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Review article

Influence of hypoxia induced by sleep disordered breathing in case of hypertension and atrial fibrillation

Shin-ichi Ando (MD, PhD)*

Sleep Apnea Center, Kyushu University Hospital, Fukuoka, Japan

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ABSTRACT

Sleep disordered breathing (SDB) has been recognized as one of the important causes or factors of worsening for various cerebro- and cardiovascular diseases. On the other hand, a recent large randomized study and meta-analysis about the effect of continuous positive airway pressure (CPAP) indicated no or only minor effects to improve the outcome of SDB patients. Accumulating evidence has indicated that the key factor of the link between SDB and cardiovascular diseases might be hypoxia caused during repetitive long apneic episodes. Hypertension and atrial fibrillation (AF) are two important cardiovascular diseases that relate to SDB and the therapeutic consequences by CPAP treatment have been studied. As for the mechanism that elevates blood pressure during night, stimulation of chemoreceptors by hypoxia and the resultant increase in sympathetic nervous activity is the first step and repetitive hypoxic stimulation changes the characteristics of chemoreceptors and baroreceptors resulting in daytime hypertension. Pathological changes in the atrial muscle in SDB patients might be a result of repetitive hypoxia and atrial expansion. As for triggering AF, several animal studies revealed that the changes in autonomic nervous system caused by hypoxia and negative intra-thoracic pressure might be crucial. However, a recent observational study could not show the relation between SDB and AF. The difference between the previous studies and this negative study seems to exist in the difference of the severity of SDB or the degree of hypoxia. Such a difference might be also one of the reasons why a recent randomized trial to prove the effect of CPAP in cardio- or cerebrovascular patients failed to improve the patient prognosis. Hence, in this review, the relationship between hypoxia and onset or continuation of hypertension and AF will be reconsidered to understand the fundamental and robust relationship between SDB and these cardiovascular diseases.

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* Correspondence to: Sleep Apnea Center, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 814-8582, Japan.
E-mail address: shinando@sleep.med.kyushu-u.ac.jp

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Introduction

For decades, the physicians and researchers in the field of cardiovascular and sleep medicine believed that treatment for sleep disordered breathing (SDB) especially using continuous positive airway pressure (CPAP) for the SDB patients with or without cardiac or vascular diseases must improve their prognostic outcome [1,2]. However, in 2016, McEvoy et al. published the results of the Sleep Apnea CardioVascular Endpoint Study (SAVE) where 2717 patients comorbid with cardiovascular or cerebrovascular diseases were randomly assigned to CPAP treatment or only medical treatment and followed up for 3.7 years on average [3]. An astounding result from the study was that the CPAP treatment could not improve the cardiovascular outcome of the patients at all compared with medical treatment without CPAP. After the publication of this study, numerous comments were published from all over the world about the possible problems in this big trial; about the low adherence rate, relatively mild degree of SDB of the participants or the type of device used to evaluate SDB. In 2017, a meta-analysis about the effect of treatment of SDB by two types of positive airway pressure (PAP) devices was published [4]. In this meta-analysis, the authors included data of 7266 patients with SDB from 9 trials with CPAP and one trial with adaptive servo-ventilator (ASV) on the severe heart failure patients. The authors concluded that "although there are other benefits of treatment with PAP for sleep apnea, these findings do not support treatment with PAP with a goal of prevention of these outcomes".

Several lines of questions arise after the results of the SAVE trial and meta-analysis. Does all the SDB not have negative impact on our body or was the degree of SDB of the patients who participated to the negative studies such as the SAVE study not serious enough to develop cardiovascular diseases? Secondly, do the all therapies for SDB fundamentally have no effect for prevention or improvement of cardiovascular disease or was the way of use of CPAP in such trials inappropriate to bring about a favorable outcome? These questions are still open and waiting for the answer.

To answer the questions, we have to reconsider the history of diagnosis and treatment of SDB and the mechanisms that relate SDB to various diseases. In the early phase of research, SDB was considered to be problematic because it brought sleepiness to the patients resulting in a decrease of productivity and social activity or increased accidents. Therefore, the measurement of the severity of SDB and the way of treatment seem to be basically arranged for the resolution of the sleepiness. Problems might have occurred when we considered prevention or removal of the negative influence of SDB on the cardiovascular system and improvement in their prognosis as new therapeutic targets. Although the previous main target of therapy was to remove arousal from SDB to prevent sleepiness, accumulating results from recent studies have suggested that the repetitive severe deoxygenation has more impact on the cardiovascular outcome than previously considered. The reason why the studies such as SAVE could not provide improvement in prognosis of SDB patients might be related to the fact that the severity of SDB was measured using apnea hypopnea index (AHI) where the degree of desaturation is not fully taken into account and that the target of treatment was not centered on the removal of severe deoxygenation. Thus, in this review, I will reconsider the meaning of deoxygenation in the mechanisms through which SDB brings about the negative impact on the cardiovascular system in order to elucidate the future direction of the research in the field of the cardiovascular SDB taking hypertension and atrial fibrillation as examples.

Discrepancy between apnea hypopnea index and desaturation

Fig. 1 describes two summaries of the results of polysomnography (hipnogram) where AHI of the patients are similar. All the readers would easily notice that, although the values of AHI are similar to each other, the degrees of desaturation are widely different and may feel that each of SDB would have different impact on the cardiovascular system, although these patients had to be categorized in a same group as AHI was mainly used in many previous studies. Generally speaking, the degree of desaturation in very severe patients, i.e. AHI $>$ 60/h tends to be large, but desaturation level in the middle range of SDB in terms of AHI (between 20 and 50/h) is widely scattered as depicted by Oldenburg et al. [5] (Fig. 2). They stressed the importance of desaturation over AHI for the evaluation of the prognosis of SDB patients with heart failure. Severe desaturation that is usually caused by a long apnea results in an abrupt increase in sympathetic nerve activity and resultant increase in heart rate and blood pressure (BP) that might be associated with brain hemorrhage or probably many of cardiac or cerebral accidents during sleeping [6–8]. We also have reported a patient with heart failure showing a profound decrease in cardiac output during severe desaturation caused by SDB which was instantaneously restored by CPAP treatment [9]. Thus, there would be no question of the fact that severe SDB with marked hypoxia and a wide fluctuation in BP or heart rate is tightly related to development of the new cardiovascular diseases and worsening prognosis of the patient. A pivotal study published 30 years ago by He et al. reported that SDB patients whose apnea index more than 20/h (which means that AHI of the patients might be approximately over 40/h) showed far worse prognosis than those with apnea index $<$ 20/h [10]. Many such severe SDB patients died of myocardial infarction or cerebral hemorrhage. However, more caution should be paid to the fact that those with apnea index $<$ 20/h, which would be approximately comparable to AHI $<$ 40/h, did not show any worsening of prognosis. Hence, it should be emphasized that SDB does negatively impact on the human cardiovascular system but it might be related to the cardiovascular diseases only when the degree of the SDB is severe enough to widely fluctuate nocturnal hemodynamics or to change hormonal equilibrium through severe desaturation.

Influence of hypoxia in hypertension and atrial fibrillation

Hypertension

Nocturnal BP

During a long apneic episode, sympathetic nervous activity (SNA) gradually increases toward the end of apnea followed by elevation of heart rate and BP especially at the start of rebreathing (Fig. 3). This acute increase in SNA is considered as a result of a combination of the following mechanisms. Firstly, stimulation of peripheral and central chemoreceptors by hypoxia and hypercapnia enhance SNA [11]. More than 20 years ago, Morgan et al. reported neuro-circulatory responses to combination of hypoxia

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