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Systolic pressure response to voluntary apnea predicts sympathetic tone in obstructive sleep apnea as a clinically useful index☆

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ABSTRACT

The present investigation tested the hypotheses that systolic arterial pressure (SAP) responses to voluntary apnea (a) serve as a surrogate of sympathetic nerve activity (SNA), (b) can distinguish Obstructive Sleep Apnea (OSA) patients from control subjects and (c) can document autonomic effects of treatment. 9 OSA and 10 control subjects were recruited in a laboratory study; 44 OSA subjects and 78 control subjects were recruited in a clinical study; and 21 untreated OSA subjects and 14 well-treated OSA subjects were recruited into a treatment study. Each subject performed hypoxic and room air voluntary apneas in triplicate. Muscle SNA (MSNA) and continuous AP were measured during each apnea in the laboratory study, while systolic arterial pressure (SAP) responses were measured continuously and by standard auscultation in the clinical and treatment studies. OSA subjects exhibited increased mean arterial pressure (MAP), SAP and MSNA responses to hypoxic apnea (all $P < 0.01$) and the SAP response highly correlated with the MSNA response ($R^2 = 0.72$, $P < 0.001$). Clinical assessment confirmed that OSA subjects exhibited markedly elevated SAP responses ($P < 0.01$), while treated OSA subjects had a decreased SAP response to apnea ($P < 0.04$) compared to poorly treated subjects. These data indicate that (a) OSA subjects exhibit increased pressor and MSNA responses to apnea, and that (b) voluntary apnea may be a clinically useful assessment tool of autonomic dysregulation and treatment efficacy in OSA.

1. Introduction

Repetitive airway obstruction accompanying Obstructive Sleep Apnea (OSA) produces hypoxia, hypercapnia and limited pulmonary inflation, all of which increase sympathetic nerve activity (SNA) and arterial pressure (AP) during each apneic event (Jouett et al., 2015; Somers et al., 1995). Elevated SNA in OSA usually persists during wakefulness, which appears to be a primary factor for the increased risk of cardiovascular disease (Bixler et al., 2000; Fletcher et al., 1985; Guilleminault, 1979) and is directly related to the hypertension observed in these patients (Fletcher et al., 1992). Previous investigations of OSA subjects demonstrate tonic and hypersensitive chemoreflex control of SNA, which has significant clinical ramifications (Cutler et al., 2004; Narkiewicz et al., 1998). However, current measures of SNA are either clinically impractical (e.g. muscle SNA (MSNA)) or shown to have limited clinical benefit (e.g. low frequency (LF) power of heart rate variability (HRV)) (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996; Martelli et al., 2014Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology). It has been suggested that OSA subjects have an enhanced pressor response to apnea; (Hedner et al., 1995) hence, demonstrating that OSA patients exhibit increased pressor responses to apnea as a surrogate of SNA would have significant clinical utility. Further, Positive Airway Pressure (PAP) treatment has been shown to decrease SNA in a compliant-dependent fashion, (Narkiewicz et al., 1999a) therefore we hypothesize that well-treated OSA patients also exhibit decreased AP responses to apnea versus poorly treated patients.

Thus, the purpose of this study was to test the hypotheses (a) that the AP response to apnea is a predictable index of sympathetic responsiveness in OSA, (b) that measuring the AP response to apnea can clinically assess the autonomic dysfunction in OSA and (c) provide an index of efficacious treatment benefit.

2. Material and methods

These hypotheses were tested in 3 distinct settings: a laboratory study that measured systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure responses to voluntary apneas and 2 clinical studies in which the SAP response to voluntary apnea was measured in OSA vs. control subjects due to the finding in the laboratory study that the SAP

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response to room air apneas in control subjects is minimal, while OSA subjects respond substantially. First, a laboratory study compared AP and SNA responses to hypoxic and normoxic voluntary apneas between OSA (N = 9) and healthy age-and BMI-matched controls (N = 10). Second, a clinical study (N = 122) compared OSA and healthy control groups and included a hypertension-matched sub-analysis (N = 39) to control for hypertension, since hypertension is present in at least 50% of OSA patients (Floras, 2015). Finally, a study to determine the effect of treatment with positive airway pressure (PAP, N = 35) was conducted to assess the utility of AP responses as a marker of treatment success in OSA patients. Each study received approval by the University of North Texas Health Science Center Institutional Review Board and informed consent was obtained according to the declaration of Helsinki.

2.1. Laboratory study

2.1.1. Subjects

Nineteen subjects without exposure to PAP treatment were recruited: 9 OSA (diagnosed by polysomnography at an American Association of Sleep Medicine-certified clinic, apnea hypopnea index (AHI) > 10 to exclude subjects with minimal disease burden) and 10 age- and weight-matched controls. The healthy control subjects scored ≤6 on the Epworth Sleepiness scale and had no reports of snoring as noted by spouse or roommates. OSA and control subjects were matched for age, gender and body mass index [BMI: calculated as (body weight in kg/(height in cm)^2], and resting AP. Demographic data of this study is provided in Table 1. All subjects were non-smokers and were free of cardiovascular, pulmonary or neurological disease. Two OSA patients used an ACE inhibitor and no subjects reported taking adrenergic-blocking agents. Female subjects all tested negative for pregnancy and were studied during the early follicular phase of their menstrual cycle (days 1–4 post menses) or during the placebo portion of their contraceptive medication. Subjects were asked to abstain from exercise and alcohol for 24 h and caffeine for 12 h prior to the start of the study.

2.1.2. Measurements

Heart rate (HR) was measured using limb-lead ECG. AP was measured on a beat-to-beat basis using non-invasive measures via photoplethysmography at the finger (Finapres Blood Pressure monitor 2300, Ohmeda, Inc., Englewood, CO). Arterial oxygen saturation (S_aO_2) was assessed at the forehead using pulse oximetry (DS-100A Durasensor, Nellcor Puritan Bennett Inc., Pleasanton, CA). Respiration was monitored using a respiratory band placed around the subject's abdomen (Grass Instruments, West Warwick, RI) and using a low-resistance turbine volume transducer (model VMM, Alpha Technologies, Inc., Laguna Hills, CA) attached to a leak-free nasal mask connected to a breathing circuit. Monitoring ensured that apneas were performed at end-expiration, similar to what occurs during sleep in an OSA subject (Sullivan and Issa, 1985). The breathing circuit consisted of the nasal mask, a 3-way Rudolph valve, and Douglas bags. End-tidal oxygen (ETO_2) and end-tidal carbon dioxide ($ETCO_2$) were measured with mass spectrometry (model MGA 1100B, PerkinElmer, St. Louis, MO) via a port at the side of the mouthpiece. Postganglionic muscle sympathetic nerve activity was directly measured from the peroneal nerve at the popliteal fossa using standard microneurographic techniques (Vallbo et al., 1979). Nerve signals were processed by a preamplifier and an amplifier (nerve traffic analyzer model 662C-3, Department of Bioengineering, University of Iowa, Iowa City, IA). Amplified signals were band-pass filtered (700–2000 Hz), rectified and discriminated. A resistance capacitance circuit with a time constant of 0.1 s was used to integrate raw nerve signals for subsequent analysis. MSNA recordings were confirmed using the following criteria: 1) pulse-synchronous bursts occurring 1.2–1.4 s after the associated QRS complex, 2) reproducible activation during apnea and phase II of the Valsalva maneuver, and 3) no activation following a pinch, skin stroking, or startle stimuli (all of which activate skin sympathetic fibers).

Table 1
Demographic characteristics of the laboratory study.

	Control N = 10	OSA N = 9	P-value
Age (yrs)	47 ± 3	53 ± 3	0.19
Sex (M/F)	8/1	8/2	–
BMI (kg/m^2)	26.95 ± 0.8	29.5 ± 1.0	0.07
Epworth	5 ± 1	10 ± 1	0.002
Baseline HR (bpm)	73.7 ± 2.8	71.4 ± 3.8	0.62
Baseline SAP (mm Hg)	130.0 ± 3.3	131.1 ± 2.8	0.80
Baseline DAP (mm Hg)	75.2 ± 2.4	79.8 ± 2.6	0.21
Baseline MAP (mm Hg)	94.3 ± 1.7	97.5 ± 1.8	0.21
Baseline S_aO_2 (%)	98.8 ± 0.2	97.9 ± 0.4	0.03

2.1.3. Experimental protocol

These studies were performed in the semi-recumbent position with an ambient temperature of 23–24 °C. Following instrumentation, 5 min of baseline data were recorded while participants breathed room air through a nasal mask. Subsequently, participants then breathed predetermined gas mixtures from a bag that were either normoxic or hypoxic (21%, 16% or 12% oxygen). After subjects breathed each mixture for one minute, a 20 s end-expiratory voluntary apnea (lung volume approximately equal to FRC) was initiated. A 5 min washout period was obtained between each trial. Three repeat bouts at each level of gas exposure was obtained and mean values for each subject were determined for each level of hypoxic gas. The order of gas administration prior to the apneas was randomized for each trial.

2.1.4. Data analyses

Basal MSNA measurements during baseline and hypoxic gas exposure reflect average values obtained over a 10 s measurement period and are reported as total activity/10 s. Total activity for MSNA was obtained as described previously (Smith et al., 1996). The Δ MSNA response to a single 20 s hypoxic apnea represents total MSNA during the apnea minus the basal MSNA (total activity) immediately prior to the gas exposure.

2.1.5. Statistics

Data are presented as mean ± SEM except where indicated. Statistical analyses were performed with significance set at an α level of 0.05. All data were tested for normality using a Shapiro–Wilk test. Differences in demographic data (Table 1) were tested using an independent two-sample t-test, or a Mann–Whitney U test on ranks if non-normal. Group comparisons for each variable were performed using a two-factor ANOVA (group × gas) with Student–Newman–Keuls *post-hoc* tests. Furthermore, because of the minimal hemodynamic responses to normoxic apnea (particularly in the control group), a one-sample t-test was performed on all forms of AP responses (MAP, SAP and DAP) to determine significant differences from zero. Spearman correlation coefficients were calculated for the relationships between AP responses immediately following apnea with the change in MSNA total activity observed after apnea

2.2. Clinical study

2.2.1. Subjects

A total of 122 OSA and control subjects were recruited from the University of North Texas Health Science Center Patient Care Clinic and Sleep Consultants of Texas (Fort Worth, TX). All subjects were free of