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Effect of rostral fluid shift on pharyngeal resistance in men with and without obstructive sleep apnea

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ABSTRACT

Background: Obstructive sleep apnea (OSA) relates to overnight rostral fluid shift, possibly because fluid accumulation around the pharynx increases pharyngeal resistance (R_{ph}). We hypothesised that R_{ph} will increase more in men with than without OSA in response to rostral fluid redistribution.
Methods: Seventeen men with, and 12 without OSA were randomized to lower body positive pressure (LBPP) for 15 min or control, then crossed over. Leg fluid volume (LFV) and R_{ph} were measured before and after each period.
Results: LBPP displaced similar amounts of fluid from the legs in both groups. However, compared to the non-OSA group, R_{ph} increased significantly more during LBPP in the OSA group (-0.38 ± 2.87 vs. 2.52 ± 2.94 cmH_2O/l/s, $p = 0.016$). Change in R_{ph} during LBPP correlated directly with baseline R_{ph} in the OSA group, but inversely in the non-OSA group.
Conclusion: OSA patients have increased susceptibility to pharyngeal obstruction in response to rostral fluid redistribution, which could predispose to pharyngeal collapse during sleep.

1. Introduction

Obstructive sleep apnea (OSA) is a common condition characterized by repetitive upper airway collapse during sleep. Upper airway collapse occurs when the normal reduction in pharyngeal dilator muscle activity at sleep onset is superimposed on a narrowed upper airway with increased collapsibility (Ryan and Bradley, 2005). The decreased upper airway luminal cross-sectional area (UA-XSA) in OSA patients is due to a mismatch between the size of the bony cage surrounding the upper airway and the soft tissues inside it. Although fat deposition in the neck may narrow the upper airway, body mass index (BMI) and neck circumference, two common indicators of adiposity, only explain approximately one third of the variability in the frequency of apneas and hypopneas per hour of sleep (apnea–hypopnea index [AHI]), suggesting that other factors are involved (Dempsey et al., 2002). Increased fluid in the neck, due to increased venous volume and/or upper airway mucosal fluid may also decrease UA-XSA and increase pharyngeal resistance (R_{ph}).

During the daytime, fluid accumulates in the intravascular and interstitial spaces of the legs due to gravity (White and Bradley, 2013). When lying down at night, fluid is redistributed rostrally, again due to gravity. If some of this fluid accumulates in the neck, it may narrow the upper airway and render it more collapsible, predisposing to OSA. In healthy non-obese men with OSA, the overnight decrease in leg fluid volume (LFV) was strongly related to the degree of overnight increase in neck circumference (Redolfi et al., 2009). In addition, the overnight change in LFV correlated strongly with the AHI and explained 64% of its variability, independently of BMI. These observations support the concept that some of the fluid shifting out of the legs was redistributed to the neck, thus predisposing to upper airway collapse and OSA. The increased prevalence of OSA in patients with fluid-retaining states, such as heart failure, may therefore be at least partly explained by increased rostral fluid shift. Indeed, we have previously shown, in men, but not in women with heart failure, that the overnight decrease in LFV correlates strongly with the AHI (Yumino et al., 2010; Kasai et al., 2012).

Application of lower body positive pressure (LBPP) redistributes fluid rostrally from the legs. We previously demonstrated that in

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men with heart failure and OSA, application of LBPP increased R_{ph} and neck circumference in proportion to the volume of fluid redistributed from the legs (Kasai et al., 2013). Change in R_{ph} and neck circumference in response to LBPP has not however been assessed in OSA patients without fluid-retaining conditions, nor in comparison to healthy subjects. Given that OSA patients are predisposed to upper airway collapse, they may be more susceptible to upper airway obstruction in response to LBPP-induced rostral fluid shift than subjects without OSA. Accordingly, we hypothesized that there would be a greater increase in R_{ph} in patients with OSA than in healthy subjects without OSA in response to LBPP. We studied men because rostral fluid shift appears to play a more important role in the pathogenesis of OSA than in women (Kasai et al., 2012).

2. Methods

2.1. Subjects

Patients with OSA were recruited from a sleep disorders clinic. Inclusion criteria were men, aged 18–80 years with an AHI $\geq$ 15 with >50% of events obstructive. Age and BMI matched men without OSA (AHI < 10) were recruited by advertisement as control subjects. Exclusion criteria for both groups were treated OSA, tonsillar hypertrophy, history of heart or renal failure, and unstable angina, myocardial infarction or cardiac surgery within the past 3 months. Subjects' baseline characteristics, medical history and medications were recorded.

2.2. Polysomnography

All subjects underwent overnight polysomnography using standard techniques and scoring criteria for sleep stages and arousals (Rechtschaffen and Kales, 1968). Thoracoabdominal motion was monitored by respiratory inductance plethysmography and nasal airflow by nasal pressure cannulae. Oxyhemoglobin saturation was monitored by oximetry. Apneas and hypopneas were defined as >90% and 50–90% reduction in tidal volume from baseline, respectively, lasting $\geq$10 s, and were classified as obstructive or central as previously described (Yumino et al., 2010). The AHI was quantified. Signals were recorded on a computerized sleep recording system (Sandman, Nellcor Puritan Bennett Ltd., Ottawa, Ontario, Canada) and scored by technicians blind to the experimental data.

2.3. Lower body positive pressure, leg fluid volume and neck circumference

With subjects lying supine, deflated medical anti-shock trousers (MAST III-AT; David Clark, Inc., Worcester, MA) were applied to both legs from the ankles to the upper thighs at the beginning of the baseline period, as previously described (Chiu et al., 2006; Shiota et al., 2007; Su et al., 2008; Kasai et al., 2013). LBPP was applied by rapidly inflating the trousers to 40 mmHg for 15 min after which the trousers were deflated. Fluid volume of each leg was measured by bio-electrical impedance (model 4200; Xitron Technologies, Inc., San Diego, CA) (Chiu et al., 2006; Shiota et al., 2007; Kasai et al., 2013). A pair of electrodes was applied to the upper thigh and ankle of each leg. This well-validated technique (Zhu et al., 2003; Kyle et al., 2004) uses impedance to electrical current within a body segment to measure its fluid content. Changes in neck circumference were recorded using a mercury strain gauge plethysmograph, which was wrapped around the neck above the cricothyroid cartilage and secured in place with tape (Chiu et al., 2006; Shiota et al., 2007; Su et al., 2008).

2.4. Pharyngeal resistance

After application of local anesthesia using a 10% lidocaine spray to the nares and the oropharynx, two open catheters were introduced into one nostril. The first catheter was advanced to the back of the nose then withdrawn 0.5 cm to the choanae for measurement of nasopharyngeal pressure. The second catheter was advanced beyond the soft palate and base of the tongue to as far as the subjects could tolerate without gagging or discomfort, or to 18 cm from the nares, whichever was reached first, for measurement of hypopharyngeal pressure (Hudgel, 1986; Series et al., 1990; Chiu et al., 2006). The distance between the catheter tips was the same in each group (10.3 ± 0.8 cm in non-OSA vs. 10.2 ± 1.1 cm in OSA subjects, $p = 0.8$). The catheters were secured with tape to the upper lip and remained in place throughout the experiments. Each catheter was connected to a differential pressure transducer (Validyne MP45; Validyne Engineering, Northridge, CA). These pressures were referenced to pressure measured inside a face mask. Flow was measured using a pneumotachograph (Hans Rudolph Model 4700; Hans Rudolph, Inc., Kansas City, MO) connected to a tightly fitting face mask. Pressure and flow signals were amplified and fed through an analog-to-digital converter, and then stored in a computer for later analysis. Transpharyngeal pressure gradient was calculated as the difference between hypopharyngeal and nasopharyngeal pressures (Hudgel, 1986). Two to three milliliters of compressed air were injected through the proximal port of the catheters to clear secretions from the catheter tips as required.

2.5. Protocol

This was a randomized double crossover study. Experiments were performed during the daytime with subjects awake, lying supine with their head and neck in the neutral position supported by a pillow. Subjects breathed through their noses. Following a 15 min baseline period, subjects were randomized to either LBPP or a control period (anti-shock trousers worn but deflated) for 15 min. Subjects then sat upright for a 30 min washout period. They then underwent a second 15 min baseline period after which they were crossed over to the other arm for 15 min. To ensure subjects were awake throughout, sleep/wake state was assessed by polysomnography. Measurements of LFV were made at 5 min intervals during the baseline, control and LBPP periods. The protocol was approved by the Research Ethics Boards of University Health Network and Mount Sinai Hospital. All subjects provided written consent prior to participation.

2.6. Data analysis

Changes in average LFV between baseline and control or LBPP period were used for analysis. For each 30 s epoch, R_{ph} was determined at the point of greatest transpharyngeal pressure gradient. The R_{ph} values from each epoch were then averaged over each baseline and control or LBPP period. Average neck circumference was calculated for each baseline and control or LBPP period.

Data are mean ± standard deviation (SD) unless otherwise indicated. For comparisons of baseline characteristics between OSA and non-OSA groups, unpaired *t*-tests were used for normally distributed variables, Mann–Whitney *U*-tests for non-normally distributed variables and Chi-squared tests for nominal variables. Within each group, two-way repeated measures analysis of variance was used to compare changes between baseline and control and baseline and LBPP values, with post hoc analysis to compare baseline values with values during control or LBPP periods. Changes from baseline to control period were compared between OSA and non-OSA groups using unpaired *t*-tests or Mann–Whitney *U* tests