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Effect of nasal continuous positive airway pressure on edema in patients with obstructive sleep apnea

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Abstract

Background and purpose: Previous research has identified an association between idiopathic edema and obstructive sleep apnea (OSA) in women, but a causal relationship between OSA and edema has not been established. This study was undertaken to determine whether nasal continuous positive airway pressure (CPAP) lessens edema in patients with idiopathic edema and OSA.

Patients and methods: This was a case-series study that enrolled eight ambulatory, obese, adults with bilateral, pitting pre-tibial edema and OSA from an inner city family practice and a suburban family practice from July 1995 until March 2003. Enrollees underwent subjective and physical examination assessment of changes in edema after initiation of nasal CPAP.

Results: All but one of the subjects had severe OSA. The edema was typically 1+ to 2+, and the duration of the edema ranged from 6 months to more than 20 years. Seven of the eight subjects experienced a reduction in the amount of edema following nasal CPAP ($P=0.04$).

Conclusions: In subjects with OSA and idiopathic edema, nasal CPAP reduces the amount of edema. If valid, these results indicate that OSA can cause edema.

Keywords: Edema; Obstructive sleep apnea; Nasal continuous positive airway pressure

1. Introduction

A series of office-based studies from our group has identified an association between idiopathic edema (unexplained, bilateral leg edema) and obstructive sleep apnea (OSA) in women. An initial case series suggested a relationship between edema and pulmonary hypertension in ambulatory adults [1]. 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 [2]. This, in turn, led to a cross sectional study that identified associations among edema, obesity and OSA [3]. Most recently, a cross-sectional study identified an association between idiopathic edema and OSA in women, but not men [4].

These epidemiological studies do not provide information regarding the sequence of events involving OSA and edema, nor do they answer questions regarding causality. That OSA precedes and causes edema seems more plausible than vice versa. If so, then appropriate treatment of OSA would be expected to reverse edema formation. This case series study was undertaken to determine if treatment with nasal continuous positive airway pressure (CPAP) lessens idiopathic edema in patients with OSA.

2. Methods

Ambulatory adults older than age 18 who had unexplained, bilateral, pitting, pre-tibial edema and who had

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been diagnosed as having OSA were eligible to participate in the study. Mild OSA was defined as an apnea-hypopnea index (AHI) >5 and ≤ 15, moderate OSA was defined as an AHI >15 and ≤ 30, and severe OSA was defined as an AHI >30 [5].

A single physician (RPB) examined and enrolled eight subjects, one from an inner city family practice in Cleveland, Ohio from July 1995 to September 1997, and seven from a suburban family practice near Cleveland, Ohio from October 1997 to March 2003. Approximately 40 eligible subjects with OSA and edema declined treatment for OSA, primarily because they lacked symptoms of daytime somnolence. Consequently, they were not enrolled in the study.

Subjects were included provided their echocardiogram demonstrated a normal left ventricular ejection fraction (left ventricular ejection fraction $\geq 50\%$ and no focal left ventricular wall abnormality), and provided that blood tests demonstrated normal serum albumin, liver function tests, and thyroid stimulating hormone.

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

The protocol was approved by the Institutional Review Board at the Southwest General Health Center, Middleburg Heights, Ohio. 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) [6].

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.

Following initiation of treatment with nasal CPAP, subjects were evaluated for changes in the extent of the edema at the time that they subsequently presented to the office, typically for an unrelated medical problem. Compliance with CPAP was gauged by the examiner at the time of re-evaluation by asking subjects whether they were compliant or not. No objective measure of compliance was obtained, and the examiner was not blinded regarding compliance at the time the edema was re-evaluated.

Descriptive statistics, including demographic and clinical characteristics of subjects, were computed for the total sample. For the laboratory and demographic variables, standard deviations were calculated for continuous and categorical variables. The one-sample cumulative binomial test was used to test whether the observed proportion of patients with reduced edema following nasal CPAP was statistically significant.

3. Results

The demographic, clinical and laboratory characteristics of the eight subjects enrolled in the study are summarized in Table 1. All the subjects were Caucasian, and all were obese (body mass index >30 kg/m^2) [8]. The edema was

Table 1
Demographic, clinical and laboratory variables for subjects with edema treated with nasal continuous positive airway pressure

	Less edema after CPAP ($N=7$)	No change in edema after CPAP ($N=1$)
Age $\pm$ SD, years	49 $\pm$ 13	64
Sex, % female $\pm$ SD	43 $\pm$ 19	100
Body mass index $\pm$ SD, (kg/m^2)	40.4 $\pm$ 5.2	47.0
Duration of edema, years	2.1 $\pm$ 7.0	20
Apnea-hypopnea index $\pm$ SD	53 $\pm$ 27	35
Oxygen saturation (while awake), % $\pm$ SD	95 $\pm$ 2	93
Lowest oxygen sat (during sleep), % $\pm$ SD	72 $\pm$ 18	73
% time nocturnal oxygen sat <90, % $\pm$ SD	27 $\pm$ 32	6
FVC, % pred $\pm$ SD	70 $\pm$ 9	85
FEV1, % pred $\pm$ SD	71 $\pm$ 11	97
FEV1/FVC, % $\pm$ SD	103 $\pm$ 0.1	114
Cigarettes, % smokers $\pm$ SD	43 $\pm$ 19	0
Epworth sleepiness scale score $\pm$ SD	16 $\pm$ 5	20
CPAP (cmH_2O) $\pm$ SD	10 $\pm$ 3	12

typically mild, usually 1+ or 2+ pitting, and the duration of the edema ranged from half a year to more than 20 years. Seven subjects had severe OSA, their AHIs ranging from 35 to 93, while one subject had mild OSA, the AHI being nine. Half the subjects had Epworth sleepiness scale scores >16, indicative of a high level of daytime sleepiness [6].

Following treatment with nasal CPAP, seven of the eight subjects experienced a reduction in their edema ($P=0.04$), both subjectively and on physical examination, including the one subject with mild OSA. For three of the subjects, the edema resolved completely following nasal CPAP, and in another four subjects, the edema was lessened, typically from 2+ to 1+ pitting, or from 1+ to trace pitting. The interval between initiation of CPAP and re-evaluation of the edema varied from 3 months to 2 years. None of the subjects lost an appreciable amount of weight or changed their exercise habits between the time that CPAP was initiated and the time that the edema was re-evaluated. For the subjects who experienced a reduction in the edema, it was not possible to ascertain how quickly the edema improved following initiation of CPAP therapy.

With only one subject constituting the group in which nasal CPAP did not influence the edema, it is not possible to make any comparisons between the group in which nasal CPAP lessened the edema, and the group in which nasal CPAP did not lessen the edema.

4. Discussion

This study found that nasal CPAP treatment of OSA patients with idiopathic edema results in a reduction of the edema. Because of the small sample, and the possibility of selection bias, the results of this study should be interpreted with caution. A study with a larger sample will be necessary to confirm our findings. If the results are validated, then OSA can cause edema.

Assuming that the results are valid, then for the one subject whose edema did not respond to nasal CPAP, it may be that CPAP is not uniformly effective at reducing edema in patients with OSA. Alternatively, it is possible that this subject was non-compliant with CPAP.

Our data indicates that OSA causes fluid and sodium retention. In recent years OSA has been identified as a risk factor for hypertension [9–11]. Fluid retention due to OSA may help explain this relationship, at least in patients with salt-sensitive hypertension [12,13]. In addition, fluid retention due to OSA may explain why treating OSA in patients who have heart failure and OSA improves left ventricular ejection fractions [14].

While there has been speculation as to how OSA and edema are related, the explanation for this relationship is unclear [15]. Venous insufficiency is not a likely cause of fluid retention in OSA patients [1]. It is possible that edema results from intermittent, nocturnal right ventricular failure that increases pressures through the venous circulatory system and into the lower extremities. It is also possible that activation of the renin–angiotensin–aldosterone system is responsible for fluid retention in OSA patients, much as left ventricular dysfunction activates the renin–angiotensin–aldosterone system in heart failure patients. This possible explanation is strengthened by the observation that nasal CPAP lowers aldosterone levels in OSA patients [16]. In patients with OSA and normal left ventricular function, it is possible that edema results from episodic left ventricular dysfunction that occurs nocturnally, during apneic episodes. If intermittent, nocturnal left ventricular dysfunction is the ultimate cause of fluid retention of OSA, then documenting this phenomenon will require nocturnal monitoring of left ventricular function in OSA patients who have edema. Finally, it is possible that increased venous blood flow resulting from high negative intrathoracic pressures during apneic events causes central hypervolemia, thereby promoting fluid retention [17].

The main indication for treating OSA is daytime somnolence [18]. However, when OSA causes cardiovascular complications, it may be appropriate to treat the OSA even in the absence of daytime sleepiness. Based upon our work, this would include OSA patients who have leg edema [1–4], especially if they have edema-related complications such as venous stasis ulcers, cellulitis, or stasis dermatitis. It remains to be determined if this also includes OSA patients who have systemic hypertension.

Internists, family physicians, cardiologists, nephrologists, and vascular surgeons provide medical care for patients with idiopathic edema. If a sleep study is ordered for these patients, our work suggests that a diagnosis of OSA will be made in many of these individuals, and appropriate treatment of the OSA will likely lessen the edema.

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