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Original Article

Nocturnal intermittent hypoxia and short sleep duration are independently associated with elevated C-reactive protein levels in patients with coronary artery disease

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ABSTRACT

Background: Sleep-disordered breathing (SDB) or short sleep duration and coronary artery disease (CAD) are related, yet, the prevalence of SDB and short sleep duration as well as their mechanism remain unknown. Enhanced vascular inflammation is also implicated as one of the pathophysiologic mechanisms in CAD. The aims of this study were to evaluate the prevalence of patients with SDB and short sleep duration, and to examine their relationship with serum C-reactive protein (CRP) level in CAD patients.
Methods and results: We evaluated 161 CAD patients who underwent percutaneous coronary intervention, using nocturnal pulse oximetry, a non-invasive screening method for nocturnal intermittent hypoxia. Based on three percent oxygen desaturation index (3% ODI), the patients were divided into nocturnal intermittent hypoxia (3% ODI $\geq$ 15; n = 45) and control groups (3% ODI < 15, n = 116). The nocturnal intermittent hypoxia group had higher body mass index and serum CRP level compared with the control group. Short sleep duration (<6 h, n = 45) was also associated with increased CRP level compared with the control group ($\geq$6 h, n = 116). In multiple regression analysis, nocturnal intermittent hypoxia (β = 0.332, 95% confidence interval [CI] 0.102–0.562, P = 0.005) and short sleep duration (β = 0.311, 95% CI 0.097–0.526, P = 0.005) were both independent determinants for log serum CRP level.
Conclusions: Nocturnal intermittent hypoxia and short sleep duration were independently associated with elevated serum CRP level in CAD patients, suggesting that both SDB and sleep shortage are associated with enhanced inflammation in CAD patients. SDB and sleep duration may be important modifiable factors in the clinical management of patients with CAD.

1. Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive suspension or reduction of breathing, causing nocturnal intermittent hypoxia, followed by re-oxygenation. There is growing evidence that SDB is a potential risk factor for the development and progression of coronary artery disease (CAD) [1–6]. In one of the largest community-based cohort, severe SDB significantly increased the risk of fatal cardiovascular events, including myocardial infarction (MI); continuous positive airway pressure (CPAP) treatment reduces this risk [3]. A prospective cohort study found that SDB was a significant predictor of incident CAD after the adjustment for multiple risk factors [4]. In CAD patients, the treatment of SDB is also associated with a decrease in the occurrence of new cardiovascular events [2,5,6]. In addition to SDB, reduced amounts of sleep could contribute to the development of CAD [7,8]. A population-based cohort study using a self-administered questionnaire showed that short sleepers ($\leq$6 h) had a 23% higher risk of CAD incidence compared to normal sleepers after the adjustment for confounders [7]. A systematic review and meta-analysis of prospective studies revealed that short sleep duration was associated with a greater risk of developing or dying of CAD [8]. Although SDB and short sleep duration was associated with the development of CAD, their prevalence as well as the precise mechanism of these links remain unknown.

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Abbreviations

ACS	acute coronary syndrome
AHI	apnea-hypopnea index
BMI	body mass index
BNP	B-type natriuretic peptide
CAD	coronary artery disease
CPAP	continuous positive airway pressure
CRP	C-reactive protein
ESS	Epworth sleepiness scale
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MI	myocardial infarction
ODI	oxygen desaturation index
PCI	percutaneous coronary intervention
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
SDB	sleep-disordered breathing
SpO_2	oxygen saturation
TG	triglyceride
UA	uric acid

Vascular inflammation is implicated as one of the pathophysiologic mechanism in CAD. It plays a key role in the initiation and progression of atherosclerosis [9–12]. Elevated level of C-reactive protein (CRP), which is a non-specific marker of inflammation, indicate an increased risk of CAD among men and women who were free of cardiovascular disease [10]. Furthermore, among CAD patients, a higher serum CRP level is associated with further cardiovascular events [11,12]. Although enhanced inflammation could contribute to the development and progression of CAD, the clinically modifiable determinants of inflammation have not yet been elucidated. Therefore, fundamental treatments targeting enhanced inflammatory response have not yet been established. There is increasing evidence that nocturnal intermittent hypoxia in SDB patients activate the proinflammatory pathway [1,13]. Additionally, an experimental study demonstrated that acute total and short-term partial sleep deprivation resulted in enhanced inflammation in healthy adult subjects [14]. Therefore, SDB and inadequate sleep duration may be associated with the development of CAD through their proinflammatory effects.

We hypothesized that nocturnal intermittent hypoxia, a surrogate marker of SDB, and short sleep duration were associated with enhanced inflammation in CAD patients. In this study, we evaluated 1) the prevalence of nocturnal intermittent hypoxia and short sleep duration of CAD patients, 2) their relationship with the background and laboratory data of CAD patients, and 3) the relationship of nocturnal intermittent hypoxia and sleep duration with the serum CRP level of CAD patients.

2. Methods

2.1. Study population

The study included CAD patients who underwent percutaneous coronary intervention (PCI) and nocturnal pulse oximetry from June 2013 to November 2014 at Keio University Hospital. From a total of 262 consecutive patients, 101 patients (39%) were excluded due to insufficient laboratory data or previous SDB diagnosis and treatment. The final study population consisted of 161 patients. All patients provided written informed consent to participate. Forty-four patients with acute coronary syndrome (ACS) and 117 patients with stable angina or silent ischemia were included in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. ACS was defined as the patient presenting to the hospital with ST-elevation MI, non-ST-elevation MI, or unstable angina. The decision to perform PCI was made according to the investigator's clinical assessment of the patients.

2.2. Parameters for analysis

Nocturnal pulse oximetry and measurement of serum CRP levels were performed before the PCI of patients with stable angina or silent ischemia, and at discharge or the first instance of ambulation after discharge in patients with ACS. Patient background data, including the age, gender, height, weight, body mass index (BMI) and coronary risk factors (eg, obesity, hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of CAD) were collected. Serum creatinine (Cr), uric acid (UA), hemoglobin A1c (HbA1c), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and plasma B-type natriuretic peptide (BNP) levels were measured. The estimated glomerular filtration rate (eGFR), which was adjusted for age and gender, was calculated from the serum Cr level in each patient [15]. Angiographic characteristics were based on a diagnostic coronary angiogram performed prior to their PCI, and multi-vessel disease was defined as stenosis of $\geq$75% in $\geq$2 major coronary arteries or a left main trunk stenosis of $\geq$50%.

Nocturnal pulse oximetry was performed to identify the presence of nocturnal intermittent hypoxia, a surrogate marker of SDB. The arterial oxyhemoglobin saturation was recorded using a finger probe at a 1-Hz sampling frequency and 5-second average time (PULSOX-Me300, Teijin Pharma, Tokyo, Japan) [16,17] These recordings were scored using specialized software (DS-Me, Teijin Pharma, Tokyo, Japan). Because the measurement time of pulse oximetry is often longer than the true total sleep time, we used a single-night sleep log to exclude waking time from the analysis and minimize the potential for overestimating total sleep time. We used oxygen desaturation index $\geq$3% (3% ODI), which is the frequency of episodes of three percent desaturation per hour, as an indicator of nocturnal intermittent hypoxia. Based on three percent ODI, patients were divided into nocturnal intermittent hypoxia (3% ODI $\geq$ 15) and control groups (3% ODI < 15). The validity of pulse oximetry has been previously reported based on synchronous overnight recording of both pulse oximetry and standard polysomnography (PSG), and its sensitivity and specificity were 85% and 100%, respectively, in detecting an apnea-hypopnea index (AHI) of $\geq$20 by PSG using a cut-off threshold of 3% ODI = 15 [17–19].

We used Pittsburgh sleep quality index (PSQI) to assess sleep quality and duration. The PSQI is a score derived from a self-rated questionnaire consisting of 9 questions that assess a wide variety of factors related to sleep quality in the previous month. The PSQI has a sensitivity of 89.6% and specificity of 86.5% for identifying cases of poor sleep quality using a cut-off score of 5 [20]. Sleep duration was assessed with its corresponding PSQI component as follows: “During the past month, how many hours of actual sleep did you get at night? This may be different from the number of hours you spend in bed.” In a meta-analysis of 15 prospective studies that assessed the relationship of sleep duration and morbidity and mortality of CAD, 12 studies defined short sleep duration as < 6 h and showed that short sleep duration was associated with higher morbidity and mortality [21]. Therefore, we used 6 h as a cut off, and divided the patients into 2 groups: short sleep duration (<6 h) and control groups ($\geq$6 h). We also used Epworth