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Circadian rhythm and clinical characteristics in patients with acute myocardial infarction combined with obstructive sleep apnea

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Abstract

Objective: The present study aimed to investigate the circadian rhythm and clinical characteristics of patients with acute myocardial infarction (AMI) combined with obstructive sleep apnea (OSA).

Methods: Patients with AMI combined with OSA were enrolled in the study, and those that met the inclusion criteria were divided into three time-period groups based on their sleep–wake rhythm (22:00–5:59, 6:00–13:59, and 14:00–21:59). The differences between the three groups of patients in sleep-monitoring data, blood routine, biochemical indicators, and coronary angiographic parameters were analyzed and compared. Count data were expressed as the number of cases, and the chi-square test was used for statistical analysis. Continuous data were expressed as mean ± standard deviation, and analysis of variance was used for the statistical analysis of these data. The characteristics of circadian rhythm and clinical features in patients with AMI combined with OSA were analyzed.

Results: Of the 148 patients, 90/148 (61%) had chest pain and 58/148 (39%) had non-chest pain symptoms. In the 22:00–05:59 group, there were 70/148 (47%) patients with AMI (of these, 46/70 [66%] had chest pain). In the 06:00–13:59 period group, there were 44/148 (30%) patients with AMI (of these, 26/44 [60%] had chest pain). In the 14:00–21:59 period group, there were 34/148 (23%) patients with AMI (of these, 17/34 [50%] had chest pain). There was no statistically significant difference in the apnea–hypopnea index (AHI) and SYNTAX score between patients in the 22:00–5:59 and 6:00–13:59 groups. However, the AHI and SYNTAX scores in the 22:00–5:59 and 6:00–13:59 groups were higher than those in the 14:00–21:59 group, and the differences were statistically significant. In patients in the 22:00–5:59 group, the levels of serum D-dimer (DD), hemoglobin (Hb), and oxygen desaturation index (ODI3) were higher, the sleep mean oxygen saturation ($MeanSaO_2$) was lower and the percentage of nighttime spent with oxygen saturation of less than 90% ($Tsat_{90}$) and less than 85% ($Tsat_{85}$) was longer.

Fang Zhao and Xiaoyun Zhao authors contributed equally to this study.

Conclusion: The peak period for the onset of AMI in patients with OSA was 22:00–5:59, and the incidence of chest pain was high. During this period, patients had higher DD and Hb, higher ODI3, lower MeanSaO_2 during sleep, and longer $TSat_{90}$ and $TSat_{85}$. During the 22:00–5:59 and 6:00–13:59 periods, patients had higher AHI and a higher SYNTAX score.

KEYWORDS
acute myocardial infarction, chest pain, circadian rhythm, coronary angiography, obstructive sleep apnea, portable sleep monitoring

1 | INTRODUCTION

Acute myocardial infarction (AMI) has an abrupt onset, and early prevention, detection, and treatment are of the utmost importance. Among the many factors causing AMI, obstructive sleep apnea (OSA) has received considerable attention in recent years as one of the risks for coronary heart disease (CHD; Javaheri et al., 2017) and as an important modifiable risk factor (Khayat & Pleister, 2016). In the present study, the relationship between the circadian rhythm of the onset of myocardial infarction and OSA in patients with AMI combined with OSA was investigated with the aim of providing early prevention and treatment for these patients.

2 | SUBJECTS AND METHODS

2.1 | Inclusion criteria

: (1) patients with the first onset of AMI; (2) patients who had undergone percutaneous coronary intervention (PCI); and (3) patients with AMI combined with OSA. Exclusion criteria: (1) patients known to have OSA and have been treated for it; (2) patients with moderate or severe pulmonary disease (including bronchiectasis, chronic obstructive pulmonary disease, pleural effusion, pulmonary embolism, and pulmonary infection); (3) patients with tracheal intubation and mechanical ventilation; (4) patients with shock and those using hemodynamic assist devices; and (5) patients with other diseases, such as a history of a recent stroke or central sleep apnea, that seriously affect their quality of life.

2.2 | Study subjects

For this study, 148 patients with AMI who were admitted to Tianjin Chest Hospital between September 2017 and December 2018 with symptoms of chest pain and who met the study criteria were selected. The diagnosis of ST-segment elevation myocardial infarction (STEMI) was in accordance with the Chinese 2015 guidelines for the diagnosis and treatment of acute STEMI (Chinese Medical Association, Cardiovascular Disease Branch, 2015), and the diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) was in accordance with the 2016 guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes (Chinese Medical Association, Cardiovascular Disease Branch, 2017). There were 90 AMI patients with chest pain and 58 AMI cases without chest pain. The diagnosis of OSA in patients was determined according to the criteria of the Chinese 2011 "Guidelines for the diagnosis and treatment of sleep apnea hypopnea syndrome" (Sleep Apnea Group of the Chinese Medical Association Respiratory Diseases Branch, 2012). Obstructive sleep apnea–hypopnea syndrome (OSAHS) was graded according to AHI: no OSAHS (AHI < 5 times/h); mild OSAHS (5 ≤ AHI < 15 times/h); moderate to severe OSAHS (AHI ≥ 15 times/h). Sleep monitoring was conducted in patients with Class III portable sleep-monitoring devices, which recorded respiratory airflow, respiratory movement, and arterial oxygen saturation, within 7 days of admission, and none of them were administered with sedatives or muscle relaxants. General patient information was recorded, and patients and their family members signed an informed consent agreement.

2.3 | Methods

2.3.1 | Coronary angiography and PCI

All patients underwent coronary angiography, and antiplatelet and anticoagulant drugs were routinely applied during the peri-operative period. The culprit vessels were determined based on the results of coronary angiography and electrocardiogram manifestations, and thus, PCI was conducted. SYNTAX scoring system: The SYNTAX integral was calculated using a SYNTAX score II program. The algorithm contained 12 problems. The first three problems were the dominant coronary artery type, the number of lesions, and the number of vascular segments with lesions. The maximum number of lesions was 12, and each lesion was nominated as 1, 2, 3, and so on. Each lesion might be involved in one or more segments. The scores for each lesion were calculated by the number of segments they were involved in. The last nine questions were on the dysplastic features of the lesion, and the points for each lesion were derived from the dysplastic features. The SYNTAX integral was the summary of each lesion integral.

TABLE 1 Analysis of basic information

	Inclusion of patients ($n = 148$)	22:00 p.m.–5:59 a.m. $n = 70$ (47%)	6:00 a.m.–13:59 p.m. $n = 44$ (30%)	14:00 p.m.–21:59 p.m. $n = 34$ (23%)	F	p
Age (years)	56.89 ± 10.12	59.60 ± 10.88	59.72 ± 9.74	55.77 ± 10.41	1.007	.370
Gender (M/F)	90/58	41/29	28/16	21/13	chi-square 0.308	.857
BMI	19.21 ± 4.11	29.83 ± 3.98	29.26 ± 5.44	28.78 ± 5.19	0.230	.795
Neck circumference	43.23 ± 3.83	44.21 ± 3.94	42.59 ± 3.06	42.44 ± 3.36	1.958	.148
Waist circumference	107.34 ± 14.98	111.52 ± 17.40	106.70 ± 15.79	102.94 ± 11.80	1.591	.210
History of smoking		25	15	7	chi-square 2.573	.276
History of hypertension		33	26	18	chi-square 1.560	.458
History of diabetes		21	10	12	chi-square 1.527	.466

2.3.2 | Collection of data concerning sleep monitoring and grouping

All patients underwent sleep breathing monitoring within 7 days of admission using a portable sleep-monitoring system (ApneaLink Air). The parameters collected included the following: the apnea–hypopnea index (AHI), sleep mean oxygen saturation ($MeanSaO_2$), sleep minimum oxygen saturation ($LowestSaO_2$), minimum oxygen desaturation (Lowest desaturation), the oxygen desaturation index (ODI3), the percentage of nighttime spent with oxygen saturation of <90%, 85%, and 80% ($TSat_{90}$, $TSat_{85}$, $TSat_{80}$), the number of apneas, and the amount of hypopnea. Hypopnea was defined as follows: (1) the peak signal excursions drop by ≥30% of the pre-event baseline as detected by a nasal pressure transducer; (2) the duration of the ≥30% drop in the signal excursion is ≥10 s; and (3) the oxygen desaturation is ≥3% of the pre-event baseline. The AHI was the sum of the number of apneas and the amount of hypopnea per hour of sleep. The ODI_3 was defined as the number of hourly oxygen saturation levels decreasing by 3% from baseline.

2.3.3 | Baseline characteristics

The admission diagnosis, body mass index (BMI), neck circumference, history of smoking, history of alcohol consumption, previous medical history, and the number of diseased vessels were recorded for all the enrolled patients. The following indicators were detected through the collection of blood samples from the elbow vein under fasting conditions in the early morning after admission: routine blood tests (white blood cells, red blood cells, platelets, and hemoglobin [Hb]), lipid profiles (total cholesterol, triglycerides [TG], and low-density lipoprotein cholesterol [LDL-C]), and renal-function indicators (blood urea nitrogen [BUN] and serum creatinine [Scr]). The time of chest pain is recorded as the change in electrocardiogram at admission.

2.4 | Statistical analysis

Count data were expressed as the number of cases, and the chi-square test was used for statistical analysis. Continuous data were expressed as mean ± standard deviation, and analysis of variance was used for statistical analysis.

3 | RESULTS

The circadian rhythms were grouped according to the usual sleep–wake cycle (three time periods): 22:00–5:59, 6:00–13:59, and 14:00–21:59.

3.1 | Analysis of the general characteristics

There was no statistically significant difference in gender, age, BMI, neck circumference, or waist circumference between the patients in the three groups (Table 1).

There was no statistically significant difference in the incidence of hypertension and diabetes mellitus between the patients in the three groups. There was also no statistically significant difference in the TG, LDL-C, and creatinine clearance rate.

The levels of serum DD and Hb were higher in patients in the 22:00–05:59 group.

3.2 | Data concerning the period of the onset of chest pain

During the 22:00–05:59 period, there were 70/148 (47%) patients with AMI (of these, 46/70 [66%] had chest pain); during the 06:00–13:59 period, there were 44/148 (30%) patients with AMI (of these, 26/44 [60%] had chest pain); and during the 14:00–21:59 period,

there were 34/148 (23%) patients with AMI (of these, 17/34 [50%] had chest pain) (Table 2).

The incidence of AMI was high during the 22:00–05:59 period throughout the day, and the percentage relating to the incidence of chest pain was also higher.

3.3 | Analysis of the data concerning sleep monitoring

There was no statistically significant difference in the AHI between patients in the 22:00–05:59 and 06:00–13:59 periods, but the AHI in these two groups was higher than that in the 14:00–21:59 group, and the differences were statistically significant (Table 3).

In patients in the 22:00–05:59 group, the ODI3 was higher, the MeanSO_2 was lower, and the $TSat_{90}$ and $TSat_{85}$ were longer than those in patients in the other groups, and the differences were statistically significant.

3.4 | Analysis of the data concerning coronary angiography

There was no statistically significant difference in the SYNTAX score between patients in the 22:00–5:59 and 6:00–13:59 groups, but the SYNTAX score in these two groups was higher than that of the 14:00–21:59 group, and the differences were statistically significant (Table 4).

4 | DISCUSSION

Obstructive sleep apnea–hypopnea syndrome is the most common sleep-disordered breathing disorder caused by repeated collapse and obstruction of the upper airway during sleep. It may induce apnea and hypopnea, which in turn leads to the frequent occurrence of hypoxemia and hypercapnia, hyperemia, significant fluctuations in intrathoracic pressure, disturbed sleep structure, and increased sympathetic nerve activity. It may also lead to cardio-cerebrovascular complications and multi-system organ damage, which seriously affects the quality of life and life of patients.

The most common and main symptom of myocardial infarction is chest pain. Continuous strong ischemia of the myocardium causes myocardial damage or necrosis, and releases a large amount of lactic acid and mediators that cause pain, thus leading to the occurrence of chest pain. It has been shown that hypoxia has a higher predictive value for cardiovascular disease in patients with OSA than AHI per se (Li & Li, 2019). OSAHS induced long-term severe hypoxemia during nocturnal sleep, resulting in endothelial damage, abnormal changes in hemodynamics and neurohormones will increase the risk of myocardial ischemic events, which is very likely to be the predisposing factor for AMI.

In this study, by investigating the relationship between the onset and the circadian rhythm and clinical characteristics of patients with AMI and OSA, it was found that the incidence of AMI was significantly higher during the 22:00–05:59 period, and the incidence of chest pain was also higher. Patients in the 22:00–05:59 and 06:00–13:59 groups had higher AHI and higher coronary SYNTAX scores than those in the 14:00–21:59 group. Patients in the 22:00–05:59 group were more hypoxic, At the same time, it was confirmed that nearly half the patients with AMI have combined moderate/severe OSA, and the coronary artery lesions are more severe in patients when combined with moderate/severe OSA in AMI (Zhou et al., 2018). The occurrence mechanism of the above phenomena is first correlated with repeated intermittent hypoxia-mediated sympathetic excitation, inflammatory response, and oxidative stress during the night in patients with OSA (Shahar et al., 2001). Sympathetic activation increases the production of reactive oxygen species, initiates oxidative stress in cardiovascular endothelial cells, induces the release of inflammatory factors, and directly damages the vascular endothelial cells (Epstein et al., 2010), leading to impaired endothelium-dependent vasodilatory function and an enhanced vasoconstrictor response. Second, long-term

TABLE 2 Blood chemistry in patients with AMI combined with OSA at different periods

	22:00–5:59	6:00–13:59	14:00–21:59		
	n = 70 (47%)	*n* = 44 (30%)	*n* = 34 (23%)	*F*	*p*
Thrombolytic D-dimer (DD)	2.32 ± 2.78	0.63 ± 1.06	0.32 ± 0.09	3.225	.036*
Hemoglobin (Hb g/L)	153.69 ± 13.82	135.24 ± 30.65	140.66 ± 16.83	3.867	.022*
Platelet (Plt)	276.86 ± 130.46	242.56 ± 62.64	234.94 ± 78.79	1.368	.211
Triglyceride (TG)	1.63 ± 0.81	1.99 ± 0.84	1.84 ± 0.83	1.322	.295
Cholesterol (CHO)	4.51 ± 1.25	4.29 ± 0.85	4.48 ± 0.90	0.386	.698
Low-density lipoprotein (LDL)	3.19 ± 1.05	2.89 ± 0.69	3.25 ± 0.78	1.497	.198
Urea nitrogen (BUN)	5.98 ± 1.88	7.67 ± 7.69	5.54 ± 1.22	1.543	.241
Creatinine (Cr)	93.91 ± 20.63	122.97 ± 110.01	85.38 ± 27.29	2.433	.112
Creatinine clearance rate (Scr)	88.96 ± 27.97	82.73 ± 28.39	85.04 ± 37.21	0.296	.767

*$p < 0.05$, Statistically significant.

TABLE 3 Data indicators in sleep monitoring in patients with AMI combined with OSA at different periods

	22:00–5:59	6:00–13:59	14:00–21:59		
	n = 70 (47%)	*n* = 44 (30%)	*n* = 34 (23%)	*F*	*p*
AHI	44.05 ± 14.94	38.54 ± 19.84	25.12 ± 19.77	5.494	.008*
OAI	19.90 ± 17.39	21.88 ± 17.17	13.5 ± 14.67	1.543	.241
CAI	4.86 ± 3.38	5.21 ± 4.76	5.05 ± 9.24	0.386	.698
MAI	8.79 ± 9.18	3.50 ± 4.89	1.01 ± 1.81	0.919	.413
HI	11.3913 ± 10.11	6.83 ± 6.41	5.43 ± 5.19	1.368	.211
$MeanSaO_2$	91.69 ± 2.51	91.89 ± 2.13	93.33 ± 0.84	3.368	.035*
$LowdestSaO_2$	75.13 ± 8.22	72.69 ± 15.28	80.05 ± 11.32	2.654	.061
$LowestSaO_2$	72.26 ± 10.99	66.37 ± 14.78	69.11 ± 23.78	0.919	.413
ODI_3	32.08 ± 14.01	29.69 ± 17.38	21.32 ± 16.45	3.095	.043*
TSat (90)	30.56 ± 18.43	22.41 ± 13.96	10.55 ± 7.57	3.569	.028*
TSat (85)	11.91 ± 14.80	7.42 ± 10.72	1.55 ± 1.82	3.686	.027*
TSat (80)	4.65 ± 9.03	2.92 ± 5.17	0.12 ± 0.34	2.413	.101

Abbreviations: AHI, apnea–hypopnea index; CAI, central apnea index; HI, Hypopnea Index; $LowdestSaO_2$, Lowest desaturation; $LowestSaO_2$, lowest arterial oxyhemoglobin saturation; MAI, Mixed Apnea Index; $MeanSaO_2$, mean arterial blood oxygen saturation; OAI, Obstructive Apnea Index; ODI_3, oxygen desaturation index; TSat (80), oxygen saturation of less than 80%; TSat (85), oxygen saturation of less than 85%; TSat (90), oxygen saturation of less than 90%.

*$p < 0.05$, Statistically significant.

TABLE 4 Data indicators in coronary angiography in patients with AMI combined with OSA at different periods

	22:00–5:59	6:00–13:59	14:00–21:59		
	n = 70 (47%)	*n* = 44 (30%)	*n* = 34 (23%)	*F*	*p*
SYNTAx scores	22.34 ± 8.89	22.82 ± 6.46	17.86 ± 7.65	3.765	.024*

*$p < .05$, Statistically significant.

intermittent hypoxia leads to increased hematocrit and fibrinogen levels and increased blood viscosity, resulting in a tendency for hypercoagulation (Steiner et al., 2005). Patients with OSA have a two- to three-fold higher risk of thrombosis than non-OSA patients (Aziz & Chaudhary, 2016). This is consistent with the findings of the higher SYNTAX scores and increased Hb and thrombolytic DD in patients in the present study with OSA during the nighttime sleeping hours. The above factors might accelerate the process of coronary vasculopathy in patients with OSA, severe myocardial ischemia and hypoxia might lead to acute necrosis of part of the myocardium, and symptoms of chest pain might develop during sleep at night.

It was found by statistical analysis that the diurnal pattern of the onset of AMI correlated with OSA, suggesting that clinicians should screen for OSA when treating patients with AMI. Continuous positive airway pressure (CPAP) is the first-line treatment for OSA. In a meta-analysis, the nightly application of CPAP >4 h was effective in improving the prognosis in patients with OSA (Abuzaid et al., 2017). Therefore, sleep respiratory monitoring should be routinely performed in patients with CHD, and early diagnosis and treatment of sleep-disordered respiratory disease might be important to improve the quality of life and prognosis in patients with CHD.

The limitations of the present study were the high cost of polysomnography, the complexity of the operation, and the safety issues in monitoring patients with AMI. Therefore, a Class III portable instrument with high sensitivity and specificity was adopted in the present study to assess the incidence of OSA in the population with AMI by conducting sleep monitoring of patients on the ward. We hope to increase the sample size in the future and optimize the use of polysomnography in the analysis of sleep structure in patients with AMI.

AUTHOR CONTRIBUTIONS

Fang Zhao and Xiaoyun Zhao involved in conception and design of the research. Liheng Yang and Yuechuan Li involved in acquisition of data. Fang Zhao and Xiaoyun Zhao involved in analysis and interpretation of the data. Liheng Yang involved in statistical analysis. Fang Zhao and Xiaoyun Zhao involved in critical revision of the manuscript for intellectual content. All authors read and approved the final draft.

CONFLICT OF INTEREST

All of the authors have no any personal, financial, commercial, or academic conflict of interest separately.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author,upon reasonable request.

ETHICAL STATEMENT

This study was conducted with approval from the Ethics Committee of Tianjin Chest Hospital. This study was conducted in accordance

with the declaration of Helsinki. Written informed consent was obtained from all participants.

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