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ORIGINAL RESEARCH

Association of Obstructive Sleep Apnea and Nocturnal Hypoxemia With the Circadian Rhythm of Myocardial Infarction

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BACKGROUND: The circadian rhythm of myocardial infarction (MI) in patients with obstructive sleep apnea (OSA) remains disputable and no studies have directly evaluated the relationship between nocturnal hypoxemia and the circadian rhythm of MI. The aim of the current study was to evaluate the association of OSA and nocturnal hypoxemia with MI onset during the night.

METHODS: Patients with MI in the OSA-acute coronary syndrome (ACS) project (NCT03362385) were recruited. The time of MI onset was identified by patient's report of the chest pain that prompted hospital admission. All patients underwent an overnight sleep study using a type III portable sleep monitoring device after clinical stabilization during hospitalization. The difference in circadian variation of MI onset was evaluated between patients with moderate/severe OSA and non/mild OSA and those with or without nocturnal hypoxemia. Nocturnal hypoxemia was evaluated using 3 variables, including oxygen desaturation index, minimum oxygen saturation, and total sleep time with saturation <90%.

RESULTS: Among 713 patients enrolled, 398 (55.8%) had moderate/severe OSA (apnea-hypopnea index ≥15 events·h−1). Compared with the non/mild OSA group, the MI onset was significantly increased in the moderate/severe OSA group between midnight to 5:59 AM in 6-hour epochs analysis (26.9% versus 18.4%, *P*=0.008). Only in patients with both moderate/severe OSA and nocturnal hypoxemia, including oxygen desaturation index ≥15, minimum oxygen saturation ≤86%, and total sleep time with saturation <90% ≥2%, the incidence of MI onset between midnight to 5:59 AM was significantly increased. Moderate/severe OSA (adjusted odds ratio 1.66 [95% CI, 1.13–2.43]; *P*=0.01) and nocturnal hypoxemia (oxygen desaturation index ≥15 model, adjusted odds ratio 1.80, [95% CI, 1.21–2.66]; minimum oxygen saturation ≤86% model, adjusted odds ratio 1.70 [95% CI, 1.16–2.47]; *P*=0.006; total sleep time with saturation <90% ≥2% model, adjusted odds ratio 1.54 [95% CI, 1.04–2.27]; *P*=0.03) significantly predicted MI occurrence from midnight to 6:00 AM.

CONCLUSIONS: A peak of incident MI onset between midnight to 5:59 AM was observed in patients with moderate/severe OSA, especially in those presenting with nocturnal hypoxemia.

Key Words: circadian variation ■ myocardial infarction ■ nocturnal hypoxemia ■ obstructive sleep apnea

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CLINICAL PERSPECTIVE

What Is New?

- A peak in the onset of myocardial infarction was observed between midnight and 5:59 AM in patients with moderate/severe obstructive sleep apnea, particularly among those with nocturnal hypoxemia.
- Moderate/severe obstructive sleep apnea and nocturnal hypoxemia are associated with the occurrence of nocturnal myocardial infarction.

What Are the Clinical Implications?

- Whether continuous positive airway pressure therapy can prevent the nocturnal myocardial infarction onset and improve the prognosis of patients with obstructive sleep apnea and other hypoxemia-related conditions is of interest and warrants further investigation.

Nonstandard Abbreviations and Acronyms

AHI	apnea hypopnea index
minimum SaO_2	minimum oxygen saturation
ODI	oxygen desaturation index
TSA90	total sleep time with saturation <90%

Obstructive sleep apnea (OSA) is common (50%–66%) in patients with acute myocardial infarction (MI) and worsens clinical outcomes.[1–4] Repeated apnea in patients with OSA can lead to hypoxemia and hypercapnia, further contributing to sympathetic nerve, blood pressure, and glucose disorders.[5–7] OSA is also associated with oxidative stress, systemic inflammation, hypercoagulation, endothelial dysfunction, and metabolic disorders, all of which may increase the risk of MI.[8–12] Consequently, patients with OSA experience significant neurohumoral disturbances during sleep compared with those with normal sleep, suggesting that OSA may be a predisposing factor for the occurrence of nocturnal MI. However, the circadian rhythm of MI in patients with OSA remains disputable.[13–17]

Clinically, nocturnal hypoxia is independently associated with the prevalence of cardiovascular diseases.[18] Previous studies have demonstrated that nocturnal hypoxemia plays an important part in the progression of coronary atherosclerosis.[19,20] Currently, no studies have directly evaluated the relationship between nocturnal hypoxemia and the circadian rhythm of MI. Understanding how OSA and nocturnal hypoxia interact in relation to MI occurrence could help to clarify the attribution of mechanisms.

Therefore, in the present post-hoc analysis of the OSA-acute coronary syndrome (ACS) project, we investigate the association of OSA and nocturnal hypoxemia with MI onset during the night and evaluate whether nocturnal hypoxemia is a trigger for MI onset during the night. The nocturnal hypoxemia was evaluated by 3 primary independent variables, including oxygen desaturation index (ODI), the minimum oxygen saturation (minimum SaO_2) during sleep, and the percentage of total sleep time with saturation <90% (TSA90). We hypothesize that OSA and nocturnal hypoxemia may increase MI occurrence during the night.

METHODS

Study Design and Participants

The OSA-ACS project (NCT03362385) is a large-scale, prospective, observational study designed to investigate the relationship between OSA and cardiovascular outcomes among patients with ACS. The study design has been described previously.[4] From June 2015 to January 2020, patients with ACS aged 18 to 85 years admitted to Beijing Anzhen Hospital, Capital Medical University were enrolled and underwent overnight sleep studies. The exclusion criteria were as follows: cardiac arrest or cardiogenic shock, malignancy, and unsuccessful sleep studies (ie, inadequate and unsatisfactory recordings). Furthermore, patients with predominantly central sleep apnea (≥50% central events and a central apnea hypopnea index [AHI] ≥10/h), or those receiving regular continuous positive airway pressure therapy (>4 h/d and >21 days/mo) were excluded. In the present post-hoc analysis of the OSA-ACS project, we only included patients with clear time of MI onset. MI was defined as ischemic symptoms, persistent ST-segment elevation (≥1 mm), and an elevation of creatine-phosphokinase concentration >2 times the upper limit of normal, along with cardiac troponin T levels ≥0.1 ng/mL. The time of MI onset was determined by an individual patient's report of the chest pain that prompted hospital admission, which has been previously validated.[21] All the patients with an MI onset between midnight to 5:59 AM were asleep at the onset of the chest pain that led to their hospital admission. Hypercholesterolemia was defined as treatment with lipid-lowering agents such as statins, or a low-density lipoprotein cholesterol ≥70 mg/dL in individuals with clinical coronary artery disease.[22] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.[23,24] Diabetes was defined as treatment with hypoglycemic agents or insulin, or a fasting plasma glucose level ≥126 mg/dL.[25]

The protocol has been approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (2013025). All participants provided written

informed consent. The current study complied with the Declaration of Helsinki.

Sleep Study

For eligible patients with a hospital stay between 24 and 72 hours, an overnight sleep study was conducted using a type III portable cardiorespiratory polygraphy (Apnea Link Air, ResMed, Australia) after clinical stabilization, which has been previously validated.[26] Clinical stabilization was defined as follows[27,28]: stable cardiac function and hemodynamics, with no evidence of persistent ischemic symptoms or mechanical and electrical complications. The following signals were recorded: nasal airflow, thoracoabdominal movements, snoring episodes, heart rate, and pulse oximetry. Data from the portable diagnostic device were manually recorded by 2 sleep specialists who were blinded to the patient's clinical characteristics, in accordance with the American Academy of Sleep Medicine criteria (2007). Apnea was defined as the absence of airflow for 10 s or more. Hypopnea was defined as a reduction in airflow of at least 30% for ≥10 s, with a decrease in arterial oxygen saturation (SaO_2) >4%. AHI was calculated as the number of episodes of apnea followed by hypopnea per hour of recording.

The severity of nocturnal hypoxemia was assessed using 3 independent variables: ODI, minimum SaO_2, and TSA90, which had been validated in the previous study.[29] ODI was calculated as the amount of time when the oxygen saturation dropped by ≥4% from baseline, per hour of recording. Minimum SaO_2 during sleep was recorded by a pulse oximeter. The severity of hypoxemia was quantified with minimum SaO_2, and the duration of hypoxemia was calculated using TSA90. Patients with AHI <15 events/h were categorized into the non/mild OSA group, and those with AHI ≥15 events/h were categorized into the moderate/severe OSA group, which was consistent with the guidelines and previous studies.[3,4,13,15]

Analysis of Circadian Variation of MI Onset

To evaluate the circadian variation of MI onset, we divided the day into four 6-hour epochs (midnight to 5:59 AM, 6:00 AM to 11:59 AM, noon to 5:59 PM, and 6:00 PM to 11:59 PM). The circadian variation in MI onset was evaluated between patients with moderate/severe OSA and those with non/mild OSA. We also evaluated the effects of ODI, minimum SaO_2, and TSA90 on diurnal variations of MI in both non/mild OSA and moderate/severe OSA population.

Statistical Analysis

The current analysis primarily aimed to examine the association between OSA and circadian variation of MI. Based on previous published data, assuming a 18.0% prevalence of MI onset between midnight and 5:59 AM in the non/mild OSA group, compared with 30.0% in the moderate/severe OSA group,[13,16] we estimated that 522 patients would be required with 90% power. Data were compared using the Student *t* test or Mann–Whitney *U* test for continuous variables, expressed as mean±SD or median (interquartile range). Categorical variables were compared using Fisher exact test or χ^2 statistics, depending on their appropriateness. Intragroup comparisons were conducted to determine the odds ratio (OR) of having OSA in patients who experienced MI during each 6-hour interval compared with the remaining 18 hours of the day. The relationship between risk factors (including age, male, body mass index [BMI], current smoking, OSA severity, diabetes, hypercholesterolemia, and hypertension) and MI onset during the first quarter of the day was examined using univariate and multiple logistic regression analyses. To investigate the predictors of nocturnal hypoxemia for morning MI onset, patients were divided into subgroups based on median values of minimum SaO_2 (86%) and TSA90 (2.0%). The effects of nocturnal hypoxemia, including ODI ≥15, minimum SaO_2 ≤86%, and TSA90 ≥2% on the occurrence of nocturnal MI in both non/mild OSA and moderate/severe OSA population, were evaluated using logistic regression to estimate the ORs and robust SEs for the 95% CI. Both unadjusted and adjusted logistic regression models were applied to evaluate the effects of nocturnal hypoxemia on the occurrence of nocturnal MI in both OSA groups. Model covariates were selected based on clinical relevance or variables that showed a univariate relationship with MI onset. These included age, male, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension. We used multiple imputation, based on 5 replications and the Markov-chain Monte Carlo method in the SPSS, to account for 6 missing BMI values in logistic regression models. The results obtained from each completed-data analyses were pooled based on the Rubin rule. All analyses were conducted with SPSS V.26.0 (IBM SPSS, Armonk, NY). P <0.05 was considered statistically significant on a 2-sided basis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Baseline Characteristics

A total of 2130 patients were assessed for eligibility. Patients with unstable angina (n=1132), cardiogenic shock or cardiac arrest (n=14), malignancy (n=20), or failed sleep study (n=68) were excluded, of whom 896 patients received a successful sleep study. After

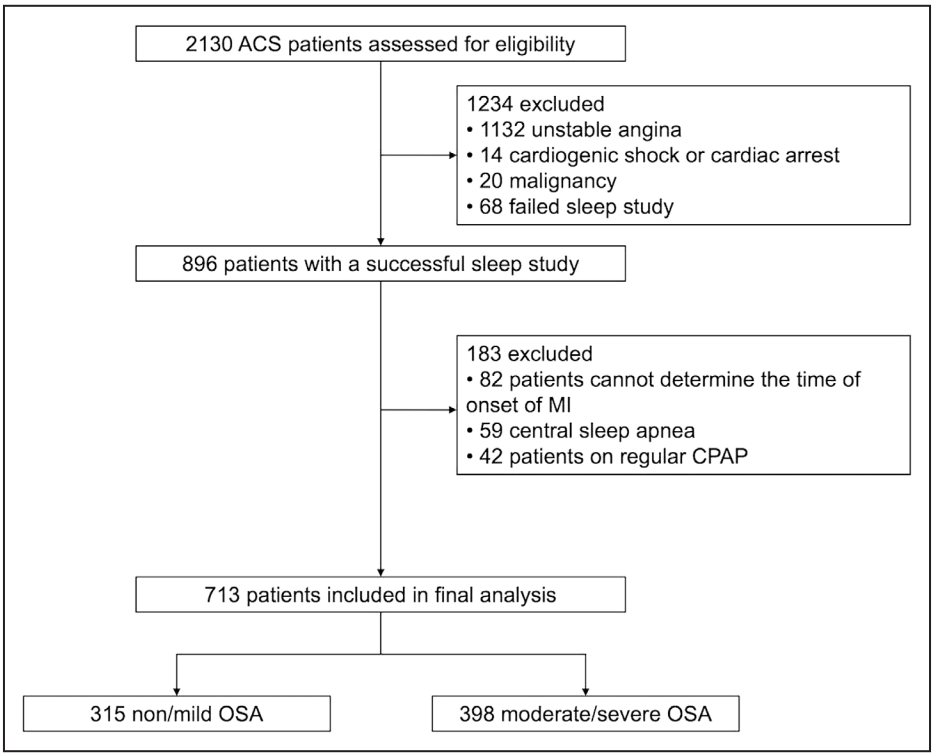

Figure 1. Study flow chart.
ACS indicates acute coronary syndrome; CPAP, continuous positive airway pressure; MI, myocardial infarction; and OSA, obstructive sleep apnea.

excluding patients with central sleep apnea (n=59), regular continuous positive airway pressure therapy (n=42), and those without clearly defined time of onset of MI (n=82), 713 patients were finally included with a mean age of 55.4±11.1 years. Of these, 630 (88.4%) were men and 398 (55.8%) had moderate/severe OSA (Figure 1). In the subgroup analyses, patients were further categorized into 4 groups based on the severity of OSA and the presence of nocturnal hypoxemia.

The proportion of men was higher in the moderate/severe OSA group compared with the non/mild OSA group (91.2% versus 84.8%, P <0.01). Patients with moderate/severe OSA had a larger neck circumference and were more likely to have hypertension, prior MI, prior percutaneous coronary intervention, and worse left ventricular function. There was no other significant difference between the 2 groups. Characteristics of the study population are described in Table 1.

Results of Sleep Study

The median AHI was 29.6 events/h in the moderate/severe OSA group, with 7.0 events/h in the non/mild OSA group. Patients with moderate/severe OSA showed significant lower minimum SaO_2 and higher Epworth Sleepiness Scale (ESS) score than those with non/mild OSA. The detailed findings are listed in Table 2.

Circadian Variation of MI Onset

The frequency of MI onset by a 24-hour period according to the severity of OSA is shown in Figure 2. All patients with non/mild OSA showed a circadian variation with a morning peak of MI onset between 6:00 AM and 11:59 AM, whereas in the moderate/severe OSA group, this morning peak of MI onset has been attenuated, primarily due to an increased risk of MI onset during bedtime (between midnight and 5:59 AM).

The incidence of MI onset between midnight and 5:59 AM was significantly higher in patients with moderate/severe OSA compared with those with non/mild OSA (26.9% versus 18.4%, P=0.008). Moreover, within the moderate/severe OSA group, patients with nocturnal hypoxemia (defined by ODI ≥15, minimum SaO_2 ≤86%, and TSA90 ≥2%) had a significantly higher incidence of MI onset between midnight and 5:59 AM (Figure 3).

Predictors for MI Nocturnal Onset

Univariate analysis showed that moderate/severe OSA, ODI ≥15, minimum SaO_2 ≤86%, and TSA90 ≥2% were associated with MI onset between midnight and 6:00 AM. Multivariate analysis adjusted for age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension showed that moderate/severe OSA was positively associated

Table 1. Baseline Patient Characteristics in the Moderate/Severe OSA Versus Non/Mild OSA Groups

Variables	All (n=713)	Moderate/severe OSA (n=398)	Non/mild OSA (n=315)	*P* value
Demographics				
Age, y	55.4±11.1	55.6±11.1	55.2±11.0	0.89
Male	630 (88.4)	363 (91.2)	267 (84.8)	<0.01
BMI, kg/m^2	26.8±3.7	27.7±3.5	25.8±3.5	0.40
SBP, mm Hg	123.4±17.2	123.6±17.5	123.3±16.9	0.64
DBP, mm Hg	74.8±12.2	75.3±12.2	74.2±12.1	0.65
Waist-to-hip ratio	0.98±0.54	0.99±0.05	0.97±0.05	0.21
Neck circumference, cm	40.4±3.5	41.3±3.4	39.4±3.3	<0.01
Medical history				
Diabetes	192 (26.9)	112 (28.1)	80 (25.4)	0.41
Hypertension	428 (60.0)	252 (63.3)	176 (55.9)	0.04
Hyperlipidemia	169 (23.7)	95 (23.9)	74 (23.5)	0.91
Family history of premature CAD	46 (6.5)	25 (6.3)	21 (6.7)	0.84
Previous stroke	62 (8.7)	39 (9.8)	23 (7.3)	0.24
Previous myocardial infarction	91 (12.8)	60 (15.1)	31 (9.8)	0.04
Previous PCI	90 (12.6)	63 (15.8)	27 (8.6)	<0.01
Previous CABG	5 (0.7)	3 (0.8)	2 (0.6)	0.99
Smoking				0.31
No	211 (29.6)	116 (29.1)	95 (30.2)	
Current	422 (59.2)	231 (58.0)	191 (60.6)	
Previous	80 (11.2)	51 (12.8)	29 (9.2)	
Alcohol consumption history	250 (35.1%)	151 (37.9%)	99 (31.4%)	0.07
Baseline tests				
Glucose, mmol/L	7.1±2.8	7.2±2.8	6.9±2.6	0.22
Peak hs-TnI (ng/mL)	7.9 (1.4–33.2)	9.9 (1.8–32.8)	5.0 (0.7–35.4)	0.06
Triglycerides (mg/dL)	1.9±1.6	2.0±1.9	1.8±1.1	0.63
Cholesterol (mg/dL)	4.5±1.1	4.4±1.1	4.5±1.1	0.29
LDL cholesterol (mg/dL)	2.8±0.9	2.8±0.9	2.8±0.9	0.35
LVEF (%)	57.0±8.1	56.5±7.9	57.5±8.4	<0.01
Procedures				
Coronary angiography	697 (97.8)	390 (98.0)	307 (97.5)	0.64
PCI	491 (68.9)	280 (70.4)	211 (67.0)	0.34
CABG	43 (6.0)	22 (5.5)	21 (6.7)	0.53
Diuretic prescription during hospitalization	74 (10.4)	46 (8.9)	28 (11.6)	0.25
Blood pressure at the time of sleep study				
SBP, mm Hg	122.6±14.4	125.0±13.8	122.0±15.4	0.98
DBP, mm Hg	71.8±10.0	73.0±9.3	69.8±10.9	0.13
Medications on discharge				
Aspirin	705 (98.9)	392 (98.5)	313 (99.4)	0.27
$P2Y_{12}$ inhibitors	698 (97.9)	390 (98.0)	308 (97.8)	0.85
β-blockers	587 (82.3)	332 (83.4)	255 (81.0)	0.39
ACEIs/ARBs	500 (70.1)	287 (72.1)	213 (67.6)	0.19
Statins	705 (98.9)	394 (99.0)	311 (98.7)	0.74

Data are presented as mean±SD, median (IQR), or n (%). ACEI indicates angiotensin-converting enzymes inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DBP, diastolic blood pressure; hs-TnI, high-sensitivity cardiac troponin I; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

Table 2. Results of Sleep Study

Variables	All (n=713)	Moderate/severe OSA (n=398)	Non/mild OSA (n=315)	*P* value
AHI, events/h	17.4 (7.90–32.7)	29.6 (21.7–44.4)	7.0 (4.0–10.4)	<0.001
ODI, events/h	17.3 (8.7–31.6)	28.8 (21.1–43.1)	8.2 (4.4–11.8)	<0.001
Minimum SaO_2, %	86 (81–89)	84 (78–87)	88 (85–90)	<0.001
Mean SaO_2, %	94 (93–95)	93 (92–94)	95 (94–95)	<0.001
Time with SaO_2<90%, %	2.0 (0.2–9.0)	5.0 (1.2–14.0)	0.3 (0.0–2.0)	<0.001
Epworth sleepiness scale	7.0 (4.0–11.0)	8.0 (5.0–12.0)	6.0 (3.0–10.0)	<0.001

Data are presented as median (IQR). AHI indicates apnea-hypopnea index; IQR, interquartile range; minimum SaO_2, minimum arterial oxygen saturation during sleep; ODI, oxygen desaturation index; and OSA, obstructive sleep apnea.

with MI occurrence between midnight and 6:00 AM (adjusted OR, 1.66 [95% CI, 1.13–2.43, *P*=0.01]). Nocturnal hypoxemia was also positively correlated with MI that occurred from midnight to 6:00 AM in the ODI model (adjusted OR, 1.80 [95% CI, 1.21–2.66]; *P*=0.003), minimum SaO_2 ≤86% model (adjusted OR, 1.70 [95% CI, 1.16–2.47]; *P*=0.006), and TSA90 ≥2% model (adjusted OR, 1.54 [95% CI, 1.04–2.27]; *P*=0.03) (Table 3). We also conducted multivariate analysis adjusted for age, male sex, BMI, current smoking, alcohol consumption history, diabetes, moderate/severe OSA, hypercholesterolemia, hypertension, and diuretic prescription during hospitalization (Table S1). After the adjustment for the nocturnal hypoxia markers, including ODI, minimum SaO_2, TSA90, and clinical characteristics, moderate/severe OSA was no longer associated with the incidence of MI onset between midnight and 5:59 AM, which indicated that the effect of OSA on circadian variation of MI onset was primarily driven by nocturnal hypoxemia (Table 4).

Subgroup Analyses of MI Nocturnal Onset

Subgroup analyses were conducted to evaluate the association between hypoxemia, OSA severity, and nocturnal MI onset. Only in patients with both moderate/severe OSA and nocturnal hypoxemia, including ODI ≥15, minimum SaO_2 ≤86%, and TSA90 ≥2%, the risk of MI onset from midnight to 6:00 AM was significantly increased (Figure 4).

DISCUSSION

The main findings of our study are as follows. In patients with non/mild OSA, the day–night pattern of MI onset followed a peak from 6:00 AM to noon, while moderate/severe OSA and nocturnal hypoxemia, including ODI ≥15, minimum SaO_2 ≤86%, and TSA90 ≥2%, significantly affected the circadian rhythm of MI, leading to an increased incidence of MI onset between midnight and 5:59 AM. Both moderate/severe OSA and nocturnal hypoxemia were main risk factors for MI onset between midnight and 5:59 AM. Moreover, patients with moderate/severe OSA with nocturnal hypoxemia were at higher risk of MI onset between midnight and 5:59 AM.

Although the relationship between OSA and MI was well documented, data on the circadian rhythm of MI in patients with OSA were limited and conflicting. Three previous studies reported a diurnal periodicity in MI onset, with a higher likelihood of MI occurring between 6:00 AM and noon in patients with OSA.[15–17] Patients in these 3 studies were prospectively collected, which was comparable to our study design. This discrepancy may be caused by the potential heterogeneity of the ACS phenotype. In these 3 studies, the definition of OSA was different from ours: with AHI ≥10 events/h as OSA compared with ours at AHI ≥15 events/h as moderate/severe OSA.[17] Furthermore, the severity of nocturnal hypoxemia was more pronounced in our study. The minimum SaO_2 in our study was lower compared with the other study (84% versus 86%),[15] which indicated the OSA population in our study was more significantly affected by nocturnal hypoxia. Finally, study races, sample size, and medication use may also explain these differences. In contrast, Kuniyoshi et al. and Wang et al. observed a peak in MI onset between midnight and 6:00 AM in the OSA population,[13,14] which aligns with our findings. However, none of the previous studies evaluated the impact of nocturnal hypoxemia on the circadian rhythm of MI onset.

Circadian rhythm is also closely related to the prognosis of MI.[30,31] Henriques et al. found that MI occurring between 6:00 PM and 8:00 AM had a higher 30-day mortality than MI occurring between 8:00 AM and 6:00 PM.[32] Nakashima et al. found that patients with MI during 6:00 AM to 11:59 AM had a higher recurrence rate of ACS than patients with MI at other times.[30] This phenomenon can be attributed to changes in sympathetic activity, electrophysiological abnormalities, baroreflex sensitivity, and platelet aggregability when waking up in the morning.[33–37] In the current study, all the participants underwent successful overnight sleep monitoring between 24 and 72 hours after clinical stabilization. While some studies have raised concerns about the timing and reproducibility of sleep monitoring,[38] such

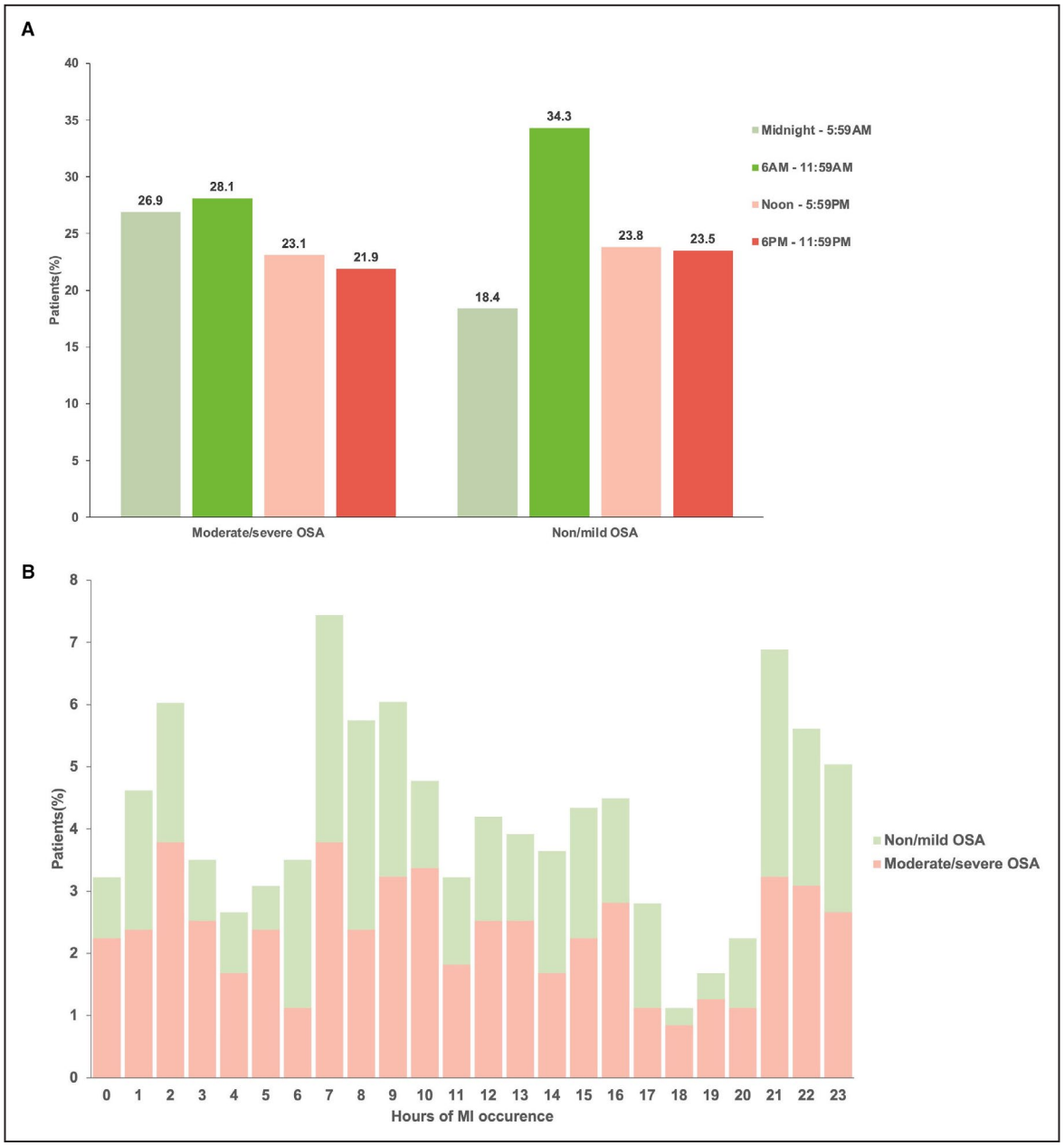

Figure 2. Distribution of MI occurrence according to the severity of OSA.
A, Distribution of MI occurrence by the four 6-h intervals according to the severity of OSA; (**B**) Distribution of MI occurrence by the 24-h period according to the severity of OSA. ACS indicates acute coronary syndrome; MI, myocardial infarction; and OSA, obstructive sleep apnea.

assessments are valid and feasible for OSA assessment in the context of high-risk acute conditions, including heart failure.[39] Buchner et al. reported a statistically nonsignificant reduction in sleep apnea prevalence at the 12-week reassessment after MI.[38] Their definition of moderate/severe OSA was AHI ≥15 events/h^{-1}, which was in consistent with our study. In other words, while the severity of OSA may be slightly overestimated in the early stage, it would not affect the recognition of moderate/severe OSA using the AHI ≥15 threshold. Given the lack of within-participant reproducibility data, the findings of this study should be interpreted with caution and validated in future research. The drugs that overestimated the severity of hypoxemia, including sedatives, analgesics, and anesthetics,[40] were not used in the current cohort.

Our data suggested that nocturnal hypoxemia may be a key risk factor for MI onset between midnight and 5:59 AM. OSA induced nocturnal hypoxemia, and the consequent nocturnal MI onset is associated with multiple critical mediators. This biological mechanism can be understood as a long-term chronic process

compounded by acute exacerbation. Previous studies revealed that patients with moderate/severe OSA had a larger total atheroma volume and a greater proportion of noncalcified plaque component.[41,42] Along with moderate/severe OSA, hypoxemia may further increase atherosclerotic plaque loads and plaque vulnerability.[20] As plaque progresses and vulnerable plaques form, multiple mediators induced by hypoxemia contribute to MI onset. The increased production of reactive oxygen species was triggered by hypoxemia, which

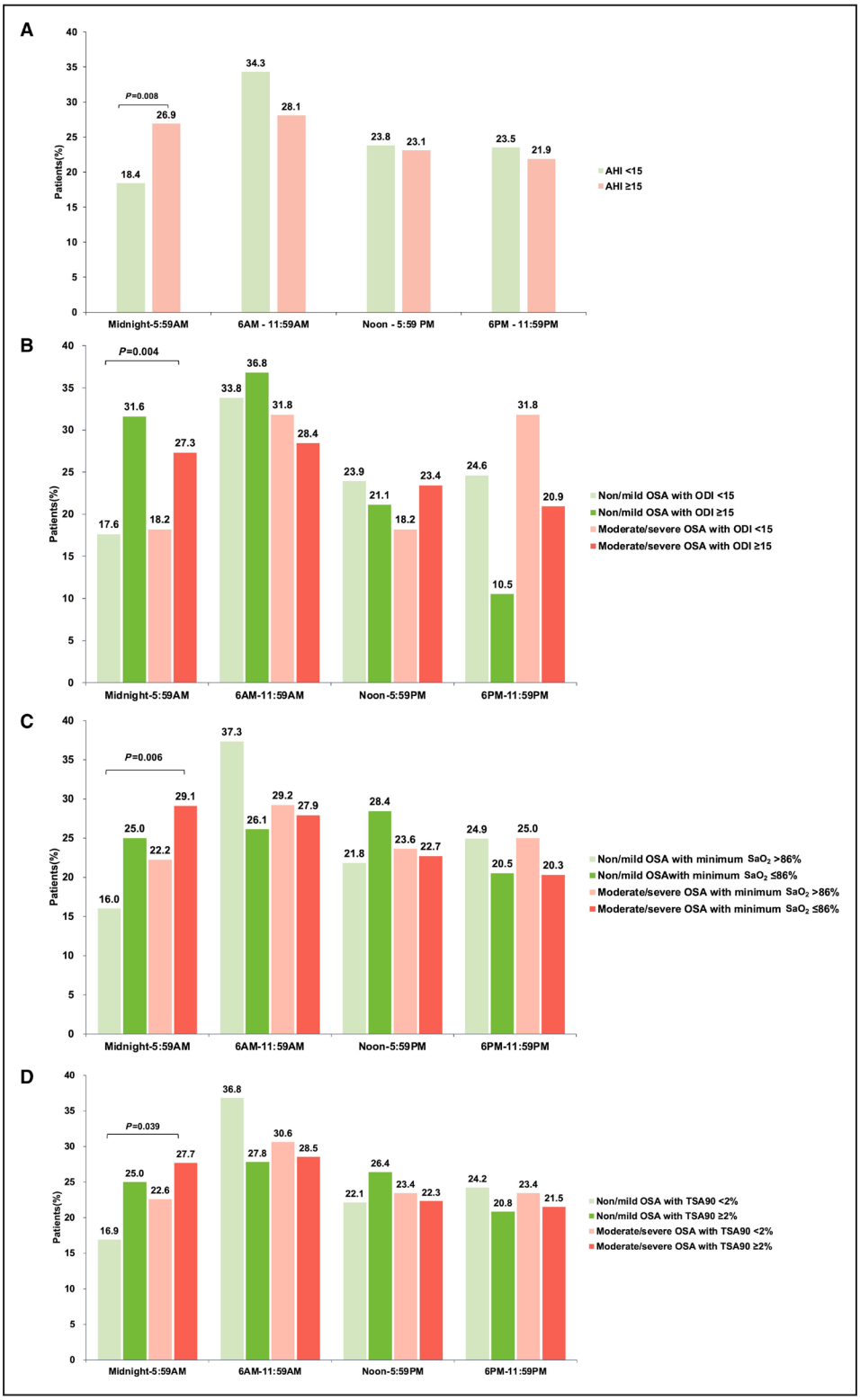

Figure 3. Circadian variations in the frequency of MI onset based on 6-h intervals.
A, Day–night pattern of MI based on 4 6-h time intervals in non/mild OSA (n=315) and moderate/severe OSA (n=398) patients; (**B**) Day–night pattern of MI based on 4 6-h time intervals in non/mild OSA with ODI<15 (n=284), non/mild OSA with ODI ≥15 (n=19), moderate/severe OSA with ODI<15 (n=22), and moderate/severe OSA with ODI ≥15 (n=359) patients; (**C**) Day–night pattern of MI based on 4 6-h time intervals in non/mild OSA with minimum SaO_2>86% (n=225), non/mild OSA with minimum SaO_2≤86% (n=88), moderate/severe OSA with minimum SaO_2>86% (n=144), and moderate/severe OSA with minimum SaO_2≤86% (n=251) patients; (**D**) Day–night pattern of MI based on 4 6-h time intervals in non/mild OSA with TSA90<2% (n=231), non/mild OSA with TSA90≥2% (n=72), moderate/severe OSA with TSA90<2% (n=124), and moderate/severe OSA with TSA90≥2% (n=242) patients. MI indicates myocardial infarction; minimum SaO_2, minimum oxygen saturation during sleep; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; and TSA90, percentage of total sleep time with saturation<90%.

promoted the vascular inflammation and led to endothelial dysfunction.[3] Hypercapnia elicited by hypoxemia stimulated chemoreflex stimulation, which resulted in sympathetic nerve activation and the secretion of serum catecholamines.[43,44] Nocturnal hypoxemia may also activate the sympathetic nerve, leading to surges

Table 3. Predictors for Nocturnal Onset in MI (Midnight to 6:00 AM)

Variables	Unadjusted OR	*P* value	Adjusted OR*	*P* value
AHI model				
AHI ≥15.0	1.63 (1.14–2.34)	0.008	1.66 (1.13–2.43)	0.01
Age	1.01 (0.99–1.02)	0.37	1.01 (0.99–1.02)	0.55
Male	0.94 (0.55–1.61)	0.83	0.86 (0.48–1.57)	0.62
BMI	1.01 (0.96–1.06)	0.82	0.99 (0.94–1.05)	0.74
Current smoking	1.18 (0.82–1.68)	0.38	1.33 (0.89–1.99)	0.17
Hypertension	1.40 (0.97–2.01)	0.07	1.39 (0.95–2.02)	0.09
Diabetes	1.29 (0.88–1.89)	0.19	1.25 (0.85–1.86)	0.26
Dyslipidemia	0.75 (0.49–1.16)	0.20	0.70 (0.45–1.09)	0.12
ODI model				
ODI ≥15.0	1.63 (1.14–2.34)	0.008	1.80 (1.21–2.66)	0.003
Age	1.01 (0.99–1.02)	0.37	1.01 (0.99–1.03)	0.51
Male	0.94 (0.55–1.61)	0.83	0.82 (0.44–1.50)	0.51
BMI	1.01 (0.96–1.06)	0.82	0.99 (0.93–1.04)	0.61
Current smoking	1.18 (0.82–1.68)	0.38	1.38 (0.90–2.10)	0.13
Hypertension	1.40 (0.97–2.01)	0.07	1.44 (0.98–2.12)	0.06
Diabetes	1.29 (0.88–1.89)	0.19	1.21 (0.81–1.81)	0.36
Dyslipidemia	0.75 (0.49–1.16)	0.20	0.73 (0.46–1.14)	0.17
Minimum SaO_2 model				
Minimum SaO_2 ≤86%	1.63 (1.14–2.34)	0.003	1.70 (1.16–2.47)	0.006
Age	1.01 (0.99–1.02)	0.37	1.01 (0.99–1.03)	0.47
Male	0.94 (0.55–1.61)	0.83	0.96 (0.52–1.75)	0.88
BMI	1.01 (0.96–1.06)	0.82	0.99 (0.94–1.04)	0.63
Current smoking	1.18 (0.82–1.68)	0.38	1.28 (0.85–1.91)	0.24
Hypertension	1.40 (0.97–2.01)	0.07	1.36 (0.93–1.99)	0.11
Diabetes	1.29 (0.88–1.89)	0.19	1.20 (0.81–1.79)	0.36
Dyslipidemia	0.75 (0.49–1.16)	0.20	0.71 (0.45–1.10)	0.13
TSA90 model				
TSA90≥2%	1.63 (1.14–2.34)	0.013	1.54 (1.04–2.27)	0.03
Age	1.01 (0.99–1.02)	0.37	1.00 (0.99–1.02)	0.65
Male	0.94 (0.55–1.61)	0.83	1.18 (0.61–2.29)	0.62
BMI	1.01 (0.96–1.06)	0.82	0.99 (0.94–1.05)	0.80
Current smoking	1.18 (0.82–1.68)	0.38	1.30 (0.85–1.98)	0.22
Hypertension	1.40 (0.97–2.01)	0.07	1.39 (0.94–2.05)	0.09
Diabetes	1.29 (0.88–1.89)	0.19	1.20 (0.80–1.81)	0.38
Dyslipidemia	0.75 (0.49–1.16)	0.20	0.70 (0.43–1.10)	0.12

AHI indicates apnea-hypopnea index; BMI, body mass index; OR, odds ratio; minimum SaO_2, minimum arterial oxygen saturation during sleep; ODI, oxygen desaturation index; and TSA90, total sleep time with saturation <90%.
*Adjusted for age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension.

Table 4. Interrelationship Between the Effects of OSA and Nocturnal Hypoxemia on MI Incidence From Midnight to 5:59 AM

Variables	Unadjusted OR	*P* value	Adjusted OR	*P* value
AHI model 1	1.63 (1.14–2.34)	0.008	0.98 (0.44–2.19)	0.97
AHI model 2	1.63 (1.14–2.34)	0.008	1.44 (0.96–2.15)	0.08
AHI model 3	1.63 (1.14–2.34)	0.008	1.33 (0.87–2.03)	0.20
ODI ≥15.0	1.01 (0.99–1.02)	0.37	1.82 (0.82–4.04)	0.14
Minimum SaO_2 ≤86%	1.06 (0.62–1.82)	0.83	1.53 (1.03–2.26)	0.03
TSA90≥2%	1.01 (0.96–1.06)	0.82	1.40 (0.92–2.13)	0.12

In AHI model 1, the OR value was adjusted for ODI ≥15.0, age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension. In AHI model 2, the OR value was adjusted for minimum SaO_2 ≤86%, age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension. In AHI model 3, the OR value was adjusted for TSA90≥2%, age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension. In ODI ≥15.0, minimum SaO_2 ≤86%, and TSA90≥2% models, the OR value was adjusted for AHI ≥15.0, age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension. AHI indicates apnea-hypopnea index; BMI, body mass index; MI, myocardial infarction; minimum SaO_2, minimum arterial oxygen saturation during sleep; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; and TSA90, total sleep time with saturation <90%.

in blood pressure and increased myocardial oxygen demand, which may ultimately result in MI.[5] Individuals with nocturnal hypoxemia experienced a paradoxical elevation in coagulability during bedtime, with platelet aggregation and plasma inhibition of fibrinolysis.[43,45] All these elements create a prothrombotic state and lead to a higher frequency of nocturnal MI onset. Our findings highlight the importance of diagnosing nocturnal hypoxemia in individuals at high risk of MI, especially in patients with OSA. However, given the complexity of the relationship between OSA and nocturnal MI onset, which cannot be fully explained by a direct acute trigger of hypoxemia, detailed analyses on MI triggers are needed to provide a deeper insight into the role of OSA in nocturnal MI onset. Furthermore, given the exploratory nature of the analysis of nocturnal hypoxia phenotypes, we did not adopt adjustments for multiple comparisons. We acknowledge that this approach increases the likelihood of false-positive results due to the inclusion of 3 nocturnal hypoxia parameters and relevant multiple grouping. Therefore, the result of the current study should be interpreted with caution and validated in future sufficiently sample-size powered studies.

Aside from hypoxemia, sleep fragmentation is a significant aspect of OSA that can exacerbate cardiovascular outcomes.[3] Sleep fragmentation caused by OSA may lead to higher risk of hypertension, diabetes, metabolic syndrome, cognitive dysfunction, and stroke,[46–50] which may result in cardiovascular events. However, one study showed that nocturnal hypoxemia, rather than sleep fragmentation, was independently

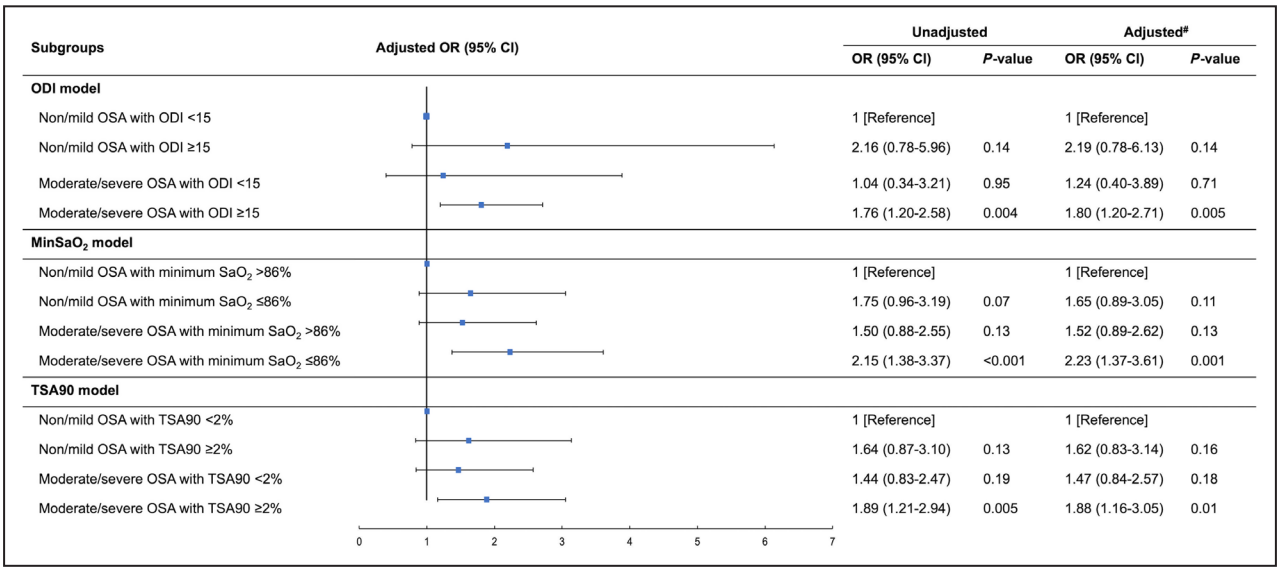

Figure 4. Incidence of nocturnal MI onset (midnight to 6:00 AM) stratified by OSA and hypoxemia.
Squares represent the ORs for each individual subgroup analysis, and horizontal lines represent the 95% CI. BMI indicates body mass index; MI, myocardial infarction; $MinSaO_2$, minimum oxygen saturation during sleep; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; and TSA90, percentage of total sleep time with saturation<90%. #Adjusted for age, male sex, BMI, current smoking, diabetes, moderate/severe OSA, hypercholesterolemia, and hypertension.

associated with both all-cause and cardiac mortality.[51] Importantly, there were potential interactions between nocturnal hypoxemia and repetitive arousals. Both play a critical role in MI onset during the night. Cyclic oxygen desaturations during bedtime lead to sustained sympathetic nervous system activation, elevated blood pressure, vasoconstriction, and disruption of sleep stages, including less deep sleep.[52] Since the current study did not evaluate the effect of sleep fragmentation on MI circadian rhythm, future research in this area is needed.

Our study suggested that both moderate/severe OSA and nocturnal hypoxemia were risk factors for nocturnal MI onset. Potential interventions including continuous positive airway pressure should be provided to those high-risk coronary artery disease populations with both moderate/severe OSA and nocturnal hypoxemia.[53] Whether continuous positive airway pressure therapy can prevent the nocturnal MI onset and improve the prognosis of patients with OSA and other hypoxemia-related conditions is of interest and warrants further investigation.

Limitations

First, the difficulty in accurately diagnosing and timing the onset of MI may have influenced the analysis of circadian variation. In the current study, we mainly used the patient's self-report of the chest pain that prompted hospital admission, which has been proved feasible in previous studies.[13] Second, the diagnosis of OSA based on portable sleep monitors may introduce potential biases and could underestimate the severity of OSA. Third, we classified patients into non/mild OSA and moderate/severe OSA using a threshold of AHI ≥15. This grouping strategy might overlook nuanced differences within the severity spectrum of OSA. Fourth, the sleep monitoring was conducted within 24 to 72 hours after admission, although OSA severity may be overestimated during the acute setting of MI; this is true for OSA assessment in the setting of any high-risk acute disease including heart failure. Fifth, we did not record the type of MI, which limits our ability to explore the mechanisms of nocturnal hypoxemia on MI onset during the night. Sixth, we did not investigate the association of hypoxic burden and the nocturnal onset of MI. Seventh, we did not collect relevant data on specific triggers of MI onset. Future studies on the direct cause for nocturnal MI onset are needed. Eighth, our study was limited by the lack of interobserver variability data. Finally, as a post-hoc analysis, this study has inherent defects of observational research. Although multiple adjustments for demographic and clinical characteristics were adopted in analysis, residual confounding and unmeasured confounding would remain. The analyses were exploratory and need to be validated in future sufficiently sample-size powered studies.

CONCLUSIONS

In summary, a peak in the onset of MI was observed between midnight and 5:59 AM in patients with moderate/severe OSA, particularly among those with nocturnal hypoxemia. Moreover, moderate/severe OSA and nocturnal hypoxemia are associated with the occurrence of nocturnal MI.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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