Original Article

Relationships between Nocturnal Intermittent Hypoxia, Arterial Stiffness and Cardiovascular Risk Factors in a Community-based Population: The Toon Health Study

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Aim: Nocturnal intermittent hypoxia (NIH), a primary marker of obstructive sleep apnea, has increasingly been linked with cardiovascular morbidity and mortality. The purpose of this study was to investigate the association between NIH and arterial stiffness as measured according to the cardio-ankle vascular index (CAVI) based on cardiovascular risk factors in a Japanese community-dwelling population.

Methods: We conducted a cross-sectional study in Toon city among 684 men and 1,241 women 30-79 years of age. The severity of NIH was defined as mild or moderate-to-severe according to five or 15 events/hour on the 3% oxygen desaturation index (ODI), respectively. Increased arterial stiffness was diagnosed according to a CAVI of ≥9.

Results: The number of subjects with no, mild and moderate-to-severe NIH was 1,348 (70%), 451 (23%) and 126 (7%), respectively. Increased arterial stiffness was detected in 21.9% of the participants. The multivariable-adjusted odds ratio (95% CI) of severe NIH related to an increased CAVI in comparison with a 3% ODI of <5 was 1.36 (0.82-2.23). The stratified logistic regression analysis showed that the multivariable-adjusted OR of severe NIH for an increased CAVI was remarkably increased in the individuals with a BMI of ≥25 (OR=2.53, 1.08-5.96; p=0.03). An interaction test showed a trend for an overweight status to be a modifier of the association between OSA and increased arterial stiffness (p=0.05).

Conclusions: NIH has a tendency to promote increased arterial stiffness as measured according to the CAVI, especially in overweight subjects.


Key words: Cardio-ankle vascular index (CAVI), Arterial stiffness, Nocturnal intermittent hypoxia (NIH), Overweight

Introduction

Nocturnal intermittent hypoxia (NIH) is a surrogate marker of Obstructive Sleep Apnea (OSA), underdiagnosed condition characterized by recurrent episodes of obstruction of the upper airway leading to sleep fragmentation and intermittent hypoxia during sleep⁴. OSA prevalence in adults has been estimated to be in the range of 3% to 7%⁵. It has been reported the association of OSA with several cardiovascular diseases (CVD), including coronary artery disease⁶, stroke⁷, atrial fibrillation⁸ and heart failure⁹. Because of the high prevalence of OSA and the growing evidence regarding the cardiovascular consequences, screening for OSA in the general population may be an important strategy for the prevention of CVD⁷.
Arterial stiffness is a major contributor to CVD. Several studies have supported its impact as an early independent marker of cardiovascular morbidity and mortality. Cardio-Ankle Vascular Index (CAVI) quantitatively reflects arteriosclerosis of the aorta, femoral and tibial arteries based on Bramwell-Hill’s equation and stiffness parameter. CAVI has been associated with risk factors for coronary disease such as diabetes mellitus (DM), dyslipidemia, metabolic syndrome and smoking. Short- and long-term continuous positive airway pressure (CPAP) therapy was found to significantly reduce CAVI. It has also been shown that short-term weight reduction therapy improves not only metabolic dysfunction, but also the severity of OSA and arterial stiffness, as measured by CAVI. The measurement of CAVI has demonstrated good reproducibility and was not affected by the blood pressure during measurement.

To date, the majority of studies linking OSA to arterial stiffness recruited participants from sleep clinic patients, but there have been only two community-based studies, which also recruited patients with sleep disorder breathing and their methodology to measure arterial stiffness was different to CAVI. The mean body mass index (BMI) of Eastern Asia is much lower than the rest of the world; OSA was found to affect cardiovascular risk factors more strongly among lower BMI populations. So far, there have been no studies on the assessment of NIH and arterial stiffness by using CAVI in a community-dwelling population. Therefore, the present study aims to clarify the association between NIH and arterial stiffness according to cardiovascular risk factors in a Japanese general community-based population.

Methods

Subjects

We carried out a cross-sectional study included in an ongoing longitudinal epidemiological study (Toon Health Study) of the general population living in Toon City, Ehime prefecture, Japan from 2009 to 2012. Toon city is a primarily rural area located on Shikoku Island in southern Japan, with a population of approximately 35,000. Of the 2,033 total participants 30-79 years of age, 1,932 subjects who underwent sleep testing with pulse oximetry and measurement of the CAVI were included in this study. Seven subjects were excluded due to having a low ankle-brachial index (ABI) of <0.9, which indicates severe arteriosclerosis of the femoral artery related to a falsely low CAVI value. Subjects with cardio- or cerebrovascular disease, heart failure, renal failure or pulmonary disorders were also excluded from the analysis.

Written informed consent was obtained from all subjects, and the study protocol was approved by the Human Ethics Review Committee of Ehime University Graduate School of Medicine.

Anthropometric and Biochemical Measurements

The BMI was calculated according to the following formula: weight in kilograms divided by height in meters squared (weight (kg)/[height (m)]²). An overweight status was defined as a BMI of ≥25 kg/m². Blood pressure was measured twice in the sitting position after resting for at least five minutes using an automatic sphygmomanometer (BP-103iII; OMRON Colin Co., Tokyo, Japan). The mean of the two measurements was used for the analysis. Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥90 mmHg and/or the current use of antihypertensive agents. DM was defined as a fasting blood glucose level of ≥126 mg/dL (7.0 mmol/L) or the use of glucose-lowering drugs. Dyslipidemia was defined as an LDL-C level of ≥140 mg/dL (3.63 mmol/L), HDL-C level of <40 mg/dL (1.04 mmol/L) or TG level of ≥150 mg/dL (1.70 mmol/L) and/or the current use of lipid-lowering drugs, according to the diagnostic criteria for dyslipidemia for Japanese individuals. A self-reported questionnaire was conducted to assess the subjects’ medical history, smoking habits (current smokers, ex-smokers and never smokers) and drinking habits (regular alcohol consumption or none). The level of physical activity was assessed based on a globally used compendium comprised of 14 questions regarding occupation, locomotion, housework, sleep time and leisure time spent in physical activity. The questionnaire data were converted to measurements of the intensity of each physical activity expressed in metabolic equivalents (METs) as METs·h/day.

Assessment of NIH

NIH was measured during sleep for one night using a pulse oximeter (PULSOX-3Si, Minolta Co., Osaka, Japan) in the participant’s home. The sensor probe was fitted to the fourth finger with tape. The data were downloaded to a personal computer via an interface (PULSOX IF-3, Minolta) and analyzed using a proprietary software program (DS-3 ver. 2.0a, Minolta). Because the measurement time for pulse oximetry is often longer than the true total sleep time, an objectively measured sleep log for a single night was utilized to exclude waking time from the analysis in order to minimize the potential for overestimating the total sleep time. The 3% ODI (oxygen desatura-
3% ODI of 5 to <15 events per hour corresponded to mild NIH and a 3% ODI of ≥15 represented moderate-to-severe NIH.

The validity of the pulse oximetry measurements obtained using synchronous overnight recordings acquired with both PULSOX-3Si and standard polysomnography (PSG) was confirmed in a previous study of 256 consecutive patients. In that study, the sensitivity and specificity were 80% and 95%, respectively, for detecting an apnea-hypopnea index (AHI) of ≥5 using PSG with a cut-off threshold of 3% ODI ≥5. Similarly, the sensitivity and specificity for detecting an AHI of ≥20 using PSG with a cut-off threshold of 3% ODI = 15 were 85% and 100%, respectively. In order to evaluate reproducibility, pulse oximetry was conducted for two nights among 61 men. The median value of 3% ODI was 5.4 on the first night and 4.8 on the second night (p for difference = 0.95, Wilcoxon’s signed-rank test). Spearman’s rank correlation coefficient was 0.81 (p < 0.001).

Measurement of CAVI

The CAVI reflects the degree of stiffness of the arteries from the heart to ankles. As arteriosclerosis progresses, the CAVI increases.

The reproducibility of the CAVI measurements was demonstrated by a 3.8% coefficient of variation (CV); this value is within a satisfactory range, as a CV of 5% is generally accepted to be the limit for clinical laboratory testing. The CAVI was measured according to a standardized method using the Vasera VS-100 (Fukuda Denshi Co., Ltd, Tokyo, Japan). All CAVI measurements were obtained during morning hours, in which cuffs were applied to the bilateral upper arms and ankles, with the subject lying supine with their head held in the midline position. The ABI was calculated concurrently with the CAVI. The ABI is the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure. The examinations were performed after the subject rested for five minutes. The CAVI was calculated based on the stiffness parameter β, which represents the natural vascular stiffness independent of blood pressure, as measured on carotid echography. The pulse wave velocity (PWV) between the heart and ankle was obtained according to the L/T ratio, where L is the distance from the aortic valve to the ankle and T is the time during which the PWV propagates from the aortic valve to the ankle. Scale conversion from the PWV to CAVI was performed using the following formula:

CAVI = a \{(2\rho/DP) \times \ln (Ps/Pd) \times PWV^2\} + b

where Ps and Pd are the systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between the heart and ankle, a and b are constants, DP = Ps – Pd and ρ is the blood density. This equation was derived from Bramwell-Hill’s equation and the stiffness parameter β. The scale conversion constants were determined so as to match the CAVI with the PWV according to Hasegawa’s method. After automatically obtaining the measurements, the right and left CAVI values were calculated and analyzed using the VSS-10 software program (Fukuda Denshi). The average value of the right and left CAVI measurements was used for the analysis.

In line with the manufacturer’s recommendation, a CAVI of < 8 was considered normal, 8 ≤ CAVI < 9 borderline and CAVI ≥ 9 abnormal. Patients with a CAVI of ≥9 have been reported to present with significantly higher mean and maximum intima-media thicknesses, carotid beta stiffness indices and levels of carotid plaque. Furthermore, it has been reported that a cut-off CAVI value of 8.81 yields maximum sensitivity and specificity for detecting coronary artery disease. We therefore defined increased arterial stiffness in this study as an abnormal CAVI (≥9), as applied in previous studies.

Statistical Analysis

The age- and sex-adjusted mean CAVI values and prevalence of selected cardiovascular risk factors related to the NIH categories were calculated using an analysis of covariance according to three 3% ODI levels: non-NIH, 0 to < 5; mild NIH, 5 to < 15 and moderate-to-severe NIH, ≥15 events/hour. A linear regression model was used to test for linear trends across the NIH categories based on a median variable of 3% ODI. Multivariable-adjusted logistic regression analyses adjusted for age (year), sex, BMI (kg/m²), physical activity (METs·h/day), smoking (y/n), alcohol consumption (y/n), hypertension (y/n), DM (y/n) and hyperlipidemia (y/n) were used to estimate the association between the severity of NIH and increased arterial stiffness. Furthermore, a stratified analysis of cardiovascular risk factors according to the NIH categories was conducted using multivariable-adjusted odds ratios and 95% confidence intervals (CIs). The SAS version 9.2 software program (SAS Institute Inc., NC, USA) was used for all statistical analyses. All probability values for the statistical tests were two-tailed, with a p value of < 0.05 considered to be statistically significant.

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Results

The age- and sex-adjusted mean CAVI values and prevalence of cardiovascular risk factors related to NIH are shown in Table 1. The number of subjects with no, mild and moderate-to-severe NIH was 1,348 (70%), 451 (23%) and 126 (7%), respectively. The mean age and proportion of men were significantly higher in the severe NIH group. The mean BMI was higher among the subjects with an increased 3% ODI, albeit most of the subjects were not overweight. Waist circumference, glucose, HbA1c, triglycerides, hypertension and hyperlipidemia were also significantly greater in the participants with an increased 3% ODI. In contrast, the HDL-C and physical activity were significantly lower in the severe NIH group than in the mild and non-disease groups. No differences were observed in the rates of alcohol consumption and smoking or the mean total cholesterol or LDL-C levels. However, the CAVI values and prevalence of DM were higher in the severe NIH group.

The number of subjects without and with increased arterial stiffness was 1,503 (78.1%) and 422 (21.9%), respectively. The age- and sex- and multi-variable-adjusted odds ratios for various cardiovascular risk factors, including age (year), sex, BMI (kg/m²), physical activity (METs · h/day), smoking (y/n), alcohol consumption (y/n), hypertension (y/n), DM (y/n) and hyperlipidemia (y/n), were used to evaluate the relationship between increased arterial stiffness and the category of 3% ODI (Table 2). The multivariable-adjusted odds ratio (95% CI) of an increased CAVI (≥ 9) for severe NIH was 1.36 (0.82-2.23)-fold higher than that for the subjects with a 3% ODI of <5; however, this association was not statistically significant (p for trend=0.26).

Furthermore, we conducted a stratified analysis of cardiovascular risk factors associated with the CAVI, such as BMI32 and age33, using a multivariable-adjusted logistic regression analysis (Table 3). The combination of severe NIH and an overweight status was found to be significantly associated with an increased CAVI (p for trend=0.03). However, no significant associations were found in the stratified analysis of age, sex, hypertension, DM, hyperlipidemia, smoking and alcohol consumption in the subjects.
with severe NIH and increased arterial stiffness. The interaction test showed a trend for an overweight status to be a modifier of the association between OSA and increased arterial stiffness ($p = 0.05$).

**Discussion**

The results of this study demonstrated that severe NIH, as evaluated based on the 3% ODI, has a tendency to be associated with increased arterial stiffness, as measured according to the CAVI, especially in overweight subjects. Previous studies have linked BMI with OSA, although most of the participants in these reports were obese. It has also been shown that subjects with OSA have a high prevalence of CVD. Therefore, we sought to investigate the relationships between NIH, a surrogate indicator of OSA, arterial stiffness and cardiovascular risk factors in a Japanese general community-dwelling population. Consequently, NIH was detected in 30% of our study population, albeit most of the subjects had mild disease. In addition, the stratified analysis of cardiovascular risk factors using a multivariable-adjusted logistic regression model showed only the combination of a 3% ODI of ≥15 and BMI of ≥25 to be significantly associated with a CAVI of ≥9.

The present findings differ from those of a previous Caucasian community-based study that reported an association between obstructive sleep apnea and increased arterial stiffness associated with aging, but not BMI. This discrepancy may be explained by the higher prevalence of obesity in the above study of Caucasians than that observed in our study of Japanese individuals (mean BMI: 32 kg/m² and 24 kg/m², respectively) as well as the use of the pulse wave velocity (PWV) to assess the degree of arterial stiffness, which tends to be overestimated in patients with hypertension and autonomic dysfunction.

Yim-Yeh et al. reported that both OSA and aging impair the endothelial function and increase arterial stiffness in patients with obesity. Although that study included patients with OSA, the mean patient age was lower (mean age: 40 versus 60 years of age) and the mean BMI was higher (37 kg/m² versus 24 kg/m²) than that observed in our population. Nevertheless, both studies indicate that subjects with obesity and OSA have a higher risk of arterial stiffness. Iguchi et al. recently reported a significant correlation between severe NIH and increased arterial stiffness, as evaluated based on the 3% ODI, has a tendency to be associated with increased arterial stiffness, as measured according to the CAVI, especially in overweight subjects. Previous studies have linked BMI with OSA, although most of the participants in these reports were obese. It has also been shown that subjects with OSA have a high prevalence of CVD. Therefore, we sought to investigate the relationships between NIH, a surrogate indicator of OSA, arterial stiffness and cardiovascular risk factors in a Japanese general community-dwelling population. Consequently, NIH was detected in 30% of our study population, albeit most of the subjects had mild disease. In addition, the stratified analysis of cardiovascular risk factors using a multivariable-adjusted logistic regression model showed only the combination of a 3% ODI of ≥15 and BMI of ≥25 to be significantly associated with a CAVI of ≥9.

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### Table 2. Age-sex and multivariable-adjusted odds ratios (95% confidence intervals) of increased arterial stiffness (CAVI ≥ 9) according to 3% ODI levels

| 3% ODI, events/hour | Male | | Female |
|---------------------|------|-----------------|
|                     | Age and sex-adjusted model | Multivariable-adjusted model | Age and sex-adjusted model | Multivariable-adjusted model | Age and sex-adjusted model | Multivariable-adjusted model |
| 0 to < 5            | 1.00 | 0.99 (0.74-1.32) | 1.00 | 0.95 (0.60-1.49) | 1.00 | 0.87 (0.34-2.21) |
| 5 to < 15           | 1.20 | 1.20 (0.75-1.39) | 1.36 | 1.07 (0.71-1.64) | 1.07 | 0.99 (0.35-2.80) |
| ≥15                 | 1.36 | 1.36 (0.82-2.23) | 1.43 | 1.07 (0.71-1.64) | 1.43 | 0.99 (0.35-2.80) |

Multivariable-adjusted for age, sex, BMI (kg/m²), physical activity (mets·hr/day), smoking (y/n), alcohol consumption (y/n), hypertension (y/n), DM (y/n), and hyperlipidemia (y/n).
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Table 3. Age-sex and multivariable-adjusted odds ratios (95% confidence intervals) of increased arterial stiffness (CAVI ≥ 9) according to 3% ODI levels and stratified by some cardiovascular risk factors (age and BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>3% ODI, events/hour</th>
<th>p for trend</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to &lt; 5</td>
<td>5 to &lt; 15</td>
<td>≥ 15</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>1106</td>
<td>281</td>
<td>65</td>
</tr>
<tr>
<td>Number of subjects with CAVI ≥ 9 (%)</td>
<td>207 (18.72)</td>
<td>96 (34.16)</td>
<td>30 (46.15)</td>
</tr>
<tr>
<td>Age and sex-adjusted OR</td>
<td>1.00</td>
<td>0.91 (0.65-1.28)</td>
<td>0.99 (0.54-1.81)</td>
</tr>
<tr>
<td>Multivariable-adjusted OR</td>
<td>1.00</td>
<td>0.93 (0.65-1.33)</td>
<td>1.01 (0.53-1.90)</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>242</td>
<td>170</td>
<td>61</td>
</tr>
<tr>
<td>Number of subjects with CAVI ≥ 9 (%)</td>
<td>27 (11.15)</td>
<td>41 (24.12)</td>
<td>21 (34.43)</td>
</tr>
<tr>
<td>Age and sex-adjusted OR</td>
<td>1.00</td>
<td>1.75 (0.96-3.21)</td>
<td>2.56 (1.15-5.68)</td>
</tr>
<tr>
<td>Multivariable-adjusted OR</td>
<td>1.00</td>
<td>1.48 (0.79-2.78)</td>
<td>2.53 (1.08-5.96)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>966</td>
<td>231</td>
<td>54</td>
</tr>
<tr>
<td>Number of subjects with CAVI ≥ 9 (%)</td>
<td>65 (6.73)</td>
<td>29 (12.55)</td>
<td>10 (18.52)</td>
</tr>
<tr>
<td>Age and sex-adjusted OR</td>
<td>1.00</td>
<td>1.00 (0.60-1.64)</td>
<td>1.52 (0.68-3.39)</td>
</tr>
<tr>
<td>Multivariable-adjusted OR</td>
<td>1.00</td>
<td>1.04 (0.60-1.81)</td>
<td>1.80 (0.73-4.42)</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>382</td>
<td>220</td>
<td>72</td>
</tr>
<tr>
<td>Number of subjects with CAVI ≥ 9 (%)</td>
<td>169 (44.24)</td>
<td>108 (49.09)</td>
<td>41 (56.94)</td>
</tr>
<tr>
<td>Age and sex-adjusted OR</td>
<td>1.00</td>
<td>0.96 (0.69-1.39)</td>
<td>1.12 (0.65-1.93)</td>
</tr>
<tr>
<td>Multivariable-adjusted OR</td>
<td>1.00</td>
<td>1.01 (0.70-1.46)</td>
<td>1.25 (0.70-2.24)</td>
</tr>
</tbody>
</table>

Multivariable-adjusted for age, sex, BMI (kg/m²), physical activity (mets·hr/day), smoking (y/n), alcohol consumption (y/n), hypertension (y/n), DM (y/n), and hyperlipidemia (y/n)

between the severity of OSA and that of metabolic syndrome and arterial stiffness in a small Japanese population of overweight and obese outpatients. Although no cardiovascular endpoints were examined in that study, the data also support the relationship between obesity and both OSA and arterial stiffness.

Obesity appears to affect the control of the upper airway during sleep via several mechanisms, including alterations in the upper airway structure and function, reductions in the resting load volume and negative effects on the respiratory drive and load compensation. Additionally, neuromuscular control of the upper airways is negatively impacted by alterations in several key cytokines related to obesity, including leptin, tumor necrosis factor-alpha and interleukin-6. The hypoxia, hypercapnia and pressure surges accompanying intermittent hypoxia events may also serve as potent stimuli for the release of vasoactive substances, leading to impairment of the endothelial function. Moreover, a low oxygen level is a trigger for the activation of neutrophils, which adhere to the endothelium and release free oxygen radicals. The phenomenon of hypoxia/reoxygenation, which frequently occurs during episodes of NIH, may elicit increased vascular oxidative stress, thus inducing arterial stiffness.

An increased severity of OSA is associated with an increased serum leptin concentration, although the hyperleptinemia observed in subjects with OSA can be normalized with treatment with nasal CPAP. Moreover, hyperleptinemia is common in patients with obesity, reflecting increased adiposity and leptin resistance, which may contribute to the development of hypertension, impaired glucose metabolism and a pro-atherogenic state. Therefore, it can be speculated that pathways leading to leptin resistance play an important role in the interactions between OSA, atherosclerotic diseases and cardiovascular risk factors.

The strengths of this study include the large sample size in a general community-based population of middle-aged and elderly subjects and the fact that most of our participants were non-obese, whereas previous studies primarily evaluated obese individuals.
Furthermore, we used the CAVI, a reliable, reproducible and novel marker of arterial stiffness. Limitations of this study include the fact that the cross-sectional design cannot be used to establish causality between NIH, arterial stiffness and an overweight status. The Toon Health Study is an ongoing longitudinal epidemiological investigation; hence, we will continue to assess our population for cause-effect relationships. In addition, we measured oxygen desaturation during sleep using pulse oximetry to estimate the presence of NIH. Because apneic episodes do not always induce oxygen desaturation, we were unable to accurately detect the presence of very mild NIH. However, the sensitivity and specificity of pulse oximetry are high, as well as the reproducibility. In addition, the convenience of pulse oximetry for assessing intermittent hypoxia at home and its utility in providing an early diagnosis and treatment for patients with NIH have been documented.

In conclusion, we herein demonstrated that NIH has a tendency to promote increased arterial stiffness, as measured according to the CAVI, especially in overweight or obese subjects. Therefore, in order to reduce cardiovascular risks, it is important to educate patients diagnosed with OSA about CPAP treatment, as well as weight reduction therapy when necessary.

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Conflicts of Interest

None.

Disclosures

None.

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