

## Age-related changes in cerebral lactate metabolism in sleep-disordered breathing

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### Abstract

Thirty-one patients, aged 22–71 years, with nocturnal apneic episodes and/or habitual snoring were studied with magnetic resonance spectroscopy (MRS) and diagnostic polysomnography separately to determine whether accumulation of lactate caused by cerebral hypoxia during sleep is associated with sleep-disordered breathing (SDB), aging and co-morbidities related to SDB. Eight proton magnetic resonance spectra for sleep and two for periods of arousal were obtained from the right centrum semiovale. All patients were evaluated for the presence or absence of co-morbidities including hypertension, cardiac disease, diabetes mellitus, and hyperlipidemia. Significant lactate signals were found in seven patients with obstructive sleep apnea–hypopnea syndrome (OSAHS) during sleep periods, and none during periods of arousal. Aging was significantly related to the presence or absence of significant lactate signals during sleep periods as determined by logistic regression analysis ( $\beta = 0.2480$ ; 95% confidence interval, 0.0905–0.5094;  $P = 0.0001$ ). Apnea index (AI), apnea–hypopnea index (AHI), and minimum value of peripheral oxyhemoglobin saturation each significantly interacted with age ( $P = 0.0081$ , 0.0284, and 0.0302, respectively). Our findings suggest that SDB combined with aging is related to accumulation of lactate during sleep.

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### 1. Introduction

Repeated apneic and hypopneic episodes during sleep may result in cerebral impairment in patients with obstructive sleep apnea–hypopnea syndrome (OSAHS) [1,9,13,19,23,28,43]. Sleep-disordered breathing (SDB) is associated with a poor cognitive performance in aged people [6]. We studied cerebral metabolic changes in patients with OSAHS during awake periods using proton magnetic resonance spectroscopy (MRS) and found a significant decrease in the *N*-acetylaspartate (NAA)/choline ratio in the cerebral deep white matter in patients with moderate to severe OSAHS [20,21]. The results of these studies suggest that OSAHS may lead to cerebral metabolic impairment. A known mechanism of cerebral circulatory regulation increases cerebral blood flow in response to hypercapnia, and

may compensate for decrease in arterial blood oxygenation during sleep apneic and hypopneic episodes. Results of recent studies of cerebral circulatory changes in patients with OSAHS suggest that this hemodynamic adjustment may not be sufficient to compensate for decrease in arterial oxyhemoglobin saturation during sleep apneic and hypopneic episodes [3,10,16,30]. Cerebral hypoxia during sleep is generally thought to play a role in inducing neuropsychological dysfunction in patients with OSAHS [1,9,13,23,28,43]. However, it remains unclear whether sleep apneic and hypopneic episodes can cause cerebral hypoxia. Cerebral hypoxia leads to accumulation of lactate as a result of anaerobic metabolism. Accumulation of lactate during sleep should provide evidence supporting the hypothesis that sleep apneic and hypopneic episodes can cause hypoxia in the brain. Proton MRS enables assessment of local changes in tissue lactate concentration [4,14,17,26,39,42].

Aging and cardiovascular co-morbidities, which are generally thought to be cerebrovascular risk factors, were found

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to be significantly related to decrease in NAA/choline ratio in the cerebral deep white matter [21]. These factors may promote cerebral ischemia, and play a role in the occurrence of cerebral hypoxia. We performed proton MRS examinations during periods of arousal and sleep to determine whether cerebral lactate metabolism changes in patients with sleep-disordered breathing, and which of these factors is significantly related to changes in cerebral lactate metabolism.

## 2. Methods

All participants were recruited at the Sleep Disorder Clinic of Totтори University Hospital. We invited 42 consecutive patients with nocturnal apneic episodes and/or habitual snoring witnessed by their family members to participate in this study. Medical records of potential participants were checked at the time of invitation. Patients with a history of central nervous system disease, congenital metabolic abnormalities including mitochondrial disorders, or medical conditions contraindicating MRS such as the presence of a cardiac pacemaker were excluded from this study. A 27-year-old female patient with an intracranial lipoma was excluded from this study. Four male patients, aged 25, 42, 63, and 66 years, refused to participate in this study. We thus enrolled 37 patients (30 men and 7 women; 22–74 years; mean, 48.3 years; standard deviation, 14.5 years) as participants. None of the participants was involved in shift work. All participants were clinically evaluated for the presence or absence of co-morbidities including hypertension, cardiac disease, diabetes mellitus, and hyperlipidemia. Evidence of hypertension was taken to be antihypertensive treatment at the time of enrolment or systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg on two independent visits. Evidence of cardiac disease was taken to be a history of documented ischemic heart disease or abnormal electrocardiogram exhibiting ischemic changes, left ventricular hypertrophy or arrhythmia. Evidence of diabetes mellitus was taken to be antidiabetic treatment at the time of enrolment or fasting blood glucose  $\geq$ 140 mg/dl. Evidence of hyperlipidemia was taken to be treatment for hyperlipidemia at the time of enrolment or total cholesterol  $\geq$ 240 mg/dl. The presence or absence of cardiovascular co-morbidities (hypertension and cardiac disease) and the presence or absence of metabolic co-morbidities (diabetes mellitus and hyperlipidemia) were used for subsequent statistical analyses. The body mass index (weight in kilograms divided by the square of height in meters) of each participant was determined at the time of polysomnographic examination. Subjective and objective measures of sleepiness, such as the Epworth Sleepiness Scale, multiple sleep latency test and maintenance of wakefulness test, were not used for analyses because such measurements were not obtained from all of the patients. After complete description of the study to the participants, written informed

consent was obtained in accordance with the Declaration of Helsinki.

Diagnostic polysomnography was performed prior to the MRS examination. Sleep state was monitored by electroencephalography (EEG) with Cz/A1 and Oz/A1 leads, electro-oculography, and submental electromyography. Air flow from the nasal and oral cavities was monitored with thermistors. Thoracic and abdominal respiratory motions were monitored with strain gauges. Arterial oxygenation was monitored with a Biox IIA finger pulse-oximeter (Ohmeda, Louisville, CO, USA) at a sampling interval of 3 s. The polysomnographic data were recorded on paper at a recording speed of 15 mm/s with an NEC 1A-96 (NEC, Tokyo, Japan). The polysomnographic records were manually assessed using conventional criteria [2,12,15]. Sleep stages were scored by the Rechtschaffen and Kales criteria every 20 s [38]. Severity of sleep-disordered breathing was assessed by apnea index (AI), apnea-hypopnea index (AHI), and minimum value of peripheral oxyhemoglobin saturation. Apneas were judged by reduction in breathing to less than 20% of baseline with a duration of 10 s or longer. Hypopnea was judged by reduction in breathing to 20–50% of baseline with a duration of 10 s or longer. Baseline was defined as the mean amplitude of stable breathing during an arousal period. AI and AHI were defined as average numbers of apneic and apneic-hypopneic events per sleeping hour, respectively. The criterion for sleep apnea syndrome was  $AI \geq 5$ .

The MRS examination was performed for each patient before treatment. Intervals between polysomnography and MRS ranged from 1 to 96 (mean, 49) days. Magnetic resonance imaging (MRI) and MRS were performed with a Magnetom Vision with a standard circulatory polarized head coil operating at 1.5 T (Siemens, Erlangen, Germany). MRI was used for anatomical localization and screening for central nervous system abnormalities. T1-weighted spin-echo images were obtained in transverse, coronal and sagittal directions. T2-weighted turbo spin-echo images were obtained in transverse direction. Patients with abnormal MRI findings including brain infarction, hemorrhage, or diffuse white matter lesions were excluded from subsequent MRS examination. Patients with only periventricular rim, periventricular cap, or punctate lesions were included among those undergoing the subsequent MRS examination [5].

Proton magnetic resonance spectra were obtained with spin-echo single volume spectroscopy [39]. We used a repetition time of 2000 ms and an echo time of 270 ms with 128 signal averaging, resulting in a measurement time of 4 min 23 s. Signals were acquired with 1024 data points and a spectral width of 1 kHz. An 8-ml (40 mm  $\times$  20 mm  $\times$  10 mm) volume of interest encompassing the centrum semiovale was selected in the right cerebral hemisphere. This location was chosen on the basis of the results of previous MRS studies indicating a relationship between severity of sleep-disordered breathing and metabolic impairment in cerebral white matter

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