Bilateral leg edema, pulmonary hypertension, and obstructive sleep apnea

A cross-sectional study

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This study was undertaken to clarify whether pulmonary hypertension is a useful marker for underlying obstructive sleep apnea in patients with edema. Twenty-eight ambulatory adults with bilateral leg edema and a normal echocardiogram were enrolled. Sixteen subjects had pulmonary hypertension, and 12 subjects had normal pulmonary artery pressures. Spirometry, pulse oximetry on room air, and polysomnography were obtained for each subject. Ten of 16 (63%) pulmonary hypertension subjects and 9 of 12 (75%) nonpulmonary hypertension subjects had obstructive sleep apnea (P = .48). Eleven of 16 (69%) pulmonary hypertension subjects and 11 of 12 (92%) nonpulmonary hypertension subjects were obese (P = .20). If these results are generalizable, obstructive sleep apnea is frequently associated with bilateral leg edema and obesity, regardless of the presence of pulmonary hypertension. Thus, especially in obese patients, bilateral leg edema may be a useful clinical marker for underlying obstructive sleep apnea.

■ KEY WORDS Edema; obesity; pulmonary hypertension; obstructive sleep apnea. (*J Fam Pract 2002; 51:561–564*)

We previously found an association between bilateral leg edema and pulmonary hypertension in primary care patients.[1] After consideration of the differential diagnosis of pulmonary hypertension, obstructive sleep apnea was deemed the most likely explanation for the high frequency of pulmonary hypertension.[2] Subsequently, we identified an association among leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea in ambulatory patients with normal left ventricular function.[3]

Our earlier data failed to clarify whether leg edema, obesity, pulmonary hypertension, or a combination thereof is the most useful marker for obstructive sleep apnea. This cross-sectional study was undertaken to determine whether subjects with bilateral leg edema and pulmonary hypertension have a higher frequency of obstructive sleep apnea than edematous subjects with normal pulmonary artery pressures.

METHODS

A single physician (R.P.B.) enrolled a convenience sample of subjects from an inner city group family practice in Cleveland OH, from July 1995 to September 1997, and from a 2-physician suburban family practice near Cleveland, OH, from October 1997 to July 2000. Ambulatory patients older than 18 years with bilateral pitting leg edema, no clinically overt lung disease, no echocardiographic evidence of a cardiac abnormality, and an echocardiogram that permitted an estimation of the pulmonary artery pressure were eligible to participate in the study. The methodology for estimating the pulmonary artery pressures has been described previously.[3–5] For this study, pulmonary hypertension was defined as an estimated pulmonary artery systolic pressure > 30 mm Hg, whereas an estimated pulmonary artery systolic pressure ≤ 30 mm Hg was considered normal.

Subjects were excluded if their echocardiogram revealed valvular heart disease, congenital heart disease, or left ventricular systolic or diastolic dysfunction; if they used dihydropyridine calcium antagonists; if they had a known pulmonary condition; or if pulmonary function evaluation indicated the presence of obstructive or restrictive lung disease. Individuals with asthma were included as long as the asthma was well controlled. The protocol was approved by the Institutional Review Board at the MetroHealth Medical Center (Cleveland, OH).

The medical history of each subject was reviewed for risk factors recognized as being associated with pulmonary hypertension,[3] and subjects answered the Epworth sleepiness scale questions.[6] The percent

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TABLE 1

Demographic characteristics, pathologic conditions, and laboratory data of subjects with bilateral leg edema

Variable	Pulmonary hypertension (n = 16)	No pulmonary hypertension (n = 12)	*P*
Age (y)	63.4 ± 13.6	52.2 ± 9.9	.02
Female sex	69%	75%	.72
White race	88%	100%	.49
Body mass index (kg/m^2)	37.2 ± 11.0	39.1 ± 12.1	.66
Obesity (BMI ≥ 30)	69%	92%	.20
Education			
High school graduate or higher	53%*	53%*	.95
Marital status			
Married	47%*	67%	.30
Duration of edema			
> 2 years	64%*	55%*	.70
Pulmonary artery pressure (mm Hg)	37.3 ± 6.0	25.4 ± 4.2	.001
Obstructive sleep apnea	63%	75%	.48
Apnea-hypopnea index	32.3 ± 28.5	31.8 ± 23.4	.96
Systemic hypertension	38%	33%	.82
Asthma	6%	17%	.56
Spirometry data			
FVC (% predicted)	77.4 ± 17.6	70.3 ± 14.2	.27
FEV_1 (% predicted)	82.8 ± 18.6	73.7 ± 15.1	.17
FEV_1/FVC (%)	106.9 ± 11.0	105.2 ± 6.5	.64
Oxygen saturation (%)	96.7 ± 1.4	97.7 ± 1.7	.31
Epworth sleepiness scale score	10.3 ± 4.9	8.0 ± 4.7	.24

Date presented as mean ± SD unless otherwise noted.
*Slightly reduced sample size due to occasional missing data.
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

predicted forced vital capacity (FVC), the percent predicted forced expiratory volume in 1 second (FEV_1), and the FEV_1 in relation to the FVC were determined by spirometry (Brentwood Spiroscan 2000, Hoks Electronics, Inc, Japan). Oxygen saturations on room air were determined by oximetry (N-20, Nellcor, Inc, Hayward, CA). Polysomnography was performed on all subjects in a sleep laboratory, and the average number of episodes of apneas and hypopneas per hour of sleep (apnea-hypopnea index) was calculated.

No universally accepted criteria exist for diagnosing obstructive sleep apnea.[7] For this study, obstructive sleep apnea was defined as an apnea-hypopnea index of ≥ 20 events per hour,[8] or a rapid eye movement-specific apnea-hypopnea index of ≥ 20 events per hour. Levels of serum albumin, antinuclear antibody, rheumatoid factor, and thyroid stimulating hormone were obtained on all subjects, as were sedimentation rate and results of liver function tests. Subjects were considered obese if they had a body mass index (weight in kg/height in m^2) of more than 30 kg/m^2.[9]

Mean values between study groups were compared with Student's *t*-test, and χ^2 statistics were used to compare differences between proportions. A final regression analysis was conducted to test whether controlling for potential confounding variables altered the univariate association observed. A hierarchical logistic regression analysis was performed by first regressing obstructive sleep apnea status on potential confounding variables as the first level, and then allowing pulmonary hypertension status to enter the equation as the second level. These analyses compared the extent to which pulmonary hypertension is associated with obstructive sleep apnea status before and after adjusting for confounding variables.

RESULTS

Twenty-eight subjects enrolled in the study, 16 with pulmonary hypertension and 12 without. Findings regarding 15 of the 16 subjects with pulmonary hypertension were reported previously.[3] The edema was mild (1+ or 2+ pitting) for most subjects, typically presenting as an incidental examination finding. Of the edematous patients recruited for enrollment, many more than the number who actually participated were ineligible because their echocardiograms did not allow an estimation of the pulmonary artery pressure.

Demographic information on the subjects with and without pulmonary hypertension is shown in Table 1. Subjects with pulmonary hypertension were older (mean age 63.4 ± 13.6 years versus 52.2 ± 9.9 years, $P = .02$). Most subjects in both groups were obese. There were no differences between the 2 groups in sex, race, education, marital status, body mass indices, or duration of edema.

Ten of 16 (63%) subjects with pulmonary hypertension and 9 of 12 (75%) subjects without pulmonary hypertension had obstructive sleep apnea ($P = .48$). There were no differences between the 2 groups in apnea-hypopnea indices, spirometry measurements, oxygen saturation, asthma, systemic hypertension, previous use of appetite suppressants, use of prescription medications, or Epworth sleepiness scale scores. Because Epworth sleepiness scale scores of 9 to 10 or less are considered mild,[6] the low Epworth sleepiness scale scores in both groups indicate that many individuals with obstructive sleep

apnea and edema lack symptoms of excessive daytime sleepiness. In the hierarchical logistic regression analysis, the probability associated with the adjusted regression coefficient for pulmonary hypertension status was .71, indicating that even with adjustment for potential confounding variables (age, duration of edema), there was no association between pulmonary hypertension and obstructive sleep apnea.

DISCUSSION

We found a high prevalence of obstructive sleep apnea (68%) in patients with bilateral leg edema, most of whom were obese. The proportion of obstructive sleep apnea was high whether or not pulmonary hypertension was present. Our findings suggest that bilateral leg edema, but not pulmonary hypertension, may be a useful marker for underlying obstructive sleep apnea, especially in obese patients. Moreover, if the data are generalizable, many individuals with bilateral leg edema and normal left ventricular systolic function may be misdiagnosed or underdiagnosed as having idiopathic edema, venous insufficiency,[1] or diastolic dysfunction.[10] The finding that subjects with pulmonary hypertension were older than those with normal pulmonary artery pressures suggests that either patient age or the duration of the obstructive sleep apnea may be important variables in the development of pulmonary hypertension in edematous patients with obstructive sleep apnea.

Because of the small sample, a type II error might be the explanation for the lack of difference between the pulmonary hypertension and nonpulmonary hypertension groups. Because of the small sample size and the possibility of selection bias, the results of this study should be interpreted with caution. These findings need to be replicated with a larger sample to confirm the association. In addition, further research is necessary to clarify whether leg edema, obesity, or a combination thereof is the most useful marker for obstructive sleep apnea.

If our patients are typical of those in other practices, we estimate that leg edema associated with obstructive sleep apnea occurs frequently compared with other cardiovascular diseases. In both the inner city and suburban family practices of one of the authors (R.P.B.), leg edema associated with obstructive sleep apnea is the third most common cardiovascular condition, occurring less often than systemic hypertension and coronary artery disease but more frequently than congestive heart failure, cerebrovascular accidents, or cardiac arrhythmias.

Because our experience represents primary care rather than tertiary or specialty care, and because our experience is similar in inner city and suburban settings, we believe that our experience may be generalizable to a variety of practice settings. We now practice according to the clinical dictum that for patients without symptoms or signs of congestive heart failure and without overt lung disease, bilateral leg edema represents obstructive sleep apnea until proven otherwise.

Our data raise the question of a possible causal relationship between obstructive sleep apnea and leg edema. Most of the participants in our study have not used nasal continuous positive airway pressure (CPAP) for long. However, using nightly nasal CPAP, 4 edematous patients experienced reduced leg edema, and 3 have stopped using diuretic medication (Blankfield, unpublished data). This small subset of obstructive sleep apnea patients suggests that obstructive sleep apnea may be a cause of edema.

Making a diagnosis of obstructive sleep apnea does not necessarily mean that treatment is indicated. An abnormal apnea-hypopnea index without excessive daytime sleepiness does not warrant treatment.[11] The results of this study have unclear clinical relevance for patients with obstructive sleep apnea and edema who lack symptoms of daytime somnolence because no study has evaluated whether treating obstructive sleep apnea alters morbidity or mortality in these individuals. Accordingly, it may be prudent for clinicians to refer edematous patients for polysomnography only if they have symptoms of excessive daytime sleepiness, desire a remedy for their edema, use diuretic medication, or develop complications of edema formation such as cellulitis, stasis dermatitis, or venous stasis ulcers.

However, if obstructive sleep apnea contributes to or causes pulmonary hypertension or edema, then it may be advisable to treat patients who have these cardiovascular complications, regardless of the presence or absence of symptoms of sleep-disordered breathing. Previous research is inconclusive regarding a causal relationship between obstructive sleep apnea and pulmonary hypertension. Most of the literature favors the premise that obstructive sleep apnea is not a cause of pulmonary hypertension,[12–17] but some studies suggest otherwise.[18,19]

If subsequent research demonstrates that obstructive sleep apnea causes either pulmonary hypertension or edema, then clinical trials will be necessary to document whether morbidity and mortality rates improve after appropriate treatment of the obstructive sleep apnea. This information will be essential to determine if treatment is warranted for obstructive sleep apnea patients who have pulmonary hypertension or edema, but who lack symptoms of excessive daytime sleepiness.

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