protocol

2.2.1. Echocardiography

As part of routine clinical care in the hemodialysis unit, all patients with ESRD undergo echocardiography yearly. Transthoracic echocardiography was performed using a sector array between 1 and 5 Hz. Two-dimensional echocardiographic images were acquired from the parasternal long and short axes, apical long axis, apical four-chamber, apical two-chamber, and subcostal views.

Variables recorded were LVEF, LV mass, and LA size. LVEF was measured using the biplane Simpson's method using the apical four-chamber and apical two-chamber views. LA size was estimated by measuring the maximum internal anteroposterior diameter of the LA, using the parasternal long axis view. *LV mass was estimated using the American Society of Echocardiography (ASE)-recommended formula:* $LV\ mass = 0.8 \times (1.04\ (LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3) + 0.6\ g$, *where LVIDD is the LV internal diameter in diastole, PWTD is the posterior wall thickness in diastole, and IVSTD is the interventricular septum thickness in diastole. LA size index and LV mass index were calculated by expressing LA size and LV mass, respectively, per unit body surface area.*

All echocardiograms were performed and reported prior to PSG so that the sonographer and reporting cardiologist were unaware of the patient's PSG findings and whether or not they had OSA.

2.2.2. Polysomnography

All subjects underwent overnight PSG the day before dialysis. Prior to PSG, demographic characteristics, medical history, and prescribed medications were recorded. PSG was performed with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep [20]. 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, USA). Arterial oxyhemoglobin saturation (SaO_2) 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. Although these methods for classifying hypopneas as obstructive or central are in keeping with the criteria recommended by the American Academy of Sleep Medicine (AASM) for scoring hypopneas [21] and in most instances the distinction is clear, in others it is not. Thus, these techniques provide a reasonable approximation of the numbers of obstructive and central hypopneas. The apnea–hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of sleep. Signals were recorded on a computerized sleep recording system (Sandman; Nellcor Puritan Bennett Ltd, Ottawa, Canada) and scored by personnel blind to measurements of leg fluid volume (LFV), neck circumference (NC), and echocardiographic findings.

2.2.3. LFV And neck circumference

A subset of patients agreed to have assessments of LFV and NC. With subjects instrumented for PSG, lying awake and supine with the legs straight, LFV was assessed by measuring the impedance to electrical flow between the electrodes placed on the ankle and upper thigh of the right leg by a bioelectrical impedance device (Xitron Hydra, model 4200, Xitron Technologies Inc., San Diego, CA, USA), as previously described [19,22–24]. This well-validated technique [25,26] uses the impedance to electric current within a body segment to measure its fluid content. Alterations in the fluid content of tissues cause proportional changes in impedance. NC was measured at the superior border of the cricothyroid cartilage with a tape measure. Lines drawn at this level ensured that measurements before and after sleep were made at the same place. On awakening the next morning, measurements made before sleep were repeated. The differences between LFV and NC, before and after sleep, were considered as the overnight changes in LFV (ΔLFV) and NC (ΔNC). Measurements of LFV and NC were made prior to scoring of the PSG by personnel unaware of the AHI.

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

2.3. Statistical analysis

Relationships between single variables were examined by the Pearson correlation coefficient. Multivariable analysis was also undertaken with AHI as the dependent variable and with age, BMI, presence or absence of hypertension, LV mass, and LA size index as the independent variables using multiple stepwise linear regression with $p < 0.05$ to enter and $p > 0.1$ to remove. A similar multivariable analysis was undertaken with LA size index as the dependent variable and with ΔLFV, age, BMI, and presence or absence of hypertension as the independent variables. Data are presented as mean ± standard deviation (SD) unless indicated otherwise. A p value <0.05 was considered significant. Analyses were performed with the use of SPSS 21.0.1 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the patients

Forty ERSD patients underwent PSG and an echocardiogram was performed. Their characteristics are shown in Table 1. The study population was receiving adequate dialysis, as indicated by a percent reduction of urea >65% in all. The great majority of apneas and hypopneas were obstructive. A subset of the last 21 patients underwent LFV assessment.