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## Obstructive sleep apnea after myocardial infarction

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Obstructive sleep apnea (OSA) is a risk factor for hypertension, myocardial ischemia and stroke, and is associated with increased mortality [1,2]. Hypoxia-induced activation of the sympathetic nervous system, inflammation and oxidative stress contribute to increase cardiovascular risk in patients with sleep disturbances [2–4]. The present study was aimed at evaluating the prevalence of OSA after a recent myocardial infarction (MI) and defining its clinical predictors.

All patients with recent MI (median time from symptoms onset: 32 days), admitted to our cardiac rehabilitation center between March 2007 and December 2008, were enrolled in the study. All subjects were in stable clinical conditions.

At baseline, patients underwent echocardiogram, ECG Holter, ergometric stress test, and blood tests. Ventricular arrhythmia risk profile was quantified on ECG Holter analysis, using the Lown and Wolf classification: frequent (>30/h) and complex (presence of couplets and tachycardia) arrhythmias [5]. Frequent supraventricular arrhythmia was defined as a number of ectopic beats >30/h. The peak CPK-MB and Troponin I values detected during acute MI were registered.

The presence of OSA was assessed by ECG Holter recording using a validated software (Lifescreen Apnea; SPACELABS Healthcare – Issaquah, Washington, USA and Hertford, UK) integrated in the Impresario Holter Analysis System (Symphony model; SPACELABS Healthcare). Briefly, the continuous change from airways obstruction

to normal air flow determines a shift from sympathetic to parasympathetic dominance, with related changes in heart rate. The software analyzes modifications in heart rate variability (HRV) and in QRS amplitude, returning the mean apnea-hypopnea index (AHI) [6,7]. Diagnostic sensitivity of this technique, compared to polysomnography, is 90% [6,7]. ECG Holter recorders had a sampling rate of 2048 Hz (EVO recorder; SPACELABS Healthcare). Patients were stratified on AHI values into three groups: normal (AHI ≤ 5), mild (AHI 5–15) and moderate-severe apnea (AHI > 15) [1,2]. Two parameters of HRV in time domain analysis were evaluated, SDNN (the standard deviation of RR intervals of the ECG Holter recording) and RMSSD (the square root of the mean squared differences of successive RR intervals), corresponding to sympathetic and parasympathetic activity – the former, and to parasympathetic activity only – the latter [8].

Exclusion criteria for the study were: dominant non-sinus rhythm; presence of an implanted pacemaker; frequent artifacts in the ECG Holter recording; diabetes mellitus type 1 and other conditions associated with a severe autonomic dysfunction.

Each patient gave written informed consent to the study; the protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Continuous and categorical variables were expressed as mean ± standard deviation (SD) and percentages, respectively. For continuous variables, Student's *t* test or analysis of variance were employed to compare two or more groups of subjects. When the variables were not normally distributed, non parametric tests were employed. The association between two continuous variables was assessed with linear regression analysis. Differences in categorical variables distribution were evaluated with  $\chi^2$  test.

To identify the clinical predictors of OSA, those factors correlated to this condition in univariate analysis, were entered into a multivariate linear regression model.

We enrolled 191 patients (Table 1), 73% after a ST-elevation MI (STEMI). Primary percutaneous coronary intervention was performed in 84% of cases. Mean peak values of CPK-MB and troponin I were 113 UI/L (25th–75th percentile: 38–145 UI/L) and 106 ng/mL (25th–75th percentile: 16–141 ng/mL), respectively (Table 2).

The maximum workload attained at the baseline ergometric stress test was 118 ± 40 Watt. The test was suggestive of myocardial ischemia only in 18 patients (9.4%).

ECG Holter recordings had a mean length of 22:09 ± 1:27 h. Mean heart rate was 66 ± 9 b/min. SDNN and RMSSD were within lower normal limits (Table 2). Second or third degree atrioventricular blocks were absent, cardiac pauses longer than 2 s were present only in 7

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**Table 1**  
Clinical characteristics of patients.

		Range
Age (years)	62 ± 13	28–94
Men (%)	81.7	
Weight (kg)	77 ± 13	47–115
BMI (kg/m <sup>2</sup> )	26.6 ± 3.5	16.3–40.2
Smokers		
Current (%)	21.6	
Past (%)	51.1	
Comorbidities		
COPD (%)	7.9	
Diabetes (%)	15.3	
Dyslipidemia (%)	45.0	
Hypertension (%)	56.3	
Previous MI (%)	8.7	
Stroke/TIA (%)	3.6	
Valvular heart diseases		
Aortic insufficiency (%)	3.2	
Aortic stenosis (%)	10.2	
Mitral insufficiency (%)	9.7	
Blood tests		
Creatinine (mg/dL)	0.95 ± 0.24	0.50–2.00
ESR (mm/h)	27.2 ± 20.1	2.0–111.0
Hemoglobin (g/dL)	13.5 ± 1.4	10.0–16.4
RBC count (10 <sup>6</sup> /mm <sup>3</sup> )	4.6 ± 0.5	3.4–7.0
Uric acid (mg/dL)	5.9 ± 1.3	2.0–9.7

BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; ESR: erythrocyte sedimentation rate.

patients (3.7%). ST segment depression was observed in 6 patients (3.1%).

Mean sleep time was 7:56 ± 1:13 h; 143 subjects (74.9%) had AHI scores >5, with a mean value of 17.7 ± 10.8 (mild: N = 67, 35.3%; moderate-severe apnea: N = 76, 40.1%).

**Table 2**  
Cardiological characteristics of patients and drug therapy.

		Range
Type of myocardial infarction		
Anterior STEMI (%)	36.6	
Inferior STEMI (%)	36.6	
NSTEMI (%)	26.8	
Primary PCI site		
Left main (%)	0.5	
Left anterior descending (%)	41.7	
Circumflex (%)	12.3	
Right CA (%)	29.4	
No PCI (%)	16.0	
LVEF (%)	52 ± 11	20–74
Preserved (%)	62.4	
Mild reduction (%)	19.4	
Moderate/severe reduction (%)	18.2	
ECG Holter monitoring		
Frequent SV arrhythmias (%)	4.7	
Frequent V arrhythmias (%)	8.4	
Complex V arrhythmias (%)	36.6	
SDNN (ms)	116 ± 34	37–222
RMSSD (ms)	33 ± 20	10–128
Drug therapy		
ASA (%)	96.9	
Clopidogrel (%)	95.3	
ACE inhibitors/ATII antagonists (%)	94.8	
β-blocking agents (%)	89.5	
Statins (%)	93.2	
K <sup>+</sup> sparing agents (%)	14.7	
Diuretics (%)	22.5	

AT: angiotensin; CA: coronary artery; LVEF: left ventricular ejection fraction – categorized as normal (>50%), mildly (41–49%), moderately (26–40%), and severely (<25%) depressed; MI: myocardial infarction; PCI: percutaneous coronary intervention; RMSSD: root mean square of the squared difference between consecutive RR intervals; SDNN: standard deviation of all RR intervals of the ECG Holter recording; STEMI/NSTEMI: ST-/non-ST-elevation MI; SV/V: supraventricular/ventricular.

Body weight correlated directly with AHI (Table 3), with the highest value observed in moderate-severe apnea patients (normal: 75 ± 13 kg, mild: 74 ± 11 kg, moderate-severe apnea: 80 ± 12 kg; *p* = 0.029).

Uncontrolled hypertension (i.e. blood pressure >130/80 mmHg at the time of enrollment), was positively associated with AHI. AHI linearly increased with uric acid and CPK-MB plasma concentrations, and RBC count (Table 3). While patients with STEMI displayed higher values of AHI (Table 3), no relation was found with residual LVEF (*p* = 0.536) (Table 3). Complex ventricular arrhythmias directly correlated with AHI (Table 3), with the highest prevalence of frequent ventricular arrhythmias in the moderate-severe group (normal: 12.5%, mild: 18.8%, moderate-severe apnea: 68.8%; *p* = 0.033).

The multivariate linear regression analysis confirmed the direct correlation of AHI with body weight, RBC count, use of K<sup>+</sup> sparing agents, presence of uncontrolled hypertension and complex ventricular arrhythmias (Table 4).

This study suggests that OSA is highly prevalent in patients with a recent MI. The study was conducted 4 weeks after MI to exclude possible confounders, such as acute inflammation and overt left ventricular failure. CPK-MB peak plasma concentration and STEMI, two indicators of MI extension, correlated with the severity of OSA. Furthermore, K<sup>+</sup> sparing agents, more frequently prescribed in patients with moderate-severe left ventricular dysfunction (*p* < 0.001), were associated with greater AHI. A strong relation was found between OSA and RBC count, corroborating previous reports of a predictive value of hemoglobin and hematocrit for the presence of sleep disturbances [9]. The correlation between AHI and plasma levels of uric acid, possibly related to enhanced ATP transformation, may suggest tissue distress [10].

**Table 3**  
Univariate analysis of apnea-hypopnea index by clinical variables.

	Condition		<i>p</i>
	–	+	
Men	8.0 ± 6.9	15.2 ± 11.8	<0.001
Present smokers	13.7 ± 11.4	14.8 ± 11.8	0.584
COPD	14.0 ± 11.6	13.6 ± 10.0	0.893
Diabetes	13.7 ± 11.6	15.3 ± 11.7	0.907
History of hypertension	13.4 ± 10.8	14.4 ± 12.0	0.551
Uncontrolled hypertension	12.5 ± 10.2	16.1 ± 13.1	0.039
Stroke/TIA	14.1 ± 11.6	9.1 ± 8.4	0.293
Aortic insufficiency	13.6 ± 11.6	22.8 ± 8.3	0.055
Aortic stenosis	14.1 ± 11.5	13.6 ± 12.1	0.868
Mitral insufficiency	14.2 ± 11.6	13.3 ± 11.4	0.515
Frequent SV arrhythmias (%)	14.4 ± 11.5	5.5 ± 6.1	0.023
Complex V arrhythmias (%)	12.5 ± 10.2	16.2 ± 13.0	0.029
STEMI	11.6 ± 10.6	15.0 ± 11.8	0.049
ACE inhibitors/AT II antagonists	19.9 ± 11.9	13.6 ± 11.4	0.092
β-blocking agents	15.1 ± 15.8	13.8 ± 10.9	0.623
Statins	12.5 ± 15.1	14.1 ± 11.2	0.645
K <sup>+</sup> sparing agents	13.3 ± 11.0	18.1 ± 13.6	0.048
Diuretics	14.5 ± 12.0	12.0 ± 9.4	0.206
	β ± se	R	<i>p</i>
Age (Δ·year)	/	0.035	0.633
Weight (Δ·kg)	0.23 ± 0.07	0.243	0.001
BMI (Δ·kg/m <sup>2</sup> )	/	0.138	0.059
CPK MB (Δ·U/L)	0.04 ± 0.01	0.364	0.001
Creatinine (Δ·mg/dL)	/	0.108	0.148
ESR (Δ·mm/h)	/	0.077	0.299
Hemoglobin (Δ·g/dL)	/	0.138	0.062
RBC count (Δ·10 <sup>6</sup> /mm <sup>3</sup> )	3.8 ± 1.5	0.179	0.015
Uricemia (Δ·mg/dL)	1.5 ± 0.7	0.159	0.032
HR (Δ·b/min)	/	0.032	0.661
SDNN (Δ·ms)	/	0.117	0.111
RMSSD (Δ·ms)	/	0.133	0.071

Uncontrolled hypertension: blood pressure >130/80 mmHg at baseline evaluation; SV/V: supraventricular/ventricular; Δ: AHI changes per unitary change of the independent variable. Variables represented in less than 5% of the study population were excluded from the analysis.

**Table 4**

Clinical predictors of apnea–hypopnea index by multivariate linear regression analysis ( $R = 0.435$ ,  $p < 0.001$ ).

	$\beta \pm se$	95%CI	<i>p</i>
Body weight ( $\Delta \cdot \text{Kg}$ )	$0.2 \pm 0.1$	0.1–0.3	0.001
RBC count ( $\Delta \cdot 10^9/\text{mm}^3$ )	$3.0 \pm 1.5$	0.1–5.8	0.043
Complex V arrhythmias (yes vs. no)	$3.5 \pm 1.6$	0.3–6.8	0.030
Frequent SV arrhythmias (yes vs. no)	$-9.5 \pm 3.7$	–(16.7–2.3)	0.010
Uncontrolled hypertension (yes vs. no)	$4.2 \pm 1.6$	1.0–7.4	0.011
$K^+$ sparing agents (yes vs. no)	$5.2 \pm 2.3$	0.7–9.8	0.024
Constant	$-20.1 \pm 8.0$	–(35.9–4.4)	0.013

$\Delta$ : AHI changes per unitary change of the independent variable; RBC: red blood cell; SV/V: supraventricular/ventricular.

The association between AHI and complex ventricular arrhythmias is an important novel finding. In the Sleep Heart Health Study, the presence of a sleep disturbance, increased about three times the risk to develop a not sustained ventricular tachycardia, and at least two times the risk to experience complex ventricular arrhythmias [11]. The correlation between OSA and ventricular arrhythmias might be explained by several factors, including increased left ventricular afterload with consequent reduction in preload, increased sympathetic outflow, and the possible presence of diastolic dysfunction [12].

Few limitations of the study need to be acknowledged. Only 2 patients reported the use of a CPAP previous to the occurrence of MI, but we cannot rule out the possibility that subclinical sleep disturbances might have been present before the acute event in a portion of our population. The technique we used to detect OSA, even if validated, employs only the electrocardiographic dimension of the polysomnography study. It is known that a recent MI may reduce HRV influencing the ability of ECG analysis to detect sleep apnea. However, HRV recorded in our study population was still within normal limits [8]; moreover, a reduction of HRV should determine an underestimation of the prevalence of sleep disturbances. Furthermore, a recent Scientific Statement on sleep apnea and cardiovascular disease, recommended to adopt new non-invasive tools of screening, less expensive and more widely applicable than standard polysomnography [1].

In conclusion, previously unrecognized OSA is highly prevalent among patients with recent MI and associates with increased body weight, uncontrolled hypertension and complex ventricular arrhythmias. Clinicians should seek and treat sleep disturbances when occurring in patients with recent MI.

Conflict of interest

None to disclose.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [13].

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