Evaluation of Cerebrovascular Reactivity in Subjects with and without Obstructive Sleep Apnea

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Background: Both obstructive sleep apnea (OSA) and altered cerebrovascular reactivity (CVR) are associated with increased stroke risk. Nevertheless, the incidence of abnormal CVR in patients with OSA is uncertain due to the high variability in the way CVR is measured both within and between studies. We hypothesized that a standardized CVR with a consistent vasoactive stimulus and cerebral blood flow (CBF) measure would be reduced in patients with severe OSA compared with healthy controls. *Methods:* This was a prospective study in which subjects with and without OSA were administered a standardized hypercapnic stimulus, and CBF was monitored by blood oxygen level-dependent magnetic resonance signal changes, a high space and time resolved surrogate for CBF. *Results:* Twenty-four subjects with OSA (mean age 45.9 years, apnea–hypopnea index [AHI] 26.8 per hour) and 6 control subjects (mean age 42.8 years, AHI 2.4 per hour) were included. Compared with controls, subjects with OSA had a significantly greater whole brain (.1565 versus .1094, $P = .013$), gray matter (.2077 versus .1423, $P = .009$), and white matter (.1109 versus .0768, $P = .024$) CVR, respectively. *Conclusions:* Contrary to expectations, subjects with OSA had *greater* CVR compared with control subjects. **Key Words:** Obstructive sleep apnea—cerebrovascular reactivity—cerebral blood flow—cerebrovascular disease.

Introduction

Obstructive sleep apnea (OSA) is a sleep breathing disorder that occurs in approximately 9%-24% of middle-aged people. Patients with OSA have more than 3-fold increase in the risk of stroke and death independent of other known risk factors for stroke.[1] Obstructive episodes are associated with severe hypoxia, hypertension, and hypercapnia, which may acutely disturb the relationship between brain oxygen requirements and supply, and in the long term may disturb normal brain blood flow regulation. However, the direct pathophysiological link between OSA and stroke remains unknown. Our aim was to study the brain blood flow regulation in patients with OSA.

Brain blood flow regulation has been studied as the cerebral blood flow (CBF) response to a vasoactive stimulus, termed cerebrovascular reactivity (CVR). Altered CVR has been shown to be a strong predictor of stroke and transient ischemic attacks in patients with carotid artery

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disease.[2] However, for the most part, CVR has been performed using either uncontrolled hypercapnic stimuli such as infusion of carbon dioxide (CO_2) into a mask[3] or breath holding or administration of acetazolamide, all of which result in high variability in stimuli between studies and between patients (see Fierstra et al for discussion[4]). Furthermore, most studies have used transcranial Doppler (TCD)-measured middle cerebral artery blood velocity as a surrogate for CBF under the assumption that the middle cerebral artery diameter remains constant with hypercapnia. More recent studies have impugned this belief.[5] Moreover, TCD provides good temporal resolution but poor spatial resolution limited to an entire vascular territory, leaving unanswered the relationship between flow velocity and actual flow, and between TCD and other surrogate flow measures such as xenon-enhanced computed tomography and positron-emission tomography imaging. Such differences in the methodology of CVR measures have resulted in an inconsistency in the findings[6] between studies and even within subjects.[7,8]

In the present study, we measured CVR by applying a standardized hypercapnic stimulus and using the blood oxygen level-dependent (BOLD) magnetic resonance signal as a surrogate for CBF.[9,10] Our hypothesis was that BOLD magnetic resonance imaging (MRI) CVR in patients with OSA would demonstrate a greater incidence of regional and/or global CVR abnormalities, compared with subjects without OSA. Some of the results have been previously reported in the form of an abstract.[11]

Methods

Subjects

Subjects between the ages of 40 and 60 years were recruited through local public advertisements. Exclusion criteria included those with (1) a known cardiac, respiratory, neurological, or major liver or kidney disease; (2) severe claustrophobia; (3) pregnancy; (4) resting SaO_2 on room air of less than 95%; (5) diabetes; and (6) contraindications for MRI. All subjects were instructed to avoid smoking, heavy exercise, or caffeine on the day of the MRI. Informed written consent was obtained from all subjects, and the protocol was approved by the research ethics board of the University Health Network.

Protocol

Following recruitment, the subjects had an overnight sleep study. The CVR measurements were made between 11 AM and 2 PM on the day after the study, or as soon as could be scheduled.

Overnight Sleep Study

The overnight sleep study was performed at the University Health Network sleep study laboratory using standard techniques and criteria for scoring sleep stages, arousals, apneas, and hypopneas.[12] Thoracoabdominal movements were monitored by a respiratory inductance plethysmograph (Respitrace; Ambulatory Monitoring Inc., White Plains, NY)[13] and airflow was measured by a 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, Canada) Hypopneas were scored when there was a drop in the peak signal by 30% or higher of 10 seconds' duration or longer, which was associated with a 3% or higher oxygen desaturation or arousal on the EEG. Hypopneas were scored as obstructive if there was thoracoabdominal paradoxical ribcage motion on the Respitrace, inspiratory flattening, or snoring. Otherwise, hypopneas were scored as central.

The severity of sleep apnea was assessed by the number of apneas and hypopneas per hour of sleep (apnea–hypopnea index [AHI]). Subjects having an AHI of 5 per hour of sleep or higher were classified as having sleep apnea, and subjects with an AHI of less than 5 were classified as the nonsleep apnea (NSA) group.[12] OSA was diagnosed when at least 85% of the respiratory events were of the obstructive type. The oxygen desaturation index (ODI) was defined as the number of oxygen desaturations per hour 3% or higher below baseline. The Epworth Sleepiness Scale, a subjective measure of daytime sleepiness, was completed on the night of the polysomnography.

Imaging

BOLD imaging was performed on a 3-T short-bore MRI system (GE Healthcare, Milwaukee, WI) using an 8-channel phased-array receiver coil. The BOLD acquisitions were obtained using an echo-planar gradient echo sequence (repetition time/echo time = 2000/30 milliseconds, $3.75 \times 3.75 \times 5.0$ mm voxels, field of view 24×24 cm, 39 slices, slice thickness 5 mm, matrix size 64×64, number of frames = 254, flip angle = 85°).[9] Each subject had an initial anatomical scan, following which the BOLD MRI scan was performed in conjunction with the dynamic hypercapnic stimulus.[14-17]

Hypercapnic Stimulus

The hypercapnic stimulus was delivered via a closed face mask using skin tape to prevent gas leaks. All gas was supplied by a computer-controlled gas blender and sequential gas delivery circuit (Respiract; Thornhill Research Institute, Toronto, ON, Canada) using the prospective targeting algorithm of Slessarev et al.[18] The repeatable stimulus took the form of 2 pseudo–square wave iso-oxic changes in the end-tidal carbon dioxide ($P_{ET}CO_2$) of 10 mm Hg