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Original article

Idiopathic edema is associated with obstructive sleep apnea in women

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Abstract

Background and purpose: This study was undertaken to clarify whether idiopathic edema is a marker for obstructive sleep apnea (OSA), independent of level of obesity, in patients with normal left ventricular function.

Patients and methods: Seventy-eight ambulatory, obese, adults, 44 with bilateral, pitting pre-tibial edema, and 34 without edema, from an inner city family practice and a suburban family practice enrolled from July 1995 until March 2003. Edematous subjects, but not non-edematous subjects, underwent echocardiography, urinalysis, and blood test evaluations to ensure that cardiac, renal, hepatic, and thyroid functions were normal. All subjects underwent spirometry, pulse oximetry on room air, and polysomnography evaluations.

Results: Compared to the non-edematous subjects, the edematous subjects were more obese (body mass index $=47.0\pm9.3$ versus 36.5 ± 4.6 kg/m^2, $P=0.002$), had more severe OSA (apnea–hypopnea index (AHI) $=34.1\pm27.7$ versus 17.0 ± 19.4, $P=0.002$), and had lower oxygen saturations (96.2 ± 2.0 versus $97.1\pm1.5\%$, $P=0.05$). Using an AHI ≥15 as the criteria for diagnosing OSA, there was an association between edema and OSA in women ($P=0.02$) but not men.

Conclusions: In subjects with normal left ventricular function, idiopathic edema is associated with OSA in women.

Keywords: Edema; Obesity; Obstructive sleep apnea

1. Introduction

Edema frequently accompanies obstructive sleep apnea (OSA) [1,2]. When edema occurs in association with OSA, the edema is usually attributed to obesity, abnormal lung function, or cor pulmonale [1–6].

A series of office-based studies from our group suggest that idiopathic edema (unexplained, bilateral leg edema) may be a marker for OSA in ambulatory adults. An initial case series suggested a relationship between edema and pulmonary hypertension, with hypoalbuminemia, renal disease, liver disease and venous insufficiency being less frequently associated with edema [7]. A subsequent study identified a high proportion of OSA and obesity in subjects with normal left ventricular function who had bilateral leg edema and pulmonary hypertension [8]. This, in turn, led to a cross-sectional study that identified associations among edema, obesity and OSA [9].

Our earlier data failed to clarify whether leg edema, independent of obesity, is associated with OSA in patients with normal left ventricular function. Accordingly, this cross-sectional study was undertaken to identify whether obese subjects with idiopathic edema have a higher frequency of OSA than obese subjects without edema.

2. Methods

All subjects were enrolled by a single physician (RPB), who consecutively enrolled 30 edematous subjects from a two physician suburban family practice near Cleveland,

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OH from October 1997 to March 2003. During this time, RPB enrolled virtually all the eligible edematous patients from his panel of patients from October 1997 until March 2003. When the second physician left the suburban practice in February 1999, virtually all the eligible, edematous patients who continued with the practice were enrolled by RPB from February 1999 until March 2003. RPB also enrolled 14 edematous adults who had been his patients when he worked in a five physician/one nurse practitioner inner city group family practice in Cleveland, OH from July 1995 to September 1997. Almost all eligible edematous patients agreed to participate.

A convenience sample of non-edematous subjects was consecutively enrolled by RPB from March 2002 to May 2003 from the suburban family practice. An effort was made to enroll non-edematous subjects such that the number of non-edematous women approximated the number of edematous women, and the number of non-edematous men approximated the number of edematous men. About half of the eligible non-edematous subjects, women as well as men, declined to participate.

Ambulatory adult, obese patients older than age 18 were eligible to participate. Obesity was defined as a body mass index (BMI) >30 kg/m^2 [10]. Edema was defined as bilateral, pitting, pre-tibial swelling.

Subjects with bilateral leg edema were eligible to participate if they had a normal left ventricular ejection fraction (left ventricular ejection fraction $\geq$50% and no focal left ventricular wall abnormality) based upon echocardiographic evaluation. Six subjects with edema, three men and three women, were excluded due to echocardiographic evidence of left ventricular dysfunction.

Subjects with asthma were allowed to participate if the asthma was under good control based upon clinical assessment, and if spirometric evaluation demonstrated that the forced expiratory volume in 1 s in relation to the forced vital capacity was $\geq$80%. Subjects enrolled in the non-edema group were not required to undergo echocardiographic evaluation, and they were eligible to participate if they were using dihydropyridine calcium antagonists.

Subjects were excluded if they had a known diagnosis of restrictive lung disease or chronic obstructive pulmonary disease; if they had hypoalbuminemia or proteinuria; if they were pregnant; or if they were non-ambulatory. Subjects were excluded from the edema group if their echocardiogram identified valvular heart disease, congenital heart disease, or left ventricular systolic or diastolic dysfunction; if they were currently using dihydropyridine calcium antagonists; if they had unilateral edema, myxedema, or idiopathic cyclic edema.

The protocol was approved by the Institutional Review Board at the Southwest General Health Center, Middleburg Heights, OH. Informed consent was obtained from each subject.

The medical history of each subject was reviewed and subjects answered the questions comprising the Epworth daytime sleepiness scale (ESS) [11]. No structured alcohol history was obtained.

The percent predicted forced vital capacity, the percent predicted forced expiratory volume in 1 s, and the forced expiratory volume in 1 s in relation to the forced vital capacity were determined by spirometry (Brentwood Spiroscan 2000, Hoks Electronics, Inc., Japan). Oxygen saturations on room air were determined via oximetry (N-20, Nellcor, Inc., Hayward, CA).

Diagnostic polysomnography was performed on all subjects in a sleep laboratory. Standard electroencephalograms, electrooculograms and submental electromyograms were used to monitor the sleep stages. Airflow was monitored by thermistors at the mouth and by nasal pressure transduction. Respiratory movements were monitored by qualitative inductance plethysmography (Respitrace, Sensormedics, Inc., CA). Snoring was detected by microphone. Arterial oxygenation was monitored by a finger pulse sensor (Ohmeda model 3700, Boulder CO). Electrocardiograms were monitored by chest wall leads. Tibial electromyography sensors recorded leg movements. Sleep was scored by the method of Rechtschaffen and Kales [12]. Apneas were defined as an absence of inspiratory air flow for 10 s or longer, and hypopneas were defined as a reduction of inspiratory air flow of 50% or more with an associated drop in arterial oxygen saturation. A desaturation event was identified when there was a reduction in the oxygen saturation of 4% or more.

The average number of episodes of apneas and hypopneas per hour of sleep (apnea–hypopnea index, AHI) was calculated**.** There are no universally accepted criteria for diagnosing OSA [13]. For this study, OSA was defined as an AHI$\geq$15 events per hour [4]. Serum albumin, liver function tests, and thyroid stimulating hormone were obtained on all edematous subjects.

Mean values between the edema and the non-edema groups were compared with Student's *t*-test, and χ^2 statistics were used to compare differences between proportions. Logistic regression analyses were conducted to test for associations between edema and OSA controlling for level of obesity.

3. Results

Seventy-eight subjects enrolled in the study, 44 with, and 34 without edema. Female enrollees outnumbered men, 48–30. For most of the subjects with edema, the edema was mild, usually 1+or 2+pitting, and typically presented as an incidental examination finding. Eighty-two percent of the edematous subjects reported that their edema had been present for 1 year or longer.

There were no differences between the two groups in age, sex, race or marital status (Table 1). Compared with the non-edematous subjects, the subjects with edema were more obese (BMI=47.0$\pm$9.3 versus 36.5$\pm$4.6 kg/m^2,

Table 1
Demographic, medical, and laboratory characteristics of obese subjects with and without bilateral leg edema

	Edema ($N=44$)	No edema ($N=34$)	P
Age (mean ± SD, years)	53.8 ± 12.9	49.1 ± 13.6	0.13
Body mass index ± SD (kg/m^2)	47.0 ± 9.3	36.5 ± 4.6	0.002[a]
Apnea–hypopnea index ± SD	34.1 ± 27.7	17.0 ± 19.4	0.002[a]
Spirometry data			
FVC, % predicted ± SD	71.1 ± 14.8	76.6 ± 13.1	0.10
FEV 1, % predicted ± SD	75.2 ± 15.6	82.0 ± 14.2	0.06
FEV 1/FVC, % ± SD	106.2 ± 8.9	106.9 ± 7.1	0.68
Oxygen saturation ± SD, awake (%)	96.2 ± 2.0	97.1 ± 1.5	0.05
Epworth sleepiness scale score ± SD	11.2 ± 5.9	5.7 ± 3.4	0.001
Cigarette smokers	58%	15%	0.001
Restrictive spirometry pattern	73%	64%	0.38
Female sex	59%	65%	0.61
Caucasian	93%	94%	0.87
Asthma	16%	15%	0.88
Hypertension	41%	41%	0.98
Diabetes mellitus	18%	18%	0.95
Varicose veins	7%	12%	0.45
Use diuretic medication	39%	9%	0.003

[a] Probabilities adjusted for unequal variances.

$P=0.002$), had more severe OSA (AHI = 34.1 ± 27.7 versus 17.0 ± 19.4, $P=0.002$), had more daytime somnolence (ESS score = 11.2 ± 5.9 versus 5.7 ± 3.4, $P=0.001$), had lower oxygen saturations (96.2 ± 2.0 versus 97.1 ± 1.5%, $P=0.05$), and were more likely to smoke cigarettes (58 versus 15%, $P<0.001$). There were some trends in the spirometry results, the percent predicted forced vital capacity (FVC, % predicted) and the percent predicted forced expiratory volume in 1 s (FEV 1, % predicted) being lower in the edematous group than the non-edematous group. In addition, edematous subjects were more likely to use diuretic medication than non-edematous subjects (39 versus 9%, $P=0.003$). All the subjects without edema who used diuretics were being treated for hypertension. There were no differences between the two groups in frequency of asthma, hypertension, diabetes mellitus, or varicose veins.

Table 2 shows that edema was associated with OSA for the entire sample, independent of BMI ($P=0.04$). Because the number of female edematous subjects outnumbered men, and because inspection of the data suggested that there might be differences between men and women with regard to the association of edema with OSA, gender specific logistic regression analyses were performed, thereby identifying that the association between edema and OSA exists for women ($P=0.02$), but not men. Adjusting for differences in body mass, 63% of the edematous women had an AHI ≥ 15, whereas 25% of the non-edematous women had an AHI ≥ 15.

Table 2
Logistic regression analyses of obstructive sleep apnea on edema status and body mass index (BMI) in obese subjects

Variable	Coefficient	95% CI	Wald	P-Value	Odds ratio
Total sample ($N=78$)					
BMI	0.09	0.004 to 0.17	4.1	0.04	1.1
Edema	1.03	0.038 to 2.03	4.1	0.04	2.8
Women ($N=48$)					
BMI	0.14	0.015 to 0.24	4.8	0.03	1.1
Edema	1.81	0.358 to 3.27	6.0	0.02	6.1
Men ($N=30$)					
BMI	0.33	−0.059 to 0.72	2.8	0.10	1.4
Edema	−0.95	−1.09 to 2.99	0.8	0.36	0.4

The severity of obesity was associated with OSA for the entire group, the more obese subjects being more likely to have OSA ($P=0.04$). Gender specific logistic regression analyses identified that the association between severity of obesity and OSA exists for women ($P=0.03$), whereas there was a trend toward an association between severity of obesity and OSA in men ($P=0.10$).

The severity of obesity was also associated in a linear fashion with leg edema for both sexes ($P=0.007$). Thirty-eight percent of subjects with a BMI >30 to <35 had edema, 54% of subjects with a BMI ≥ 35 to <40 had edema, and 75% of subjects with a BMI ≥ 40 had edema. The corresponding percentages for women were 31, 50 and 71%, respectively ($P=0.02$).

4. Discussion

This study found that idiopathic, bilateral leg edema is associated with OSA in women, independent of level of obesity, and that bilateral leg edema is associated with the severity of obesity in women, the more obese women being more likely to have edema. The study also identified some trends and associations in spirometry measures and oxygen saturation results that suggest a possible relationship between abnormal lung function and edema in OSA subjects, consistent with previous studies that identified relationships between abnormal lung function and edema in OSA subjects [2,14]. However, in our study there were more smokers in the edema group than in the non-edema group, thereby raising the possibility that cigarette smoking by subjects in the edema group may account for the abnormal lung function.

Given the high proportion of OSA identified in this cohort, one might consider that the enrollment process somehow selected for subjects with OSA. At the time of enrollment, potential subjects were not questioned regarding symptoms of sleep disordered breathing, but they were informed as to the typical symptoms of OSA. Following this discussion, most subjects assumed that they did not have OSA. Moreover, almost all of the subjects diagnosed as having OSA declined treatment, in large part because they

did not believe that they had a sleep disorder, despite the abnormal polysomnography results.

It is curious that this study identified associations between edema and OSA in women, but not men. It is possible that there are gender differences in this regard, especially since idiopathic edema is more common in women than men [15]. In addition, while this study enrolled predominantly women, a previous study that enrolled predominantly men failed to identify a relationship between edema and OSA [2]. If there are gender differences regarding the relationship between edema and OSA, additional research will be necessary to clarify why such differences exist.

On the other hand, the small sample of men provides an alternative explanation as to why edema was not associated with OSA in men. The extraordinary proportion of OSA in non-edematous men (83%) precluded identifying an association between edema and OSA in men. Other studies documenting the prevalence of OSA in obese men found rates of OSA ranging from 40–80% [16–20]. However, those studies that found a proportion of OSA exceeding 50% involved either morbidly obese men (BMI $\geq$ 40 kg/m^2), or used lower thresholds (AHIs $\geq$ 5 or $\geq$ 10) as the criteria for diagnosing OSA [18–20]. It is possible that a larger sample of non-edematous men would have found rates of OSA more in line with previous research.

This study has several limitations, the most notable being the small sample, particularly the sample of men. A further limitation is that medications that reduce edema may have resulted in misclassification of some of the subjects. The use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin blocker receptors among the subjects in the non-edema group may have resulted in misclassification of some individuals who would have had edema were it not for the use of these medications. Four men and one woman without edema, but with OSA, were using one or more of these medications for the treatment of hypertension.

A further limitation is the lack of laboratory verification of normal left ventricular function in non-edematous subjects. While it would have been optimal to obtain echocardiograms on all subjects, doing so was impractical because the study lacked sufficient resources to support echocardiograms in non-edematous subjects. We did not believe that it was justifiable to ask non-edematous subjects, or their medical insurance companies, to pay for echocardiograms. Nonetheless, it is unlikely that many of the 34 non-edematous subjects had left ventricular dysfunction. Epidemiological studies have documented the frequency of asymptomatic left ventricular systolic dysfunction as being 1–4% in the general population [21–24]. The rates of left ventricular diastolic dysfunction appear to be higher: one study found left ventricular diastolic dysfunction in 3% of the general population, but the rate was 4% in obese individuals, and 7–8% in subjects with hypertension or diabetes [25].

Our study does not address the sequence of events linking OSA and edema. Presumably OSA precedes the edema, rather than vice versa, but the data does not provide any information as to whether this is actually the case. Lacking certainty regarding the sequence of events, it may be premature to speculate as to a causal relationship between OSA and edema. However, if OSA causes leg edema, then treating a cohort of OSA patients who have edema with nasal continuous positive airway pressure should result in diminished edema.

Edema represents fluid retention, and fluid retention may be an important development in the sequence of events linking obesity and sleep disordered breathing with cardiovascular diseases. Obesity has long been recognized as a risk factor for hypertension. In recent years OSA has also been identified as a risk factor for hypertension [26–28]. Fluid retention associated with OSA may play a role in the development of systemic hypertension, at least in patients with salt-sensitive hypertension [29,30].

Obesity has recently been identified as a risk factor for heart failure [31]. Fluid retention associated with underlying OSA may help explain this relationship. In addition, fluid retention associated with OSA may help explain why treating OSA in patients who have heart failure and OSA improves left ventricular ejection fractions [32].

The main indication for treating OSA has been daytime somnolence [33]. However, if OSA causes fluid retention, then it may be appropriate to expand the indications for treating OSA to include patients who have complications resulting from edema formation, such as venous stasis ulcers, cellulitis, or stasis dermatitis, whether they have daytime somnolence or not.

Despite the prevalence of OSA, by one estimate 2–4% of the middle-aged, adult population [34], the majority of patients with OSA remain undiagnosed. One reason for this situation is that the diagnosis depends upon physicians having an appropriate index of suspicion. The results of our study should aid clinicians in this task. A physical examination finding, the presence of unexplained pedal edema, can facilitate the diagnosis of OSA, at least in women, by alerting the treating physician to the possibility of OSA, thereby leading to improved rates of detection of this serious disorder.

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