Review

Obstructive sleep apnea and coronary artery disease: An unholy nexus or a holy alliance?

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ABSTRACT

Coronary artery disease (CAD) is a significant cause of morbidity and mortality globally, and hypertension, dyslipidemia, diabetes mellitus, and smoking are major cardiovascular (CV) risk factors. Obstructive sleep apnea (OSA) and CAD share an exciting relationship, and recently, OSA has emerged as a non-traditional CV risk factor. OSA is characterized by episodic sleep state-dependent collapse of the upper airway, resulting in periodic reductions or cessations in ventilation, with consequent hypoxia, hypercapnia, or arousals from sleep. The oxidative stress and vascular inflammation resulting from the nocturnal hypoxia followed by reoxygenation cycles predispose the patients to the development of atherosclerotic cardiovascular disease (CVD). Untreated OSA is associated with long-term health consequences, including CVD, metabolic disorders, cognitive impairment, and depression. Paradoxically, some recent studies have reported that patients with OSA may suffer less severe CAD due to the development of collateral circulation due to repetitive hypoxia experienced due to OSA.

KEY WORDS: Acute coronary syndrome, coronary artery disease, sleep apnea.

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BACKGROUND

A substantial number of cardiovascular (CV) risk factors have been recognized to date. The main modifiable CV risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and smoking, are included in CV risk charts; their targets are set in the national and international guidelines. According to the World Health Organization, in terms of attributable deaths, the leading cardiovascular disease (CVD) risk factor is hypertension (attributable to 13% of global deaths), followed by tobacco use (9%), diabetes mellitus (6%), physical inactivity (6%), and overweight and obesity (5%).[1]

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The non-traditional CV risk factors that appear to be of most clinical interest include apolipoprotein A, apolipoprotein B, high-sensitivity C-reactive protein (hsCRP), homocysteine, interleukin 1, lipoprotein (a), the density of low-density lipoprotein (LDL) particles, the LDL particle number, tissue/tumor necrosis factor-α (TNF-α), and uric acid.[2] These non-traditional risk factors may be of value in adding further confirmation and attention to suspected significant CV risk. These can also help to better understand current concepts of atherogenesis (e.g., various potential mechanisms associated with inflammation) as an etiology

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and guide current plus future therapies.[2] Obstructive sleep apnea (OSA) is one of the emerging non-traditional CV risk factors.[3,4]

Sleep-disordered breathing (SDB) includes a spectrum of conditions and obstructive sleep apnea syndrome is the most severe form. OSA is characterized by episodic sleep collapse of the upper airway, resulting in periodic reductions or cessations in ventilation, consequent hypoxia, hypercapnia, or arousals from sleep. Many patients are unaware that their breathing is affected and may not visit a physician for evaluation. In addition, patients may not consider sleepiness a relevant topic to discuss with health care providers.[5] The prevalence of OSA is estimated to be 10% among men and 3% among women aged 30–49 years, whereas the prevalence increases to 17% in men and 9% among women in the population aged 50–70 years and there are estimated to be 24 million persons in the United States who have not received a diagnosis.[6]

The untreated OSA is associated with long-term health consequences, including CVD, metabolic disorders, cognitive impairment, and depression. Common symptoms include excessive daytime sleepiness, fatigue, non-refreshing sleep, nocturia, morning headache, irritability, and memory loss. Overnight polysomnography (PSG) is the gold standard for the diagnosis of OSA.[7]

Apnea is defined by a complete or almost complete (>90%) cessation of airflow (measured by nasal pressure) lasting 10 sec or longer.

Hypopnea is defined if all of the following criteria are met:

(1) Peak signal excursions drop by at least 30% of pre-event baseline using nasal pressure (diagnostic study), positive airway pressure device flow (titration study), or an alternative hypopnea sensor (diagnostic study),
(2) Duration of the at least 30% drop in the signal excursion is 10 or more sec, and
(3) There is 3% or greater oxygen desaturation from pre-event baseline and/or the event is associated with an arousal.

Obstructive Sleep Apnea is defined by ≥5 apnea and hypopnea events per hour of sleep associated with excessive sleepiness.

The apnea-hypopnea index (AHI) is widely used to diagnose and assess the severity of OSA. The AHI refers to the mean number of apneas or hypopneas per hour of sleep. An AHI of >5 on overnight PSG study is required for the diagnosis of OSA.[5,6] The American academy of sleep medicine arbitrarily classifies OSA as mild (AHI = 5–14.9/h), moderate (AHI = 15–29.9/h), and severe (AHI ≥30/h).[8]

PREVALENCE OF OSA IN CAD

The relationship of OSA with CAD is complex and is not fully understood. Many studies have been added to the literature recently, but the evidence is still evolving. OSA is a modifiable risk factor, and continuous positive airway pressure (CPAP) administration, the gold-standard treatment of OSA, may reduce the early signs of endothelial dysfunction and atherosclerosis and improve CV outcomes.[6]

In a study conducted in the general adult population by Osman *et al*.,[9] the prevalence of OSA was approximately 3–7% in men and 2–5% in women, and the prevalence of OSA was ≥50% in patients with cardiac or metabolic disorders. Thus, the identification of OSA may be difficult for the clinician, even in populations in which OSA is highly prevalent, such as patients with CV disorders, because they may not present with the cardinal signs of the disease, for example, excessive sleepiness and obesity.

In a study by Sílvia *et al*.,[10] OSA was diagnosed in 46 (63%) of 73 patients admitted to the cardiac intensive care unit (CICU) for acute coronary syndrome (ACS). They concluded that OSA is an underdiagnosed disease with high prevalence in patients with ACS, and it was urgent to establish screening protocols with high diagnostic yield to identify patients with unfavorable prognoses. Martinez *et al*.[3] conducted a study on 55 patients to verify the association between OSA and angiographically proven CAD. The classic CAD risk factors like fasting glucose; total, HDL, and LDL cholesterols; triglycerides; uric acid, and hsCRP were also measured. They excluded patients older than 65 years with a body mass index (BMI) higher than 40 kg/m^2, diabetes mellitus, and history of smoking in the last year. Of the total 55 patients studied, 29 patients without CAD had an AHI of 11 ± 11/h, whereas AHI was 23 ± 14/h in 26 patients with CAD (P = 0.001). In a binary logistic regression to predict CAD, after controlling for all the above risk factors, they concluded that in a sample without smokers, morbidly obese, or diabetic patients, AHI was the main predictor of CAD and concluded that sleep apnea should integrate into the set of risk factors routinely assessed in the clinical investigation for CAD risk stratification.

The data regarding the relationship between OSA and CAD in India is sparse. Mahajan SK *et al*. conducted a pilot study on OSA prevalence among patients admitted with ACS in a tertiary care institute in northern India. Sixty-six patients were subjected to overnight PSG within 8 weeks of the index ACS event. A cut-off of AHI ≥5/h was defined as OSA and AHI ≥15/h was taken to describe the presence of moderate to severe OSA. The prevalence of OSA (AHI ≥5/h) was 78.8% [95% confidence interval (CI) = 67.0–87.9], while 31 (46.9%) patients of ACS had moderate to severe OSA. The results again emphasized that there is a significantly high prevalence of moderate to severe OSA among patients with ACS.[11]

PROPOSED MECHANISMS EXPLAINING THE LINK BETWEEN SLEEP APNEA AND CVD

Although several intermediate mechanisms are proposed, the underlying mechanisms explaining the associations between OSA and CVD are not entirely understood. The sustained sympathetic activation, intra-thoracic pressure changes, and vascular inflammation resulting from the nocturnal hypoxia and reoxygenation cycles are postulated to be contributing factors. Concerning the role of sympathetic activation, investigators have posited that repetitive apnea/hypopnea events along with ensuing arterial desaturation and hypercapnia cause activation of the sympathetic nervous system resulting in increased systolic blood pressure that might ultimately lead to hypertension or exacerbation of this condition [Figure 1].[12] The other abnormalities observed among patients with OSA might also be involved in the pathogenesis of the CVD. These include coagulation disorders, endothelial damage, platelet activation, and an increase in inflammatory mediators. Furthermore, the patients with OSA have characteristically greater levels of endothelin and lower levels of nitric oxide than healthy sleepers. This elevated endothelin is believed to impair blood pressure regulation as well. Thus, patients with OSA often experience greater blood vessel constriction.[13]

There is evidence that hypoxia promotes the formation of reactive oxygen species, which could activate the transcriptional activator hypoxia-inducible factor 1, particularly during the reoxygenation period. Reactive oxygen species regulate the activation of critical transcription factors that are redox sensitive, resulting in increased expression of genes, which encode proteins promoting adaptation to hypoxia. It has also been suggested that redox-sensitive transcription factors are also activated, which elicit inflammatory and immune responses by promoting the activation of endothelial cells, leukocytes, and platelets. Once activated, those cells express adhesion molecules and proinflammatory cytokines that may lead to endothelial injury and dysfunction. If left untreated, this cascade of events may eventually lead to overt CV morbidity.[13]

NATURAL COURSE OF SLEEP APNEA IN PATIENTS WITH ACS

Buchner *et al*.[14] studied 40 consecutive patients with acute myocardial infarction (MI) who underwent PSG and CV magnetic resonance imaging within 5 days and 12 weeks after the event to assess sleep apnea and cardiac function. The patients were stratified in improved left ventricular ejection fraction (EF) within 12 weeks by ≥5% (improved EF group, n = 16) and in those who did not (unchanged EF group, n = 24). The prevalence of sleep apnea (AHI ≥15) within ≤five days after MI was noted at 55%. They observed that AHI was significantly more reduced in patients in whom EF improved in comparison to those with the unchanged EF group ($P = 0.036$). This reduction was based on a significant alleviation of obstructive events ($P = 0.009$), while the reduction of central events was similar between groups ($P = 0.906$). They concluded that improvement in cardiac function early after MI was associated with an alleviation of sleep apnea.

SLEEP LOSS AND CVD

In two studies by Buchner *et al*. and Schiza *et al*., the natural course of sleep apnea was observed by PSG within the first month after ACS. At baseline, average left ventricular functions were mildly impaired in both study populations. Both studies found a very high prevalence of sleep apnea within the first day after the acute coronary event [AHI ≥10/h: 55% (Buchner *et al*.) and AHI ≥15/h: 54% (Schiza *et al*.)], but AHI decreased with time after the coronary event, which was mainly due to a reduction in obstructive apneas and hypopneas. Both studies confirm a strikingly high prevalence of moderate to severe sleep apnea early after ACS, and a progressive improvement of sleep apnea was noted in some of the patients early, which may be partly explained by the changes in fluid overload or content.[14,15]

PROGNOSTIC IMPLICATIONS OF OSA IN PATIENTS WITH CDA: UNHOLY NEXUS?

Population, Intervention, Control, and Outcomes (PICO) analysis of various studies showing a relationship with

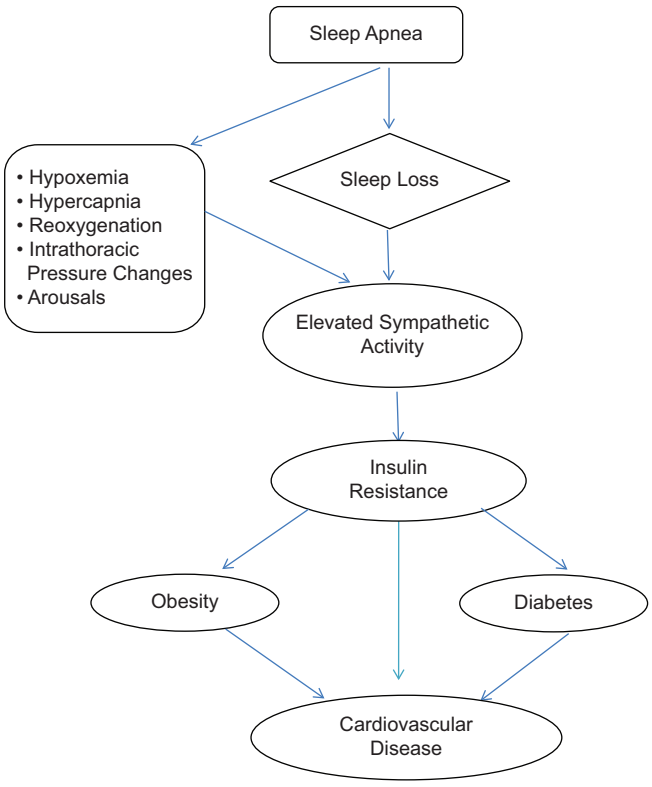

Figure 1: Proposed pathway linking sleep loss to CVD. (Adapted from Jean-Louis *et al*.[12])

CAD[14-19] is summarized in Table 1. Investigators in various studies summarized that atherogenesis started soon after the onset of sleep apnea. Likely, substantial atherosclerotic insults have already been incurred when a diagnosis is rendered since symptoms often become apparent around the age of 45. This might explain, to some extent, the reason why many patients with sleep apnea present primarily with CV morbidity.[13] There is evidence that the patients with OSA have increased arterial stiffness, premature atherosclerosis, coronary artery calcification, coronary plaque instability, and increased plaque vulnerability.[4] Schäfer *et al*.[4] performed overnight non-laboratory-monitoring-system recordings to detect OSA in 223 male patients with angiographically proven CAD. They found that 30.5% of patients with CAD had OSA, whereas OSA was observed in 19.7% of patients in the control group and found that OSA of moderate severity (AHI ≥20) was independently associated with MI.

Fan *et al*.[16] conducted a prospective cohort study in 804 patients to study the association of OSA with subsequent CV events after ACS onset. The primary endpoint was a major adverse cardiovascular and cerebrovascular event (MACCE), including CV death, MI, stroke, ischemia-driven revascularization, or hospitalization for unstable angina or heart failure. OSA was present in 403 (50.1%) patients. During a median follow-up of 1 year, the cumulative incidence of MACCE was significantly higher in the OSA group than in the non-OSA group (log-rank $P = 0.041$). Multivariate analysis showed that OSA was nominally associated with the incidence of MACCE [adjusted hazard ratio (HR): 1.55; 95% CI: 0.94–2.57; $P = 0.085$]. In the landmark analysis, patients with OSA had 3.9 times the risk of incurring a MACCE after 1 year (adjusted HR: 3.87; 95% CI: 1.20–12.46; $P = 0.023$), but no increased risk was found within 1 year follow-up (adjusted HR: 1.18; 95% CI: 0.67–2.09; $P = 0.575$). No significant differences were found in the incidence of CV death, MI, and ischemia-driven revascularization, except for a higher rate of hospitalization for unstable angina in the OSA group than in the non-OSA group.

Jia *et al*.[17] conducted a prospective cohort study and enrolled patients with ACS who were hospitalized for coronary angiogram/percutaneous coronary intervention and undergone PSG. They divided the patients into moderate to severe OSA group (AHI >15/h) and control group (AHI ≤15/h) and followed up for 32 months and compared the severity of ACS and long-term major adverse cardiovascular events (MACE) in two groups. Of the total 529 patients included in the final analysis, 70.5% (373/529) had moderate to severe OSA, and 29.5% (156/529) were assigned to the control group. When compared with controls, patients with moderate or severe OSA exhibited a higher prevalence of hypertension and higher BMI, SYNTAX score (an angiographic tool grading

Table 1: Relationship of OSA with CAD PICO Analysis

Study	P	I/E	C	O
Sílvia *et al*.[10]	Patients of ACS admitted to the CICU	ACS	None	63% of ACS patients had OSA
Schäfer *et al*.[4]	Male angiographically proven CAD patients	CAD	Without CAD	30.5% of patients with CAD had OSA, whereas in control group OSA was observed in 19.7% of patients.
Martinez *et al*.[3]		CAD	Without CAD	AHI was higher in patients with CAD than in those without CAD
Mahajan SK *et al*.[11]	Patients admitted with ACS in a tertiary care institute in northern India	ACS	None	The prevalence of OSA (AHI>5/h) was 78.8% in patients with ACS
Buchner *et al*.[14]	patients with acute MI	MI	Improved EF group, n=16; unchanged EF group, n=24	AHI significantly reduced improved EF group than the unchanged EF group. Improvement in cardiac function early after MI was associated with an alleviation of sleep apnea.
Fan *et al*.[16]	Patients with ACS	OSA	Without OSA	OSA group had a significantly higher cumulative incidence of MACCE than the non-OSA group. No significant differences were found in the incidence of CV death, MI, and ischemia-driven revascularization, in the OSA group than in the non-OSA group.
Jia *et al*.[17]	Patients with ACS	OSA	OSA group (AHI>15/h) and control group (AHI≤15/h)	Moderate or severe OSA group exhibited a higher prevalence of hypertension and higher BMI, SYNTAX score than controls. Moderate or severe OSA group had a higher accumulative rate of MACE than the control group.
Maia *et al*.[18]	Patients with ACS	OSA	High-risk OSA group and low-risk OSA group	High-risk group for OSA had higher frequencies of previous personal/family history of CHD and diabetes, in addition to poorer event-free survival than low-risk group. HR for fatal or recurrent non-fatal CHD was more in the high-risk group than in the low-risk group.
Shah *et al*.[19]	Patients with Acute MI	OSA	Without OSA	Patients with OSA had a less severe cardiac injury during an acute non-fatal MI than patients without OSA
Sánchez-de-la-Torre *et al*.[20]	ACS patients	OSA	Without OSA	The peak cTnI value was significantly higher in patients without OSA than in those with OSA (P=0.04).

Abbreviations: ACS: Acute Coronary Syndrome; OSA: Obstructive Sleep Apnea; CAD: Coronary Artery Disease; MI: Myocardial Infarction

the complexity of CAD), Epworth score, and length of hospitalization. With a median follow-up duration of 30 months, the accumulative rate of MACE was also higher in patients with moderate or severe OSA than that in the control group (8.6 vs. 3.2%, $P = 0.028$). After adjusting for baseline confounders by the Cox regression model, moderate to severe OSA was an independent risk factor of long-term MACE ($P = 0.047$; HR: 1.618; 95% CI: 1.069–3.869). They concluded that moderate or severe OSA correlated with disease severity and associated with worse long-term prognosis in ACS patients and raised the possibility that early diagnosis and interventions of OSA could improve long-term outcomes in ACS patients.

Maia *et al*.[18] evaluated the long-term influence of the high risk for OSA on fatal and non-fatal outcomes after ACS in the Acute Coronary Syndrome Registry Strategy (ERICO) Study using the Berlin questionnaire in 639 cases within 30 days after the index event. Cox regression proportional-hazards model was used to calculate the hazard ratio (HR) of all-cause, cardiovascular and coronary heart disease (CHD) related mortality, as well as, the combined endpoint of fatal or recurrent non-fatal CHD. The high-risk group for OSA had higher frequencies of previous personal/family history of CHD and diabetes, in addition to poorer event-free survival, as compared to the low-risk group (log-rank $P = 0.03$). After a 2.6-year mean follow-up, the HR for fatal or recurrent non-fatal CHD was 4.26 (95% CI: 1.18–15.36) in patients at high risk for OSA compared to those at low risk for OSA. They were able to identify the high risk for OSA as an independent predictor of non-fatal reinfarction or CHD mortality in post-ACS individuals in a long-term follow-up using the Berlin questionnaire.

In Sleep Heart Health Study, 6424 community-dwelling individuals underwent home PSG. It revealed a documented increased risk of CAD among patients with severe sleep apnea that odds for CHD (Odds Ratio (OR): 4.02; 95% CI: 1.03–15.74) were significantly greater among individuals with sleep apnea.[22] Arzt *et al*.[23] also provided the evidence behind SDB being a risk factor for CAD. In the early phase after MI, the heart might be in a vulnerable state sensitive to the negative consequences of SDB, including increased cardiac workload and endothelial dysfunction, which might ultimately lead to a mismatch between oxygen demand and supply. Despite the successful percutaneous coronary intervention, patients with acute MI and SDB have prolonged myocardial ischemia, less salvaged myocardium, and impaired left and right ventricular remodeling than those without SDB, all of which predispose to heart failure. Thus, suppression of SDB with positive airway pressure therapy in the early phase after MI is feasible; however, whether the treatment of SDB with positive airway pressure will be an efficient non-pharmacological treatment approach that will prevent the development of heart failure after MI is still questionable.

In the RICCADSA (Continuous Positive Airway Pressure [CPAP] Treatment in Coronary Artery Disease and Sleep Apnea) trial, patients with moderate or severe OSA (but with no daytime sleepiness) were randomized to CPAP or control after coronary revascularization, and followed up for a mean of 57 months. Interestingly, there was no change in CVD endpoints including repeat revascularization with the use of CPAP, although the subgroup using CPAP >4 h per night had a lower CV risk (HR: 0.29; 95% CI: 0.10–0.86).[24] In another study (ISAACC [Continuous Positive Airway Pressure (CPAP) in Patients with Acute Coronary Syndrome and Obstructive Sleep Apnea (OSA)] trial), patients with ACS and moderate or severe OSA, the use of CPAP did not decrease the primary composite end point of CVD events or death. The ISAACC trial did not show any relationship between the hours of CPAP use and outcomes, although median adherence to CPAP was low at 2.78 h per night. Nevertheless, CPAP users did have an improvement in hypertension control and daytime sleepiness, but not in the quality of life.[25]

CAN OSA BE BENEFICIAL IN PATIENTS WITH CAD: HOLY ALLIANCE?

Most of the studies in the literature have shown an adverse association between OSA on pathogenesis and outcomes in patients with CAD. However, others have discussed that intermittent hypoxemia may have protective effects on the heart because of ischemic preconditioning and the development of collateral vessels. Shah *et al*.[19] conducted a study among the entire cohort of acute MI patients; 77% had evidence of SDB, and 35% of them fulfilled the criteria OSA (AHI >5/h). Higher AHI was associated with lower peak troponin-T levels in partially adjusted models ($\beta = -0.0320$; $P = 0.0074$, adjusted for age, gender, and race) and fully adjusted models ($\beta = -0.0322$; $P = 0.0085$) (additionally adjusted for smoking, hypertension, hyperlipidemia, BMI, history of prior CV or cerebrovascular disease, diabetes, and baseline admission creatinine levels). The mean value of the log-transformed peak troponin-T variable was used to dichotomize the outcome variable. In both partially (OR: 0.949; CI: 0.905–0.995, $P = 0.03$) and fully adjusted (OR: 0.918, CI: 0.856–0.984, $P = 0.0151$) logistic regression models, the OR for AHI suggested a protective effect on high troponin-T levels. Thus the patients with OSA had a less severe cardiac injury during an acute non-fatal MI when compared to patients without OSA, suggesting a cardio-protective role of sleep apnea during acute MI via ischemic preconditioning. Sánchez-de-la-Torre studied 89 patients with ACS and OSA and 38 ACS patients without OSA with an AHI of a median of 32. The peak cardiac troponin I (cTnI) value was significantly higher in patients without OSA than those with OSA ($P = 0.04$). The multivariable linear regression analysis of the relationship between peak cTnI value and patient group, age, sex, and type of ACS showed that the presence of OSA significantly contributed to the peak cTnI level, which was 54% lower in patients with OSA than in those without OSA. Moreover, in the multivariable linear regression model that categorized patients based on OSA

severity, patients with severe OSA had 61% lower cTnI levels than patients without OSA.[20]

Ben Ahmed *et al*.[21] studied prospectively 71 patients with MI who underwent coronary angiography within 24 h of the onset of the index event. All patients underwent an overnight polygraph before discharge and were classified according to AHI. Coronary collaterals were scored by visual analyses and according to the Rentrop grading system. All patients had complete or subtotal occlusion of the infarct-related artery. Patients with OSA (AHI > 15/h) showed better collateral vessel development (Rentrop score ≥ 1) compared to non-OSA patients (68 vs. 41%, $P = 0.032$). In addition, AHI was significantly higher in patients with developed coronary collaterals (Rentrop ≥ 1) than those without collaterals (17.74 ± 13.2 vs. 12.24 ± 10.9, $P = 0.025$) and concluded that coronary collateral development might be enhanced in OSA patients who presented with a first MI.

CONCLUSIONS

Atherosclerotic CAD is a complex disease with multiple pathogenic mechanisms and pathways involved. OSA is also a complex condition that is highly prevalent but often under-recognized. CAD and OSA share common risk factors and pathophysiological pathways. OSA has numerous systemic manifestations which can influence the pathogenesis and prognosis of CAD. There is compelling data that the presence of OSA has an adverse relationship with the outcomes in patients with CAD. On the contrary, few authors report the beneficial effects of OSA in CAD through the promotion of inter-coronary collateral formation and subsequent ischemic preconditioning. Further focused research in the form of large randomized trials is needed in this field.

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Conflicts of interest
There are no conflicts of interest.

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