

Severe obstructive sleep apnea is associated with coronary microvascular dysfunction and obstruction in patients with ST-elevation myocardial infarction

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本研究のポイント	◇閉塞性睡眠時無呼吸症候群が重症なほど、MRI 検査で急性心筋梗塞後の心筋障害が悪化することが明らかに ◇微小血管障害の程度との関連により、閉塞性睡眠時無呼吸症候群が心血管疾患リスク因子であることを示唆
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<p>概要</p>	<p>研究グループは、閉塞性睡眠時無呼吸症候群 が重症なほど、急性心筋梗塞後の心筋障害が悪化することを明らかにしました。</p> <p>急性心筋梗塞は心臓に栄養を供給する冠状動脈が塞がることで心臓の筋肉が壊死する病気で、わが国での発症数は増加傾向にあります。致死率が高く、最も有効な治療法は発症早期にカテーテル治療で塞がった血管の血流を再開させることです。しかしながら、カテーテル治療により詰まった血管が開通した後も心臓の筋肉へ十分な血流が行き渡らない症例が存在し、その原因として心臓の筋肉内の目に見えないような非常に小さな血管(微小血管)の障害が原因であると報告されています。近年、閉塞性睡眠時無呼吸症候群は、急性心筋梗塞を含む心血管疾患の発症及び重症化のリスク因子であると考えられていますが、その関係については明らかにされていませんでした。</p> <p>そこで本研究では、急性心筋梗塞後の患者さんを対象として、心臓 MRI により心臓の筋肉内の微小血管障害を評価し、閉塞性睡眠時無呼吸の重症度との相関を調べました。その結果、閉塞性睡眠時無呼吸が重症になるにつれ、微小血管障害を認める患者さんの割合が高くなることが明らかになりました。また、重症の閉塞性睡眠時無呼吸は急性心筋梗塞後の微小血管障害の程度と関連があり、心筋梗塞後の症状が悪化するかどうかの判断材料であることが示唆されました。この結果から、閉塞性睡眠時無呼吸症候群が診断されず、あるいは治療せず放置されていて急性心筋梗塞を発症してしまうと心臓へのダメージが大きくなってしまうことが示唆されました。</p> <p>‘閉塞性睡眠時無呼吸症候群が重症になると急性心筋梗塞後の心筋障害が悪化’. 大阪市立大学. https://www.osaka-cu.ac.jp/ja/news/2020/200430-1. (参照 2020-04-30)</p>
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ORIGINAL SCIENTIFIC PAPER

**Severe Obstructive Sleep Apnea is Associated with Coronary Microvascular
Dysfunction and Obstruction in Patients with ST-Elevation Myocardial Infarction**

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Abstract

BACKGROUND: Coronary microvascular dysfunction and obstruction (CMVO) is a strong predictor of a poor prognosis in patients with ST-segment elevation myocardial infarction (STEMI). Although research has suggested that obstructive sleep apnea (OSA) exacerbates CMVO after primary percutaneous coronary intervention (PCI), data supporting a correlation between OSA and CMVO are limited. This study was performed

to investigate whether OSA is associated with CMVO, detected as microvascular obstruction (MO) on cardiovascular magnetic resonance images (CMR), in patients with STEMI.

METHODS: 249 patients with a first STEMI underwent primary PCI. CMVO was evaluated on CMR based on the presence of MO. OSA was classified into four levels of severity based on the respiratory event index (REI): absent (REI of <5), mild (REI of ≥ 5 to <15), moderate (REI of ≥ 15 to <30), and severe (REI of ≥ 30).

RESULTS: The REI was significantly higher in the presence of MO ($n=139$) than in its absence ($n=110$) (REI of 12.8 vs. 10.7, respectively; $p=0.023$). MO was observed in 42%, 58%, 57%, and 70% of patients in the absent, mild, moderate, and severe OSA groups, respectively. Multiple logistic regression analysis showed that severe OSA was associated with increased odds of MO [odds ratio (OR), 5.10; 95% confidence interval (CI), 1.61–16.2; $p=0.006$]. Mild and moderate OSA were also associated with increased odds of MO (mild OSA: OR, 2.88; 95% CI, 1.19–7.00; $p=0.019$ and moderate OSA: OR, 3.79; 95% CI, 1.43–10.1; $p=0.008$).

CONCLUSION: Severe OSA was associated with CMVO after primary PCI in patients with STEMI.

Key Words: Cardiovascular magnetic resonance imaging • Coronary microvascular dysfunction and obstruction • Microvascular obstruction • Obstructive sleep apnea • ST-segment elevation myocardial infarction

INTRODUCTION

For patients with ST-elevation myocardial infarction (STEMI), immediate reperfusion via primary percutaneous coronary intervention (PCI) can salvage the myocardium and reduce mortality.^{1,2} However, the area of myocardial hypoperfusion persists in some patients despite prompt epicardial recanalization of the infarct-related artery.³ This phenomenon, known as no reflow, is caused by coronary microvascular dysfunction and obstruction (CMVO), which has been shown to be associated with adverse ventricular remodeling and a poor prognosis after STEMI.^{2,4-7} CMVO can be detected as microvascular obstruction (MO) using cardiovascular magnetic resonance imaging (CMR).^{2,4-7} MO is revealed by the lack of gadolinium enhancement within the hyper-enhanced infarcted area. It appears in two patterns, referred to as early and late MO. Although late MO is less sensitive than early MO and may lead to underestimation of the presence of CMVO, it is a strong predictor of clinical endpoints after the STEMI has been reperfused during primary PCI.⁶⁻⁹ The discovery of a crucial target for preventive therapy for CMVO may lead to an improved prognosis after STEMI; however, the mechanisms and causes of CMVO are complex and are not yet fully understood.⁴

Increasing evidence indicates that obstructive sleep apnea (OSA) is a significant risk factor for cardiovascular disease, including acute myocardial infarction, and is

associated with increased morbidity and mortality.^{10,11} OSA is characterized by repetitive episodes of apnea or reduced inspiratory airflow due to upper airway obstruction during sleep. These events provoke intermittent hypoxemia and hypercapnia and are associated with hemodynamic alterations, oxidative stress, sympathetic hyperactivity, inflammatory response, endothelial dysfunction, and hypercoagulability.¹² These alterations are major contributors to cardiovascular diseases and may exacerbate CMVO. Although a previous study showed that OSA impairs CMVO in patients with STEMI after primary PCI,¹³ the association between OSA and CMVO remains controversial, partially because of the difficulty of evaluating CMVO. Because CMR enables precise detection of CMVO, we investigated the relation between OSA and CMVO determined by CMR in patients with acute STEMI.

METHODS

Patients

We enrolled patients admitted to Nishinomiya Watanabe Cardiovascular Center in Japan from January 2010 to December 2016 who were diagnosed with STEMI and who underwent primary PCI within 24 h after symptom onset. STEMI was diagnosed based on the presence of symptoms consistent with myocardial ischemia and signs of ST-

segment elevation (measured at the J-point) of ≥ 1 mm in at least two contiguous leads on a 12-lead electrocardiogram. The exclusion criteria were death, previous myocardial infarction, unsuccessful PCI, heart failure and/or cardiogenic shock treated with intravenous inotropes and/or mechanical support, complications requiring surgery, other severe disease, lack of CMR, OSA that was already being treated with continuous positive airway pressure (CPAP) therapy, lack of sleep studies, and central sleep apnea. Lack of CMR was due to patients who had refused the test, had claustrophobia, or had a contraindication for contrast medium (hypersensitivity or severe kidney disease defined as an estimated glomerular filtration rate of <30 mL/min/1.73 m²). Lack of sleep studies was due to patients who had refused the study or who had had an incomplete sleep study.

Study Design

This prospective observational study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Ethics Committee of Nishinomiya Watanabe Cardiovascular Center (approval number 2009-006). All patients provided written informed consent.

Patients were treated and medicated following contemporary clinical practice and guidelines by each cardiologist in our hospital. Unless contraindicated, β -blockers,

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins as lipid-lowering therapy were given as early as possible after PCI.

Definitions

Hypertension was defined as use of antihypertensive medication and/or a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg on admission.

Dyslipidemia was defined as a low-density lipoprotein cholesterol level of ≥ 140 mg/dL and/or use of lipid-lowering agents on admission. *Diabetes* mellitus was defined as a glycated hemoglobin A1c concentration of $\geq 6.5\%$ and/or current use of insulin or oral hypoglycemic agents on admission. *Smokers* were defined as patients who were previous and current smokers.

Primary Percutaneous Coronary Intervention

All patients received a bolus injection of unfractionated heparin (5000 U) in the emergency room as soon as diagnosed. Following oral administration of aspirin (200 mg) and an adenosine diphosphate receptor inhibitor (clopidogrel 300 mg or prasugrel 20 mg), primary PCI was performed according to standard methods. Thrombectomy was performed at the operator's discretion. Glycoprotein IIb and IIIa were not used because

these drugs were not approved for use in Japan. Whether to use bare-metal stents, drug-eluting stents, or neither in the infarct-related artery was determined by each operator.

Spontaneous recanalization of the infarct-related artery was defined as a thrombolysis in myocardial infarction (TIMI) flow grade of 2 to 3 at the pre-PCI time point. *Unsuccessful PCI* was defined as a TIMI flow grade of 0 to 1 after PCI.

Cardiovascular Magnetic Resonance Imaging

Within 4 days after primary PCI, eligible patients underwent contrast-enhanced CMR to establish the presence or absence of late MO. CMR studies were performed on a whole-body 1.5-T MR scanner (Intera Achieva; Philips Medical Systems, Best, The Netherlands) equipped with a six-element cardiac phased-array coil for signal reception. Patients were examined at rest in the supine position. Images were gated to the electrocardiogram and obtained during repeated breath-holds. Localizers and left ventricular (LV) function assessment included determining the LV ejection fraction, LV end-diastolic volume, and LV end-systolic volume using steady-static, free-procession images. In the short-axis orientation, the left ventricle was completely encompassed by contiguous slices. Late gadolinium enhancement images were obtained from contiguous short-axis slices and representative long-axis slices of the left ventricle 10 to 15 min after

intravenous injection of gadolinium-diethylenetriamine pentaacetic acid at 0.1 mmol/kg (Magnevist; Schering AG, Berlin, Germany). A breath-hold, three-dimensional inversion recovery gradient-echo pulse sequence (recovery time, 4.0 ms; echo time, 1.93 ms; flip angle, 20°; typical spatial resolution, 1.56×1.56×10 mm) was used for image acquisition. We optimized the inversion time (250–300 ms) to null the normal myocardium. All analyses were interpreted by consensus of two blinded observers at an offline workstation (ViewForum; Philips Medical Systems).

Sleep Study

During the first week, eligible patients underwent an overnight sleep study to measure the severity of their OSA. The sleep study was performed using a portable sleep apnea type 3 test (Somté; Compumedics, Melbourne, Australia) (SAS-3200; Nihon Kohden, Tokyo, Japan). These devices measured cardiopulmonary parameters, naso-oral airflow, and thoracoabdominal movements to determine the type of apnea. Arterial oxyhemoglobin saturation was recorded using a pulse oximeter, and electrocardiographic recordings were obtained from a single lead. *Apnea* was defined as the cessation of inspiratory air flow lasting ≥ 10 s. *Hypopnea* was defined as a $\geq 50\%$ reduction in airflow lasting ≥ 10 s associated with a 4% decrease in oxygen saturation (i.e., the oxygen saturation index),

and a state of arousal. The *respiratory event index* (REI) was defined as the number of apnea and hypopnea events per hour. *OSA* was defined as the absence of airflow despite respiratory movement or exertion and an REI of ≥ 5 events/h, with $>50\%$ of them obstructive. OSA was thus classified into four categories based on the REI: absent (REI of <5), mild (REI of ≥ 5 to <15), moderate (REI of ≥ 15 to <30), and severe (REI of ≥ 30). *Central sleep apnea* was defined as the absence of both airflow and respiratory movement.

Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation or median (first and third quartiles). Categorical variables are expressed as number and percentage. Patients were divided into two groups according to the absence or presence of MO. Comparison analyses between groups were performed using Student's t test or the Mann–Whitney U test for continuous variables and by χ^2 statistics or Fisher's exact test for categorical variables, as appropriate. In the next analysis, patients were divided into four groups based on the severity of their OSA. Comparison analyses among groups were performed by trend testing according to the Jonckheere–Terpstra test for continuous variables and the Cochran–Armitage test for categorical variables. Univariate logistic regression analysis was performed to assess the relation between the presence of MO and multiple

factors. A multivariate logistic regression analysis was performed to investigate the association between the severity of OSA and the presence of MO, adjusting for age, male sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, spontaneous recanalization, anterior infarct, multivessel disease, and a final TIMI flow grade of 3. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed with EZR version 1.37 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During our study period, 370 patients with STEMI underwent primary PCI. The study flowchart is shown in Figure 1. Among the 370 patients, 121 were excluded from this study. The final study population comprised 249 patients [insert Figure 1].

To evaluate the relation between the presence of MO and the extent of myocardial injury after STEMI, patients were divided into two groups according to the presence (n=139) or absence (n=110) of MO (Table 1). Patients with MO were significantly younger and comprised significantly more males than patients without MO. The peak creatine kinase level was higher and the incidence of anterior infarcts was

significantly higher among patients with than without MO. The number of patients with spontaneous recanalization, the number of patients with a final TIMI flow grade of 3, and the LV ejection fraction measured on CMR were all significantly lower in patients with than without MO. The REI was significantly higher in patients with than without MO ($p=0.023$). These results suggest that the presence of MO reflects exacerbated myocardial damage after STEMI [insert Table 1].

To investigate the relation between OSA and MO, the patients were divided into four groups according to the severity of OSA based on their REI. The patients' baseline characteristics are shown in Table 2. Age, body mass index, and the incidences of diabetes mellitus and dyslipidemia were significantly higher in patients with more severe OSA. There were no significant differences in angiographic findings or in the LV function parameters (ejection fraction, end-diastolic volume, or end-systolic volume) measured by CMR among the four groups. MO was present in 42%, 58%, 57%, and 70% of the absent, mild, moderate, and severe OSA groups, respectively (for trend, $p<0.001$) (Figure 2). These results indicate a significantly greater presence of MO in patients with more severe OSA [insert Table 2], [insert Figure 2].

The univariate logistic analysis showed that age, spontaneous recanalization, and a final TIMI flow grade of 3 were significantly associated with decreased odds of MO

(Table 3). In contrast, male sex and an anterior infarct were significantly associated with increased odds of MO. Severe OSA was significantly associated with increased odds of MO [odds ratio (OR), 3.29; 95% confidence interval (CI), 1.36–7.97; $p=0.008$]. The multivariate logistic regression analysis adjusted for age, sex, body mass index, hypertension, diabetes mellitus, hyperlipidemia, smoking, spontaneous recanalization, anterior infarct, multivessel disease, and final TIMI flow grade of 3 revealed that OSA was independently associated with the presence of MO in a severity-dependent manner (mild: OR, 5.10; 95% CI, 1.61–16.2; $p=0.006$, moderate: OR, 3.79; 95% CI, 1.43–10.10; $p=0.008$, and severe: OR, 2.88; 95% CI, 1.19–7.00; $p=0.019$, respectively) (Table 4) [insert Table 3], [insert Table 4].

DISCUSSION

This prospective observational study showed that OSA is associated with the presence of MO in a severity-dependent manner in patients with acute STEMI. We measured MO by CMR, which enables precise detection of localized CMVO. It has been reported that CMVO is a strong independent prognosticator in patients with acute STEMI.^{2,4,5} Thus, the correlation between OSA and the presence of MO indicates that OSA is a predictor of adverse events in patients with acute STEMI after primary PCI. Previous studies have

shown that OSA is associated with poor outcomes after primary PCI in patients with STEMI during follow-up.^{10,14-16} Additionally, the mechanisms of OSA-related cardiovascular disease are considered to be associated with microvascular dysfunction.¹⁷ However, little clinical evidence is available to support these speculations in the setting of STEMI. Our study supports previous findings and may explain the causes of a poor prognosis from the viewpoint of the coronary microcirculation.

Previous studies have shown that coronary microvascular dysfunction can result from functional and/or structural alterations, the relative importance of which can vary depending on the clinical setting.¹⁸ We speculate that the mechanisms underlying the CMVO detected by CMR in patients with STEMI and OSA in the present study involved both functional and structural abnormalities. Morra and Roubille¹⁷ reported that OSA causes vascular remodeling (structural) and dysfunction of both endothelial cells and smooth muscle cells (functional). OSA causes intermittent and chronic transmural pressure variations that increase circumferential wall stress in the left ventricle. These changes might trigger structural vascular remodeling processes such as vascular smooth muscle cell hypertrophy and wall thickening.¹⁷ Additionally, OSA-induced intermittent hypoxia and generation of reactive oxygen species cause oxidative stress and stimulate proinflammatory processes, which result in endothelial dysfunction.¹⁹ Moreover, hypoxia

itself can cause the deterioration of vascular endothelial function because oxygen is essential for nitric oxide biosynthesis from L-arginine, and hypoxia may reduce nitric oxide production.¹³ One study showed that endothelium-dependent vasodilation was significantly impaired in patients with OSA,²⁰ and endothelial dysfunction is a well-known prognostic factor for various cardiovascular events.^{21,22} In our study population, structural and functional abnormalities in the microcirculation were already present prior to the onset of STEMI in patients with OSA. These pre-existing coronary microvascular dysfunctions might contribute to the development and poor prognosis of STEMI.

Ischemia–reperfusion injury and distal embolism are other mechanisms of CMVO after primary PCI in patients with STEMI.⁴ These alterations result from various intracellular and extracellular responses, such as neutrophil infiltration, swelling of vascular cells and cardiomyocytes, and micro-obstruction of small arteries and arterioles.¹⁸ Oxidative stress, inflammation, and vasoconstriction, which are triggered by OSA-mediated intermittent hypoxia, are functionally involved in these mechanisms¹²; therefore, in our study, CMVO could be exacerbated in STEMI patients with OSA because of the presence of both functional and structural alterations.

Diabetes and dyslipidemia also reportedly cause endothelial dysfunction.²³ As shown in our study, patients with severe OSA were highly susceptible to complications

associated with these diseases. These data suggest that the adverse interaction between these comorbidities and OSA synergistically impairs endothelial dysfunction, leading to MO in a severity-dependent manner.

Interventions to address the impaired microcirculation caused and exacerbated by OSA may be a new therapeutic approach to preventing CMVO, which would improve the prognosis of patients with STEMI. Administration of CPAP is the standard treatment for OSA. Although several studies have shown that treatment of OSA with CPAP reduces the incidence of acute coronary syndrome,²⁴ the effect of acute coronary syndrome on patients' prognosis has not been established. As shown in this study, severe OSA exacerbates CMVO and may lead to a poor prognosis in patients with STEMI. Therefore, research that focuses on alleviating the OSA-related CMVO is needed. In addition, none of the patients in our study had been diagnosed with OSA at the time of their inclusion in the study. Hence, we cardiologists should be more attuned to diagnosing OSA at an earlier time and start an intervention before the onset of cardiovascular events.

Limitations

This study has several limitations. First, myocardial infarction and heart failure may exacerbate breathing disorders during sleep.²⁵ In this study, whether OSA was the cause

or result of the cardiac problems was unclear because the sleep studies were performed in patients with acute STEMI only after primary PCI. To minimize the effects of the acute phase as much as possible, we excluded patients with heart failure and/or cardiogenic shock treated with intravenous injection of inotropes and/or mechanical support, patients with central sleep apnea, and performed sleep studies ≥ 1 week after onset. Second, although we clearly showed that the presence of MO was associated with severe OSA, MO was not evaluated quantitatively. Therefore, the association between the extent of MO and OSA could not be investigated. Because quantitative evaluation of MO may explain the strong correlation between MO and OSA, additional studies are needed. Third, after the onset of STEMI, CMVO is caused by structural and functional cardiovascular abnormalities. Which factor is more strongly involved in these processes remains unclear. CMR might provide additional clues to this question by evaluating the presence of intramyocardial hemorrhage (IMH), which appears to be a consequence of microvascular injury.⁴ IMH is caused by the destruction of endothelial walls due to the sudden appearance of intravascular positive pressure after reperfusion, resulting in microvascular dysfunction.⁵ Because the presence of IMH reflects irreversible myocardial damage and may be affected by structural rather than functional cardiovascular abnormalities, assessing the presence of IMH may help to identify whether structural or functional

abnormalities are having a stronger effect. However, we could not evaluate IMH in the present study, and further research is required. Fourth, the serum levels of inflammatory markers such as C-reactive protein, tumor necrosis factor-alpha, interleukin 6, and interleukin 8 may provide additional information to clarify the mechanism of CMVO in the setting of STEMI. Moreover, recent studies have shown that the skin and retinal microcirculation which are closely related to OSA is structurally and functionally similar to the microcirculation of other organs, such as the coronary artery.^{26,27} Thus, noninvasive evaluation of the microcirculation in the skin and retina can reflect coronary microvascular dysfunction in patients with OSA. Overall, using these modalities to assess functional and/or structural alterations may clarify the mechanisms of CMVO; further research is needed. Finally, although we showed the association between OSA and CMVO, evaluation of clinical follow-up data can reveal the patients' actual prognosis. However, follow-up data were available for only some patients; therefore, we were unable to analyze the patients' prognosis in this study. We plan to continue accumulating more data and provide new findings in the future.

Conclusion

The severity of OSA is independently associated with CMVO as evaluated by CMR in

patients with acute STEMI after primary PCI. Because severe OSA causes CMVO and may lead to a poor prognosis in patients with STEMI, therapeutic interventions to alleviate the CMVO caused by OSA should be investigated.

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Disclosures

None.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Table 1. Patient Characteristics according to the absence or presence of MO

	MO absence n=110	MO presence n=139	P-value
Basal characteristics			
Age, years	68±11	64±12	0.008
Male	81 (74%)	123 (89%)	0.002
BMI, kg/m ²	24.1±3.6	24.0±3.5	0.820
Peak CK, IU/L	929 (605-1409)	3279 (2285-4787)	<0.001
Cardiovascular risk factors			
Hypertension	66 (60%)	76 (55%)	0.399
Diabetes mellitus	20 (18%)	28 (20%)	0.697
Dyslipidemia	46 (42%)	69 (50%)	0.219
Smoking	66 (60%)	87 (63%)	0.677
Angiographic findings			
Onset to reperfusion time, h	2.9 (2.0-4.5)	3.3 (2.1-5.4)	0.866
Infarct-related artery; LAD/LCX/RCA	45 (41%) / 8 (7%) / 57 (52%)	80 (58%) / 13 (9%) / 46 (33%)	0.013
Anterior infarct	45 (41%)	80 (58%)	0.011
Stent	103 (94%)	131 (94%)	1.000
Multivessel disease	37 (34%)	49 (35%)	0.895
Spontaneous recanalization	45 (41%)	15 (11%)	<0.001
Final TIMI flow grade 3	107 (97%)	124 (89%)	0.015
CMR results			
LV EF, %	54.7±10.9	46.2±9.3	<0.001
LV EDV, mL	108.2±31.9	120.6±34.1	0.004
LV ESV, mL	50.7±25.1	66.6±27.8	<0.001
Sleep study			
REI, events/h	10.7 (4.2-21.0)	12.8 (7.3-24.3)	0.023
4% ODI, events/h	6.7 (2.5-13.6)	9.8 (3.9-18.3)	0.063
Minimum SaO ₂ , %	86 (83-89)	87 (83-89)	0.811

Data are presented as mean±SD, median (first quartile, third quartile), or n(%). MO, microvascular obstruction; BMI, body mass index; CK, creatine kinase; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; CMR, cardiovascular magnetic resonance imaging; LV, left ventricular; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; REI, respiratory event index; ODI, decrease in oxygen saturation.

Table 2. Patient Characteristics according to the severity of OSA

	absent n= 55	mild n= 92	moderate n= 65	severe n= 37	P-value
Basal characteristics					
Age, years	60±12	65±13	69±11	68±9	<0.001
Male	42 (76%)	79 (86%)	51 (79%)	32 (87%)	0.483
BMI, kg/m ²	23.3±3.3	23.8±3.3	24.7±4.0	24.3±3.7	0.017
Peak CK, IU/L	1627 (828-3326)	2062 (829-3569)	2114 (1333-3678)	2135 (1247-3917)	0.126
Cardiovascular risk factors					
Hypertension	24 (44%)	52 (57%)	47 (72%)	19 (51%)	0.088
Diabetes mellitus	5 (9%)	16 (17%)	18 (28%)	9 (24%)	0.015
dyslipidemia	18 (33%)	42 (46%)	34 (52%)	21 (57%)	0.013
Smoking	34 (62%)	60 (65%)	35 (54%)	24 (65%)	0.729
Angiographic findings					
Onset to reperfusion time, h	3.1 (2.1-5.5)	3.1 (2.0-5.1)	3.2 (2.1-5.5)	3.3 (2-4.6)	0.866
Infarct-related artery; LAD/LCX/RCA	32, 1, 22	39, 10, 43	31, 7, 27	23, 3, 11	0.381
Anterior infarct	32 (58%)	39 (42%)	31 (48%)	23 (62%)	0.715
Stent	52 (95%)	86 (94%)	62 (95%)	34 (92%)	0.799
Multivessel disease	12 (22%)	44 (48%)	21 (32%)	9 (24%)	0.785
Spontaneous recanalization	16 (29%)	20 (22%)	17 (26%)	7 (19%)	0.429
Final TIMI flow grade 3	52 (95%)	86 (94%)	58 (89%)	35 (95%)	0.631
CMR results					
LV EF, %	49.7±9.6	51.7 ±11.3	49.1±11.3	47.7±10.7	0.288
LV EDV, mL	124.1 ±35.0	112.8 ±35.9	112.3 ±30.9	112.5 ±29.4	0.242
LV ESV, mL	64.2 ±29.3	57.3 ±30.5	58.5 ±24.6	60.5 ±23.2	0.923
MO presence	23 (42%)	53 (58%)	37 (57%)	26 (70%)	0.013
Sleep study					
REI, events/h	2.3 (0.6-3.3)	9.7 (7.3-11.6)	22.0 (18.9-25.8)	36.8 (32.8-39.4)	<0.001
4% ODI, events/h	1.1 (0.5-2.1)	5.5 (3.5-7.9)	14.7 (12-19.7)	28.5 (22.2-34.9)	<0.001
Minimum SaO ₂ , %	91 (88-92)	87 (84-90)	85 (82-88)	83 (77-85)	<0.001

Data are presented as mean±SD, median (first quartile, third quartile), or n (%). OSA, obstructive sleep apnea; MO, microvascular obstruction; BMI, body mass index; CK, creatine kinase; OTR, onset to reperfusion; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; CMR, cardiovascular magnetic resonance imaging; LV, left ventricular; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; REI, respiratory event index; ODI, decrease in oxygen saturation.

Table 3. Univariate logistic analysis according to MO presence

Univariate factors	OR	95% CI	P value
Age	0.972	0.951-0.993	0.009
Male	2.75	1.41-5.39	0.003
BMI	0.992	0.924-1.06	0.819
Hypertension	0.804	0.484-1.34	0.400
Diabetes mellitus	1.14	0.600-2.15	0.697
Dyslipidemia	1.37	0.828-2.27	0.219
Smoking	1.12	0.668-1.86	0.677
Onset to reperfusion time	1.05	0.980-1.13	0.162
Spontaneous recanalization	0.175	0.091-0.337	<0.001
Anterior infarct	1.96	1.18-3.25	0.009
Multivessel disease	1.07	0.634-1.82	0.790
Final TIMI flow grade 3	0.232	0.065-0.822	0.023
REI	1.020	1.00-1.04	0.038
Severity of OSA			
absent	1 [Reference]	-	-
mild	1.89	0.961-3.72	0.065
moderate	1.840	0.889-3.80	0.101
severe	3.29	1.36-7.97	0.008

MO, microvascular obstruction; OR, odds ratio; CI, confidence interval; BMI, body mass index; TIMI, thrombolysis in myocardial infarction; REI, respiratory event index; OSA, obstructive sleep apnea.

Table 4. Multivariate logistic analysis according to MO presence

Multivariate factors	OR	95%CI	P value
Severity of OSA			
absent	1 [Reference]	-	-
mild	2.88	1.19-7.00	0.019
moderate	3.79	1.43-10.1	0.008
severe	5.10	1.61-16.2	0.006

Adjusting to age, sex, BMI, hypertension, diabetes mellitus, dyslipidemia, smoking, spontaneous recanalization, anterior infarct, multivessel disease, final TIMI flow grade 3. MO, microvascular obstruction; OR, odds ratio; CI, confidence interval; BMI, body mass index; TIMI, thrombolysis in myocardial infarction; OSA, obstructive sleep apnea.

Figure Legends

Figure 1. Study flowchart. CMR, cardiovascular magnetic resonance imaging; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Figure1

Figure 1.

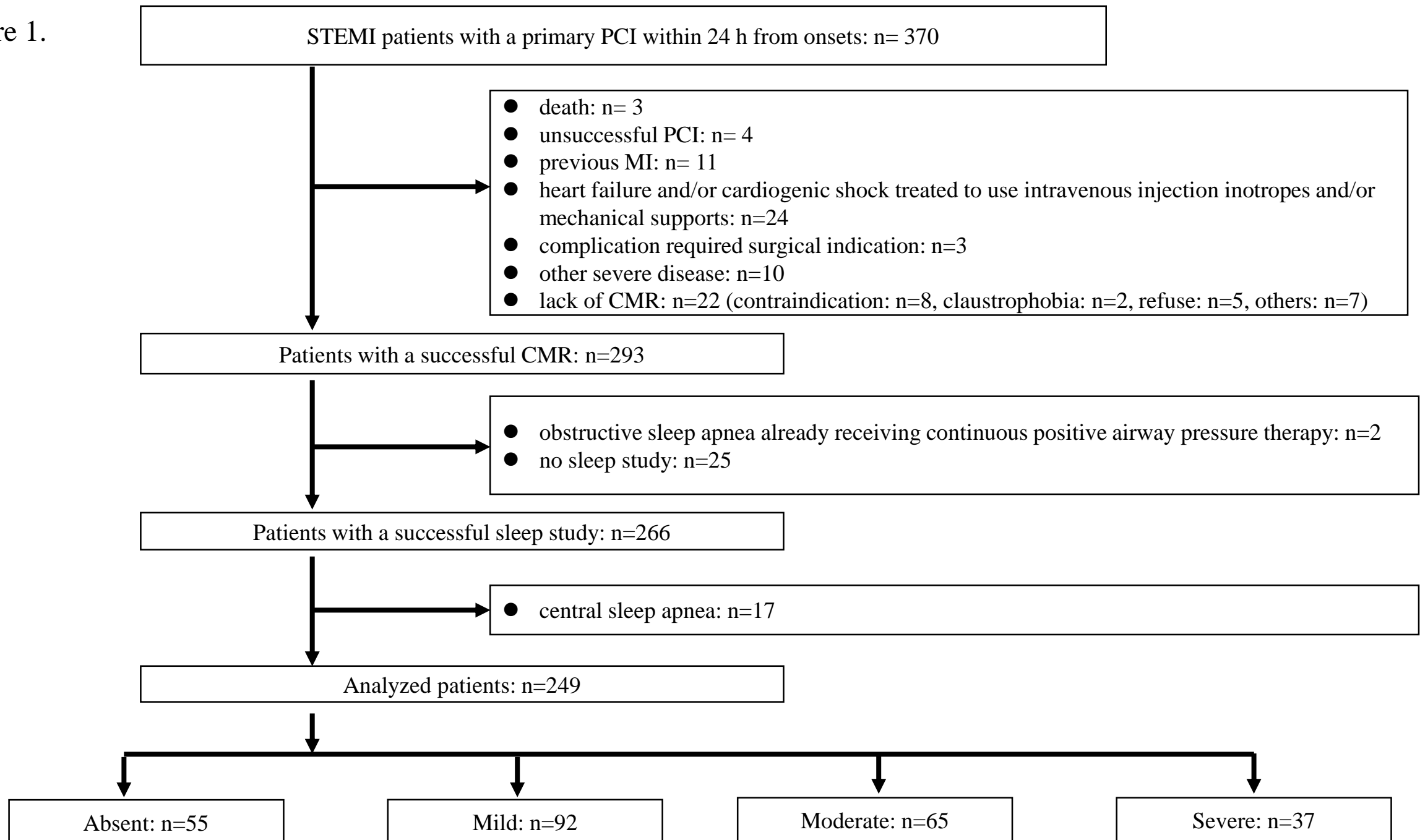


Figure 2. Incidence of MO at various levels of OSA severity. The incidence of MO was 42%, 58%, 57%, and 70% in the absence of OSA and with mild, moderate, and severe OSA, respectively (for trend, $p < 0.001$). MO, microvascular obstruction; OSA, obstructive sleep apnea.

Figure2

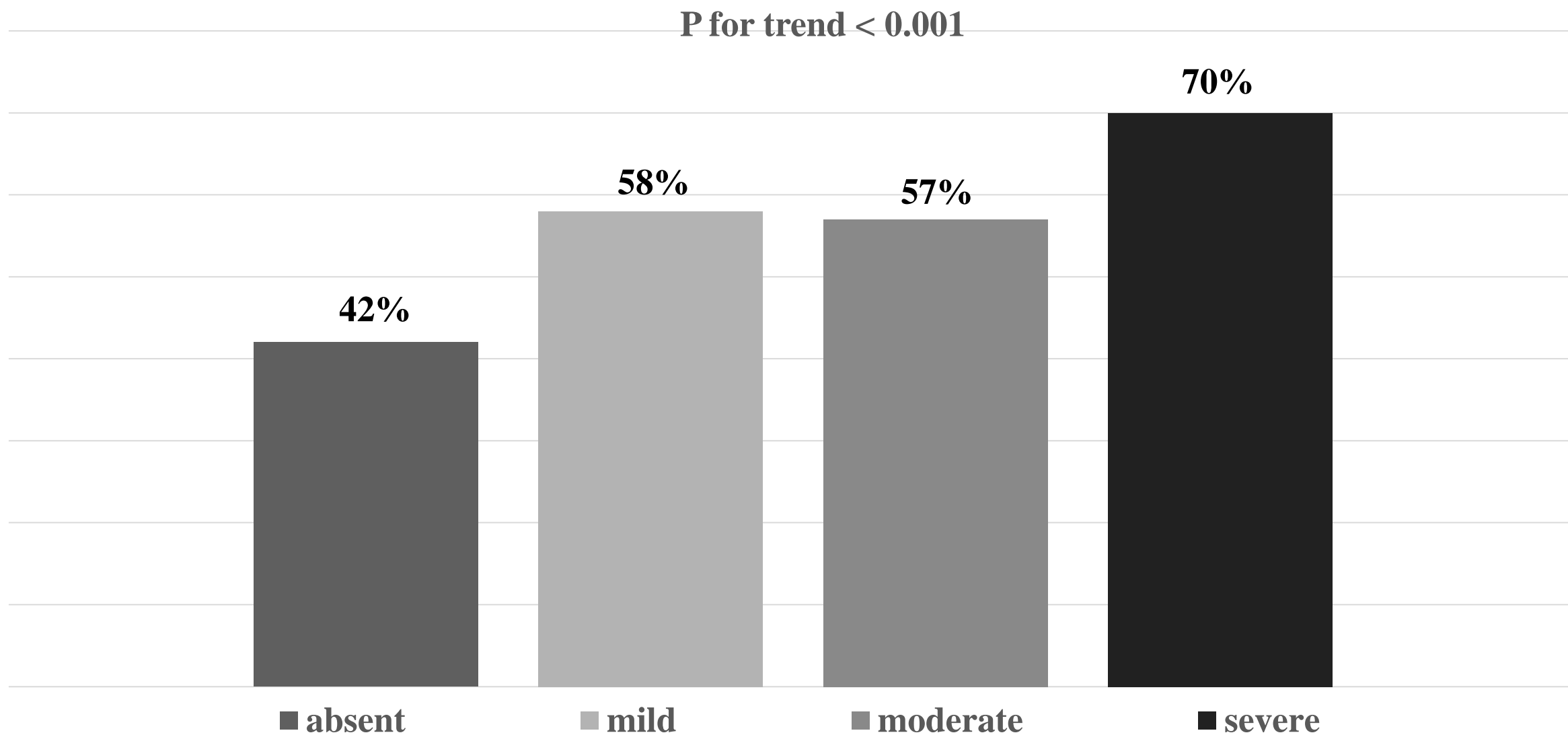


Figure 2.