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Normal hypercapnic cerebrovascular conductance in obstructive sleep apnea

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ABSTRACT

Both obstructive sleep apnoea (OSA) and impaired cerebrovascular reactivity (CVR) are associated with an increased risk of stroke. We therefore hypothesized that CVR would be decreased in OSA patients. Since OSA is associated with altered endothelial function and this dysfunction may in turn lead to impaired CVR, we further hypothesized that a CVR decrease could be the responsible mechanism for stroke. Middle cerebral artery blood flow velocity (MCAv) and mean arterial blood pressure (MAP) responses to hypercapnia were measured to determine cerebrovascular conductance (MCAv/MAP). Overnight changes in conductance CVR were assessed in treatment naïve, otherwise healthy OSA ($n = 13$) and non-OSA ($n = 9$) subjects at two isoxic tensions (150 and 50 mmHg). We found no significant overnight changes in CVR for either group. There were no differences in CVR between OSA and non-OSA subjects for either isoxic tension, although CVR was increased in hypoxia.

1. Introduction

Obstructive sleep apnoea (OSA) is a breathing disorder characterized by intermittent and repetitive collapse of the pharyngeal airway with resulting intermittent hypoxia and hypercapnia occurring during sleep. Moderate to severe OSA is associated with a 2–3 fold increased risk of stroke (Arzt et al., 2005; Redline et al., 2010). The etiology of this association is uncertain and many mechanisms including inflammation, pro-coagulation, endothelial dysfunction, hypertension and atrial fibrillation have been proposed as significant factors. Reductions in cerebral blood flow following obstructive events may also be a significant contributor to this increased risk (Balfors and Franklin, 1994). Cerebrovascular reactivity (CVR) is defined as the ratio of the change in cerebral blood flow to the change in vasodilatory stimulus such as hypercapnia. Reduced CVR has been shown to be associated with stroke (Stevenson et al., 2010; Wijnhoud et al., 2006).

OSA is associated with intermittent hypoxia which predisposes to increased oxidative stress, inflammation and subsequent endothelial dysfunction (Atkeson et al., 2009). The presence of endothelial dysfunction, a precursor of atherosclerosis will lead to altered vascular tone. An impaired CVR as a result of this endothelial dysfunction, has been suggested as one of the mechanisms underlying the predisposition to stroke in the morning (Manfredini et al., 2005; Qureshi et al., 1999; Ainslie et al., 2007). However, the overnight changes in CVR have not been determined for OSA patients. The evidence for overnight changes in CVR in OSA patients is indirect. Cummings et al. (2007) demonstrated a link between respiratory chemoreflex sensitivity and CVR in healthy individuals. This linkage occurs because cerebral blood flow regulation affects the central chemoreceptor environment and hence the respiratory chemoreflex response (Ainslie and Duffin, 2009). Since OSA is associated with an overnight increase in respiratory chemoreflex sensitivity (Mahamed et al., 2005), the linkage suggests that the overnight increase in respiratory chemoreflex sensitivity in OSA patients may indicate an overnight decrease in CVR. Only one study has compared their CVR to normal subjects (Morgan et al., 2010). That study found hyperoxic hypercapnic vasodilation in the cerebral circulation was blunted in individuals with sleep-disordered breathing, but, Foster et al. (2009) using end-tidal forcing to produce a step hypercapnia, isoxic at 88 mmHg O_2 tension, did not find CVR differed between OSA and normal subjects.

Accordingly, we hypothesized that in OSA subjects, CVR in the early morning would be reduced from that in the evening, and that the morning CVR would be less than that in the healthy cohort. We

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performed CVR under hyperoxic and hypoxic conditions to identify possible independent effects of PO_2 on CVR in patients with OSA. Whereas in some previous studies of CVR, the hypercapnic stimulus was poorly controlled, resulting in high variability of repeated measures of CVR (Morgan et al., 2010; Totaro et al., 1999), we used very precise and repeatable hypercapnic stimulation in the form of isoxic dynamic rebreathing (Duffin, 2011) to minimize stimulus-related intra and inter-subject variability (Jensen et al., 2010).

2. Materials and methods

2.1. Subjects

This prospective study recruited healthy subjects between the ages of 40 and 60 years through local public advertisements. Exclusion Criteria included those with (1) known cardiac, respiratory, neurological or major liver or kidney disease (2) resting SaO_2 on room air <95% (3) insulin-dependent diabetes (4) major depression, and (5) on any medication. Subjects were advised to abstain from caffeine, alcohol, smoking, over-the-counter medication or unusual physical activity for 12 h prior to testing. Informed and written consent was obtained from all subjects and the protocol was approved by the research ethics board of the University Health Network (REB #:09-0831).

2.2. Protocol

Following recruitment all subjects had (1) evening measurements of CVR (session 1) (2) an overnight sleep study performed and (3) repeat measurements of CVR in the early morning immediately after waking (session 2).

2.3. Transcranial Doppler measurement

2.3.1. Apparatus

During testing subjects were seated on a comfortable chair in a quiet room and, following baseline measurements of blood pressure, heart rate, ECG and oxygen saturation, were fitted with a face mask. The face mask was connected to a three-way manually operated valve via a mass flow sensor (AWM720P1 Airflow, Honeywell; Freeport, Illinois, USA). One way of the three-way valve was left open to room air and the other to a 2-m length of rebreathing tubing. This rebreathing tubing was supplied with gas from a programmable gas mixing system (Respiract™, TRI; Toronto, Canada) at the 3-way valve and left open to room air at its distal end. This setup allowed us to quickly and easily switch the subject between breathing room air and mixed gas. MCAv was measured using bilateral trans-cranial 2 MHz pulsed Doppler (ST3 Transcranial Doppler, Spencer Technologies; Seattle, USA) sampled at 125 Hz. Other measures were mean arterial blood pressure (MAP) determined by finger plethysmography (Nexfin, BMYE; Amsterdam, The Netherlands) sampled at 200 Hz, and end-tidal partial pressures of CO_2 (P_{ETCO2}) and O_2 (P_{ETO2}) (Respiract™, TRI; Toronto, Canada) sampled at 20 Hz. Each of these instruments saved a digital record for later analysis.

2.3.2. Protocol

We measured the cerebrovascular response hypercapnia at hyperoxic and hypoxic isoxic tensions (150 and 50 mmHg respectively) using the Duffin dynamic rebreathing method (Duffin, 2011). Each test consisted of three phases; a resting phase where the subjects breathed room air at rest; a hyperventilation phase where the subjects hyperventilated to a target P_{ETCO2} between 20 and 25 mmHg for 5 min; followed immediately by dynamic rebreathing. After the last breath of the hyperventilation phase the subject exhales completely and is then switched to the rebreathing tubing, taking 3 deep breaths before relaxing. During these three breaths the gas mixing device provided mixtures of 6% CO_2 and either 7% O_2 (hypoxic test) or 26% O_2 (hyperoxic test). Then, dynamic rebreathing was implemented by programming the gas mixing device to supply a flow of gas with a PCO_2 equal to the P_{ETCO2} of the previous breath and O_2 sufficient to maintain an isoxic $PETO_2$ at either 150 mmHg (hyperoxic test) or 50 mmHg (hypoxic test). The hyperoxic and hypoxic rebreathing tests were separated by at least 10 min of rest and their order was randomized by a blind choice of cards.

2.4. Overnight sleep study

The overnight sleep study was performed using standard techniques and criteria for scoring sleep stages and arousals (Berry et al., 2012). Thoracoabdominal movements and tidal volume (VT) were monitored by a respiratory inductance plethysmograph (Respitrace; Ambulatory Monitoring Inc., White Plains, NY) (Chadha et al., 1982) and airflow by nasal pressure cannulae (BiNAPS ®, Salter Labs Inc., Arvin, CA). Arterial oxygen saturation (SaO_2) was continuously monitored by a pulse oximeter (Nellcor; Sensormedics Corp., Anaheim, CA). An electrocardiogram was monitored. All the signals were recorded on a computerized sleep scoring system (Sandman, Nellcor Puritan Bennett Ltd., Ottawa, ON). Apneas and hypopneas were scored according to the American Academy of Sleep Medicine (AASM) criteria, with the optional parameter used for scoring of hypopneas (Berry et al., 2012). The frequency of apneas and hypopneas per hour of sleep were quantified as the AHI. Subjects having an AHI of $\geq$5 per hour of sleep were classified as having sleep apnea and with an AHI < 5 were classified as controls (AASM, 2005). OSA was diagnosed when at least 85% of the respiratory events are of the obstructive type.

2.5. Analysis

2.5.1. Data analysis

For each test, beat-by-beat values of MAP and HR and 4-s averages of MCAv were recorded. Then these measures were time aligned with breath-by-breath V_E, P_{ETCO2} and P_{ETO2} measures, and breath-by-breath values calculated. Breath-by-breath MCA conductance (MCAc) was estimated as MCAv/MAP. Baseline reference measures of MAP, MCAv and MCAc were determined as the average of the last 2-min of the hyperventilation period of the protocol. Changes in MCAc were then expressed as percent change from baseline and plotted vs. P_{ETCO2}. The conductance CVR was the slope of the linear regression for these plots.

2.5.2. Statistical analysis

Data are expressed as the mean ± SD. Subject ages and body mass index were compared between OSA and NSA groups with 1-way ANOVA. CVR for the hyperoxic and hypoxic rebreathing tests were tested for difference between OSA and NSA subjects and evening and morning sessions with 2-way repeated measures analyses of variance (rmANOVA). Differences in CVR between hypoxic and hyperoxic tests and evening and morning sessions for all subjects were detected with 2-way rmANOVA. All analyses were performed with SigmaPlot 12.2.

3. Results

25 subjects met our inclusion criteria, however, 4 subjects had inadequate data for analysis and were subsequently excluded. That