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Low sleep quality is associated with progression of arterial stiffness in patients with cardiovascular risk factors: HSCAA study

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ABSTRACT

Background and aims: Improvement in sleep quality is considered to be a viable target for prevention and treatment of cardiovascular diseases. To gain insight into its underlying mechanisms, we evaluated the significance of objectively measured sleep quality in patients with regard to progression of arterial stiffness over a 3-year follow-up period.

Methods: This prospective cohort study included 306 serial patients registered in the Hyogo Sleep Cardio-Autonomic Atherosclerosis (HSCAA) study. In addition to classical cardiovascular risk factors (body mass index, current smoking, past history of cardiovascular disease, dyslipidemia, diabetes mellitus), the participants were examined for ambulatory blood pressure (BP), apnea-hypopnea index (AHI), standard deviation of the NN (RR) interval (SDNN) for heart rate variability (HRV), and objective sleep quality using actigraphy findings. Brachial-ankle pulse wave velocity (baPWV) was measured at both baseline and follow-up (36.6 ± 6.8 months) as a parameter of arterial stiffness.

Results: Increases in PWV (%) were greater ($p = 0.03$) in the low sleep quality (LSQ) group (5.75 ± 1.15%) as compared to the normal sleep quality group (2.69 ± 0.85%). Patients with the greatest increase (≥20%) from baseline exhibited a significantly ($p < 0.05$) larger percentage of LSQ (75% *vs.* 49.6%) as compared to those without PWV progression (<0%), with the association still significant (odds ratio 3.62, 95% confidence interval 1.04–12.55, $p = 0.04$) even after adjustment for other clinical risk factors. For all subjects, univariate logistic regression analyses showed that diabetes and LSQ were significantly associated with the greatest increase of PWV. Comparisons of characteristics among specific subgroups showed more prominent associations of LSQ with the greatest increase of PWV in patients with greater age, dyslipidemia, and higher AHI.

Conclusions: LSQ was associated with progression of arterial stiffness over a 3-year period, independent of cardiovascular risk factors such as BP, AHI, and HRV.

1. Introduction

The importance of behavioral factors is increasingly becoming recognized for prevention, development, and treatment of cardiovascular disease (CVD), as shown in epidemiological findings [1,2]. Furthermore, sleep quality has been found to be one of the most important behavioral factors involved in CVD occurrence [3,4]. We recently reported associations of sleep quality with carotid atherosclerosis and nocturnal hypertension in subjects who participated in the Hyogo Sleep Cardio-Autonomic Atherosclerosis (HSCAA) study [5,6], which was designed to examine the impacts of sleep disorder, ambulatory blood pressure (ABPM), and autonomic nervous dysfunction on subclinical atherosclerosis and cardiovascular events [7–10].

Brachial-ankle pulse wave velocity (baPWV), a non-invasive measurement of arterial stiffness [11], has become established as a predictor of cardiovascular events [12–14], and sleep duration and quality have been shown to be associated with PWV findings

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[15–19]. In those previous cross-sectional examinations, self-reported poor sleep quality was significantly correlated with higher PWV. However, no prospective studies have examined the effects of sleep quality on PWV progression and a longitudinal study to examine the impact of objectively measured sleep quality on arterial stiffness has yet to be conducted. Additionally, hypertension, reduced heart rate variability (HRV), showing autonomic nervous dysfunction, and high apnea-hypopnea index (AHI), showing the presence of obstructive sleep apnea (OSA), have been reported to be associated with higher PWV values [20–22]. However, no known studies have investigated the associations of sleep quality with PWV, together with these important confounding factors.

In the present study, data obtained from follow-up examinations of subjects who participated in the HSCAA Study over a period of 3 years were analyzed to determine whether objectively-measured sleep quality, together with ABPM, HRV, and AHI, can predict progression of arterial stiffness.

2. Patients and methods

2.1. Study design and participants

This cohort study was conducted from October 2010 to July 2014 and included 735 registered patients who were part of the ongoing HSCAA Study. All agreed to participate by providing written informed consent and the study was approved by the Ethics Committee of Hyogo College of Medicine (approval No. 2351). Patients with 1 or more cardiovascular risk factors, (obesity, smoking, presence of cardiovascular event history, hypertension, dyslipidemia, diabetes mellitus) and treated at the Division of Diabetes, Endocrinology and Metabolism of Hyogo Medical College Hospital (Hyogo, Japan), were registered. Among them, 591 subjects had baseline PWV measured and 511 completed objective sleep quality evaluations. Finally, 3-year follow-up (36.6 ± 6.8 months) findings including PWV measurements were used for our analyses. Patients with mental illness or treated with sleep medication were not included in the present analyses.

2.2. Assessment of classical cardiovascular risk factors

We obtained the medical history of each subject, and measured height and body weight. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Smoking status was based on self-reported history of cigarette smoking. We defined a previous cardiovascular event (myocardial infarction, coronary intervention) as history of coronary heart disease. Dyslipidemia was defined as the presence of low density lipoprotein cholesterol ($\geq$140 mg/dl), high density lipoprotein cholesterol ($\leq$40 mg/dl), elevated triglyceride level ($\geq$150 mg/dl), or treatment for dyslipidemia [23]. Type 2 diabetes was diagnosed by fasting plasma glucose $\geq$126 mg/dl, causal plasma glucose $\geq$200 mg/dl, or 2-h plasma glucose $\geq$200 mg/dl during a 75-g oral glucose tolerance test, or previous therapy for diabetes [24].

2.3. Assessment of ambulatory blood pressure

To investigate systolic (SBP) and diastolic (DBP) blood pressure, 24-h ABPM was performed using a TM-2431 digital recorder and the obtained data were analyzed using the TM-9503 Doctor Pro 3 software package (A&D Co. Ltd., Tokyo, Japan), as previously described [7,25]. The major quality criteria used for an acceptable ABPM recording included the following: (1) minimum of 80% of the BP readings expected during the 24-h period; (2) no more than 2 nonconsecutive hours with <1 valid BP reading; and (3) no behaviors seriously affecting BP (afternoon nap, drinking, etc.), as previously described [7]. SBP and DBP were defined as the mean value of each of the respective blood pressure measurements obtained over 24 h.

2.4. Assessment of autonomic nervous function

HRV was used to noninvasively measure cardiac modulation based on autonomic nervous function, as reported in previous studies [5–7], using an Active Tracer (AC-301A®, Arm Electronics, Tokyo, Japan), which monitors surface electrocardiogram findings from the upper limbs via 3 channels. We sequentially recorded HRV for 48 h, as HRV parameters obtained for more than 24 h have been shown to be highly reproducible in healthy subjects and moderately reproducible in diseased populations. The latter 24-hseries of data from the 48-our recording was analyzed using the MemCalc Chiram 3 system, version 2.0 (Suwa Trust, Tokyo, Japan). Ectopic beats, noise data, and artifacts were manually corrected or excluded from the calculations. According to the recommendations for clinical use of HRV [26], the standard deviation of the NN(RR) interval (SDNN) was calculated. The coefficient of variation (10 subjects) of SDNN for repeated 24-h measurements was 8.2%.

2.5. Assessment of sleep apnea and quality

To determine the presence of sleep apnea (apnea hypopnea index, AHI) and sleep quality, we used an Apnomonitor (SAS-2100®, Teijin, Tokyo, Japan) and Actigraph (Ambulatory Monitoring, Inc., Ardley, New York, USA), as previously described [5–7]. Percutaneous oxygen saturation (SpO2) was recorded using a pulse oximeter. Apnea was defined as complete cessation of air flow lasting $\geq$10 s, hypopnea as a $\geq$50% reduction in air flow lasting $\geq$10 s associated with a 4% decrease in oxygen saturation, and AHI as the average number of apnea and hypopnea episodes per hour. The actigraph, placed on the wrist of the non-dominant arm, senses motion as acceleration, and we used standard criteria to identify the onset and offset of sleep periods with the built-in algorithm. Obtained data were stored in the device memory and based on clock time. Subjects wore the accelerometer for 2 consecutive days. According to published recommendations for clinical use of an actigraph [27], activity index as a parameter of sleep quality was calculated as total body motion during sleep time. Thus, a higher activity index value was considered to be related to lower sleep quality.

2.6. Assessment of arterial stiffness

After the subject had rested for at least 5 min, a volume-plethysmographic device was used to measure baPWV (Form PWV/ABI; model BP-203RPEII, Colin Co., Komaki, Japan) [15,28]. This device records a phonocardiogram, electrocardiogram, and volume pulse form, as well as arterial blood pressure at the left and right brachial and bilateral ankles. Time-phase analysis between right brachial and volume wave-forms at both ankles was used for calculating baPWV. The distance between the brachial and ankle was automatically calculated according to subject height. After measurement of right and left baPWV, we used the higher value as a marker of arterial stiffness at baseline and follow-up examinations. The rate (%) of change of PWV was calculated as [100 $\times$ (follow-up PWV/baseline PWV ratio-1)]. We categorized the subjects based on change rate into 4 groups ($\geq$20%, $\geq$10% to <20%, $\geq$0% to < 10%, <0%). The validity, reliability, and reproducibility of the equipment utilized have been demonstrated in previous studies [28].