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Original Article

Impaired cerebrovascular reactivity in obstructive sleep apnea: a case-control study

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is an independent risk factor for stroke. Little is known about the cerebrovascular hemodynamic changes during apnea. Hypercapnia occurs in apneas and hypopneas, and a reduced cerebral vasodilatory response to CO_2 could compromise the cerebral blood flow (CBF). Therefore, we aimed to evaluate whether the apnea–hypopnea index (AHI) affected the cerebrovascular response to CO_2.

Methods: A total of 11 patients with OSA were compared to 16 controls. We assessed the cerebrovascular responses with arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) magnetic resonance imaging during hypercapnia or breath-holding tasks.

Results: The CBF response to CO_2 was impaired with increasing AHI (average CBF: $p = 0.018$; gray matter: $p = 0.038$; white matter: $p = 0.045$), that is, increased OSA severity. When comparing the OSA patients to the control subjects, the OSA patients had a significantly reduced CO_2 response of the white matter CBF ($p = 0.04$). However, the BOLD response to CO_2 and the breath-holding task did not show any significant differences between OSA patients and control subjects.

Conclusion: The cerebrovascular CO_2 reactivity, measured by the CBF, was impaired with increasing AHI, that is, OSA severity. These findings may add to the understanding of the increased stroke risk found in OSA patients.

1. Introduction

Obstructive sleep apnea (OSA) is a common disorder and is believed to be a major, predisposing factor for cardio- and cerebrovascular morbidity and mortality [1–6], in part related to apnea–hypopnea index (AHI) severity [6,7].

Stroke is among the most common brain disorders and the most frequent cause of acquired disability in adults, the second leading cause of death, and the third leading cause of dementia. Stroke survivors often have permanent functional and cognitive impairments, with significant socioeconomic consequences for the patients, their partners, and society [8].

However, the mechanisms for stroke in OSA patients are poorly understood. Several factors may be associated including hypoxemia, hypercapnia, fluctuations in cerebral perfusion, and potentially incomplete regulation of the cerebral blood flow (CBF) [9]. The cerebrovascular response to hypercapnia is considered a sign of the ability of the cerebral vessels to react to the brain's metabolic demands. A reduced response may be seen as an increased susceptibility to ischemia [10].

During apneas/hypopneas, the intracranial pressure increases, and the cerebral perfusion pressure decreases [9]. The increased intracranial pressure is probably due to an increased intracranial blood volume during the apnea [11]. The negative intrathoracic pressure in the course of apneas/hypopneas is thought to further contribute to a reduction of the CBF [2]. In this way, each apnea/hypopnea may affect the blood pressure and CBF directly [9].

Perfusion pressure and CBF decrease throughout the apneas/hypopneas, whereas hypercapnia develops several seconds after

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apnea/hypopnea onset [9]. An impaired cerebrovascular response to CO_2 may delay the normalization of the CBF and thereby prolong the adverse effects of the apneas/hypopneas. It is still not known, however, whether the CBF shows an attenuated response to CO_2 with increasing AHI. An impaired cerebrovascular response to breath-holding has been found in OSA patients compared to controls with BOLD [12] and flow-sensitive alternating inversion recovery (FAIR) magnetic resonance imaging (MRI) [13]. These data suggest that OSA patients have smaller cerebrovascular responses to hypercapnia than controls. If so, the brain is at higher risk for suffering from brain ischemia during apnea in OSA patients.

MRI with certain types of contrast is a method for investigating the CBF response in OSA patients. The BOLD contrast signal depends on the change from oxyhemoglobin to deoxyhemoglobin, the latter being paramagnetic. BOLD signal changes may be due to alterations in the CBF or blood volume or to removal of oxygen. In contrast to BOLD, in arterial spin labeling (ASL), the blood water is magnetically labeled (typically at neck-level), and the amount of labeled water is measured at brain level, thus providing a direct measure of the CBF.

In this study, we aimed to evaluate whether the AHI influences the cerebrovascular response to CO_2 and to investigate the BOLD response to CO_2 and breath-holding in OSA patients and control subjects assessed by MRI (BOLD and ASL).

2. Methods

The study design was case-control. Polysomnography (PSG) or home sleep apnea testing (HSAT) was carried out from October 2010 to July 2012 at the Danish Center for Sleep Medicine, Rigshospitalet, and MRI from March 2011 to August 2012 at the Functional Imaging Unit, Rigshospitalet. All MRI scans were performed within six months after PSG/HSAT. This time limit was set in order to include healthy subjects from other PSG/HSAT studies. In OSA patients, MRI was carried out before initiation of continuous positive airway pressure (CPAP) treatment.

The OSA patients were recruited from the Danish Center for Sleep Medicine. The inclusion criteria were an AHI >15 and no CPAP treatment for at least six months. The diagnosis was made with PSG/HSAT. For further details, see Supporting Information.

Controls were included at a similar age (>45 years old) as OSA patients. Exclusion criteria were known OSA or an AHI >10. We recruited the controls from a volunteers' homepage, information at lectures, a researchers' network, and staff from our departments who were not involved in the study.

Exclusion criteria for both groups were clinical information indicating previous or current disease in the central nervous system that could influence the scan results (eg, major psychiatric, neurodegenerative diseases, or a previous stroke). However, silent infarction found on MRI was not a reason for exclusion. Participants also had to be cooperative enough to complete the functional MRI (fMRI) scans and be without contraindications to MRI.

2.1. PSG and HSAT setup

PSGs and HSAT were set up and scored according to the American Academy of Sleep Medicine (AASM) 2007 guidelines (see Supporting Information). Hypopnea scoring followed the 2007 recommended A-criteria [14].

2.2. MRI and fMRI setup

The scans were performed in the late afternoon/evening (15:30–23:00). The anatomical MRIs consisted of axial and sagittal T2 sequences, fluid-attenuated inversion recovery (FLAIR), ADNI MPRAGE (Alzheimer's Disease Neuroimaging Initiative, magnetization prepared rapid gradient echo), and diffusion weighted imaging. All anatomical MRI scans were evaluated for pathology by an experienced neuro-radiologist (K.K.) who was blinded to the OSA/control status. The number and size of deep white matter hyperintensities (DWMH) seen on the FLAIR and T2 weighted images were evaluated using a visual semi-quantitative rating scale [15].

2.2.1. fMRI setup

Participants were placed in the head coil with a mouthpiece containing a one-way valve and with a nose clip in order to avoid admixture of ambient air.

In the breath-holding setup, the subjects additionally looked into a set of goggles with instructions for the breath-holding task (see below).

2.2.2. fMRI tasks (BOLD)

The hypercapnia task followed a three-min block setup with three resting periods of breathing ambient air, and two active blocks with a 5% CO_2-enriched air mixture (5% CO_2, 20% O_2, and 75% N_2).

The breath-holding task was performed with five active 55-second-periods, in which one period consisted of 36 s of normal breathing and breath-holding for 19 s. The last period was followed by 36 s of normal breathing. During the breath-holding task, the participants followed instructions ("breathe normally," "exhale," and "hold your breath") presented through goggles, placed on the head coil. Prior to the breath-holding, the participants exhaled to a normal, unforced breathing depth, making the breath-holding postexpiratory in order to best mimic an apnea during sleep.

2.2.3. fMRI acquisition

Functional images were acquired on a three T Philips Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil (In Vivo Inc.).

We defined the region of interest (ROI) for the BOLD sequences as a) the white matter and b) the gray matter, and reported the results for the two ROIs separately.

For further details, see the Supporting Information.

2.2.4. Perfusion acquisition

The QUASAR pulsed arterial spin labeling (ASL) sequence was used in order to measure the CBF [16]. Seven slices centered on the corpus callosum were acquired. For details on sequence parameters, see Henriksen et al. [17]. ASL consisted of two scanning sequences of six min duration, one with ambient air and one with CO_2-enriched air (see above).

2.2.5. Data processing

All fMRI data were processed using FEAT (fMRI Expert Analysis Tool), part of the FSL analysis package (FMRIB Expert Analysis Tool, v5.98 [18], Oxford University, UK) [19].

For further details, see the Supporting Information.

2.3. Ethical standards

The Institutional Review Board approved the study (file number H-3-2010-126).

Informed consent was obtained from all individual participants included in the study prior to their inclusion.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.