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Original Article

Factors predisposing to worsening of sleep apnea in response to fluid overload in men

Bojan Gavrilovic [a,b], T. Douglas Bradley [a,c], Daniel Vena [a,b], Owen D. Lyons [a], Joseph M. Gabriel [a], Milos R. Popovic [a,b], Azadeh Yadollahi [a,b,*]

[a] Toronto Rehabilitation Institute, University Health Network, Toronto, Canada
[b] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada
[c] Department of Medicine, University of Toronto, Toronto, Canada

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ABSTRACT

Objectives: Obstructive sleep apnea (OSA) is highly prevalent in patients with fluid-retaining conditions. Using bioimpedance measurements, previous studies have shown that the greater the amount of fluid redistributed from the legs to the neck overnight, the greater the severity of OSA. Our objective was to investigate factors that predispose the development or worsening of OSA in response to experimental fluid overload.

Methods: Fifteen normotensive and non-obese adult men with and without OSA underwent polysomnography (PSG) during which normal saline was infused intravenously at a minimal rate to keep the vein open (control) or as a bolus of 22 ml/kg body weight (approximately 2 L) in a random order and crossed over after a week.

Results and Conclusions: Before and after sleep, neck circumference and bioimpedance were measured to calculate neck resistance, reactance, phase angle, and fluid volume. Subjects who experienced more than a twofold increase in apnea–hypopnea index (AHI) or obstructive AHI from control to intervention and had an AHI>10 during intervention were considered susceptible to the development or worsening of OSA. Baseline neck circumference and phase angle before saline infusion were independently associated with increased susceptibility to developing or worsening OSA in response to saline infusion. In non-obese men, a larger neck circumference and bioimpedance phase angle of the neck, which may be associated with larger pharyngeal tissue content, is associated with increased susceptibility for worsening of OSA in response to fluid overloading.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder that occurs in approximately 10% of adults [1,2] and increases the risk of hypertension, stroke, heart failure, and car accidents [3–7]. OSA occurs due to repetitive complete or partial collapse of the pharynx during sleep [8,9]. However, the underlying mechanism that drives this collapse is not fully understood. There are several independent risk factors for OSA, such as age, male sex, and high body mass index (BMI). However, not all patients with OSA have these risk factors [10,11]. Therefore, other factors such as fluid retention and nocturnal rostral fluid shift may be involved. Recent studies performed by our team provide compelling evidence that the nocturnal fluid redistribution out of the legs and into the neck plays a critical role in pharyngeal airway narrowing and OSA severity [8,12–16]. Using bioelectrical impedance to measure fluid volume, we demonstrated that while supine, leg fluid volume decreases and thoracic and neck fluid volumes (NFVs) increase progressively over time [17]. We also found that fluid accumulation in the neck narrows the pharynx and worsens OSA [18–24], while reducing fluid retention in the legs; its nocturnal rostral shift can therefore attenuate OSA [13–15].

We also showed that removal of approximately two liters of fluid by ultrafiltration in patients with end-stage renal disease reduced the frequency of apneas and hypopneas (apnea–hypopnea index (AHI)) in patients with OSA by 36% [16]. Furthermore, intravenous infusion of about two liters of normal saline in healthy men during sleep increased the AHI significantly in older men [12]. This experimental paradigm closely resembles a postoperative situation in which patients received significant amounts of fluid intravenously during and following surgery [25]. Such fluid infusion and its accumulation in the neck could be one mechanism contributing

Experiments were performed in the Sleep Research Laboratory of the Toronto Rehabilitation Institute University Health Network, Toronto, Canada.

There was no off-label or investigational use of a therapeutic product in this study.

* Corresponding author. Toronto Rehabilitation Institute, University Health Network, 12-106, 550 University Ave, Toronto, ON M5G 2A2, Canada. Fax: 416 597 8959.
E-mail address: Azadeh.Yadollahi@uhn.ca (A. Yadollahi).

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to postoperative worsening of OSA [25–27]. While our studies that investigated the effects of rostral fluid shift on OSA have shown a significant contribution of fluid, and in particular fluid overload, on sleep apnea severity, they do not provide objective measures to determine the subjects who are at higher risk of developing OSA due to fluid overloading. A clinical tool that would allow for such risk stratification is desirable.

Bioelectrical impedance analysis is a measurement technique that has recently gained popularity among medical professionals to measure tissue impedance. The total impedance is composed of multiple parameters: the resistance, reactance, and phase angle, all of which may vary according to tissue composition. For example, a decrease in resistance is associated with an increase in hydration of the tissue under test [28], while a lower phase angle has shown to be associated with a lower muscle mass and increased mortality in heart failure patients [29].

Accordingly, the objective of this study was to investigate factors that could put subjects at higher risk of developing OSA or exacerbating already existing OSA due to fluid overload. In particular, we investigate pre-sleep bioelectrical impedance variables of the neck, such as the phase angle, resistance, and reactance, as well as other risk factors of OSA such as neck circumference, BMI, and age. Subjects who experienced an increase in OSA severity as a result of saline infusion were labeled as susceptible, while other participants were labeled as non-susceptible.

2. Material and methods

2.1. Subjects

This study is a retrospective analysis of data previously published by our laboratory. [12]. Our previous studies showed that men are more susceptible to the adverse effects of rostral fluid shift than women [17,21,30]; therefore, only men between the ages of 20 and 70 years were included in this study. Subjects were excluded from the study if their BMI exceeded 30 kg/m^2 or if they had a blood pressure greater than 140/90 mmHg. Further exclusion criteria were tonsillar hypertrophy, a history of renal, cardiovascular, neurological, or respiratory disease, or the taking of any prescribed medication for these disorders, as well as taking any over-the-counter medication that could influence fluid retention. Individuals with a previous diagnosis of OSA, sleep time of less than one hour during the protocol, or having central dominant sleep apnea (more than 50% of central apneas and hypopneas) were also excluded. Subjects were recruited by advertisement.

2.2. Polysomnography

Subjects underwent daytime polysomnography (PSG). To promote sleepiness during the study, participants were instructed to restrict their sleep to less than four hours the night prior to the study. Sleep stages and arousals from sleep were scored according to standard criteria [31]. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, nasal pressure by nasal cannulae, and arterial oxyhemoglobin saturation (SaO_2) by oximetry [32]. Apneas were defined as more than 90% reduction in airflow or thoracoabdominal motion from the baseline, lasting more than 10 s. Hypopneas were defined as more than 30% reduction in airflow lasting more than 10 s, associated with a minimum 4% desaturation or an arousal from sleep [31]. Apneas and hypopneas were classified as either obstructive or central as previously described [33]. The AHI was calculated as the number of apneas and hypopneas per hour of sleep. The participants slept in the supine position with a single foam pillow to eliminate any effects of postural changes on AHI and sleep structure.

2.3. Neck bioelectrical impedance and circumference

Bioelectrical impedance analysis is a non-invasive method that can be used to assess extracellular fluid volumes. On the basis of Ohm's law, the tissue impedance is inversely proportional to its fluid volume. Therefore, by passing a current through the tissue and measuring its voltage, the impedance and fluid volume can be estimated. This relationship has been widely used to estimate the total body water and the fluid content in body segments such as legs, thorax, and neck [12,16,17,28,34]. The measured impedance comprises the resistance and reactance of the tissue, whereby the reactance is a result of the capacitive effects of the tissue, and resistance is directly related to the fluid in the tissue. Furthermore, the capacitive effects of the tissue also result in a phase shift between the current and voltage, and this phase shift is represented as the phase angle in the impedance measurements (Fig. 1B).

During the study protocol, bioelectrical impedance parameters of the neck were measured using the MP150 and EBI100C modules (Biopac Inc., Goleta, CA) before and after the sleep while the subjects were supine. Two electrodes, which were used to measure voltage, were placed on the right side of the neck below the right ear and at the base of the neck (Fig. 1A). Two more electrodes were placed 2.5 cm apart from the voltage-measuring electrodes to inject a 400-μA sinusoidal current at a 50-kHz frequency (Fig. 1A). Neck bioimpedance was estimated as the measured

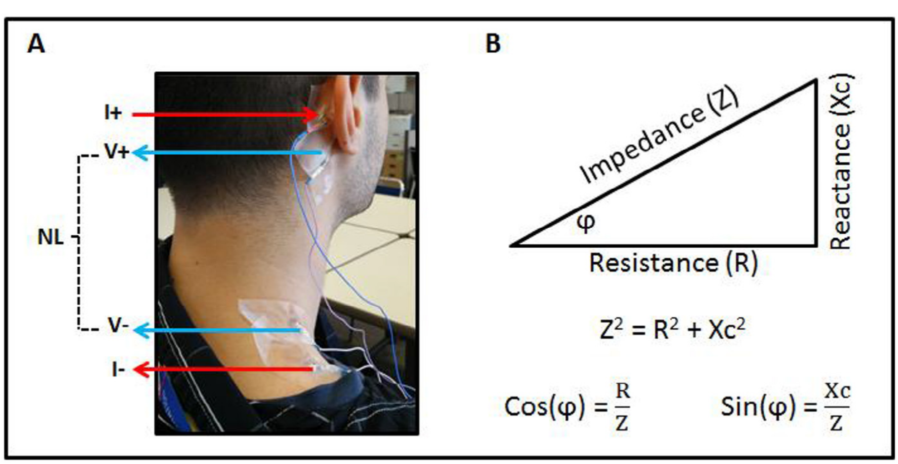

Fig. 1. A. Electrode placement for measuring bioelectrical impedance of the neck. **B.** Relationship between impedance, resistance, reactance, and phase angle.