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Incidence of bradyarrhythmias in hypertensive and chronic kidney disease patients with mild *vs*. severe obstructive sleep apnea

Márcio Galindo Kiuchi[1]* and Shaojie Chen[2]

[1]Division of Cardiac Surgery and Artificial Cardiac Stimulation, Department of Medicine, Hospital e Clínica São Gonçalo, São Gonçalo, RJ, Brazil

[2]Department of Cardiology, Shanghai First People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Obstructive sleep apnea (OSA) may lead to atrial fibrillation (AF), a common cardiac arrhythmia. Particularly, OSA is a risk factor for stroke and hypertension [1,2]. Further, continuous positive airway pressure (CPAP) reduces death and cardiovascular events and improves hypertension control [3,4]. Accentuated sympathetic nerve activity is a robust risk factor for cardiovascular events, such as cerebral infarction and myocardial infarction [5]. Peripheral sympathetic nerve activity is accentuated in patients with hypertension, congestive heart failure, OSA, obesity, diabetes, and chronic renal illnesses. The obstructive events result in sleep disruption, hypoxemia, and are associated with an increased prevalence of arrhythmias [6].

We aim to compare the incidence of bradyarrhythmic events in CKD and hypertensive patients with mild *vs*. severe OSA, recorded by the 24-hour-Holter monitoring after OSA degree diagnosed by the polysomnography. This retrospective study involved 182 subjects divided into mild OSA (n=94) and severe OSA (n=88). The study was conducted in accordance with the Helsinki declaration and was approved by the ethics committee of our institution. All patients signed the informed consent before inclusion. Patients were evaluated between January 2013 and January 2016 at the Arrhythmias and Artificial Cardiac Pacing Service at Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients who met the following criteria were consecutively enrolled: (i) essential hypertension more than one year; (ii) Mild OSA: 5 to 15 Apnea/Hypopnea index (AHI) events/hour; (iii) Severe OSA: >30 AHI events/hour; (iv) age between 18 and 80 years; (v) structurally normal heart to myocardial scintigraphy, without ischemia or fibrosis area, previously diagnosed, presenting left ventricular ejection fraction measured by Simpson's method >50%; (vi) glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation [7], eGFR >60 mL/min/1.73 m^2 with microalbuminuria or eGFR <60 mL/min/1.73 m^2); and (vii) capacity to read, comprehend, and sign the informed consent form and attend the clinical tests. Patients that presented any of the subsequent criteria were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) unstable angina, myocardial infarction, transient ischemic attack or stroke; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) known addiction to drugs or alcohol that affects the intellect; (vii) serious health condition that, in the investigator opinion's, may adversely affect the safety and/or efficacy of the participant or the study; (viii) congestive heart failure of functional class II to IV according to the New York Heart Association. The primary endpoint was to record episodes of bradyarrhythmias registered by the 24-hour-Holter monitoring.

The 24-hour ABPM [8] and polysomnography [9] execution were previously described. The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. All statistical tests were two-sided. Comparisons between two-paired values were performed with the paired t-test in cases of normally distributed variables, and by the Wilcoxon test in cases of non-normally distributed variables. Comparisons between more than two-paired values were made by repeated-measures analysis of variance or by Kruskal–Wallis analysis of variance as appropriate, complemented by a post-hoc test. Categorical variables were compared with Fisher's exact test. A P-value <0.05 was considered significant. Correlations between two variables were performed by Pearson's chi-square test in case of a Gaussian distribution and with the Spearman correlation test otherwise. All statistical analyses were performed using the program Graph pad Prism v 7.0 (Graph pad Software, La Jolla, CA, USA).

The general features of both groups are disposed of in Table 1. Analyzing the events of bradyarrhythmia recorded by the 24-hour-Holter monitoring, pauses >3 seconds, 2nd degree atrioventricular (AVB) Mobitz I, 2nd degree AVB Mobitz II, and 3rd degree AVB occurrence was much higher in the group with severe OSA (68.2%, 56.9%, 46.8%, and 36.4%, respectively) than in the group presenting mild OSA (11.7%, 21.3%, 26.6%, and 16.0%, respectively), P<0.0001, P<0.0001, P=0.0063, and P=0.0022, respectively, as shown in (Figure 1). The relative risk for bradyarrhythmic events in hypertensive CKD patients evaluated by Fisher's exact test was presented in Figure 1. Our data showed that in patients with severe OSA, the risk of bradyarrhythmic events occurrence is significantly higher than in patients only with mild OSA.

Conflict of interest

None declared.

Correspondence to: Márcio Galindo Kiuchi, Division of Cardiac Surgery and Artificial Cardiac Stimulation, Department of Medicine, Hospital e Clínica São Gonçalo Rua Cel. Moreira César, 138- Centro, Rio de Janeiro 24440-400, Brazil, Tel/Fax: +55(21) 26047744; E-mail: marciokiuchi@gmail.com

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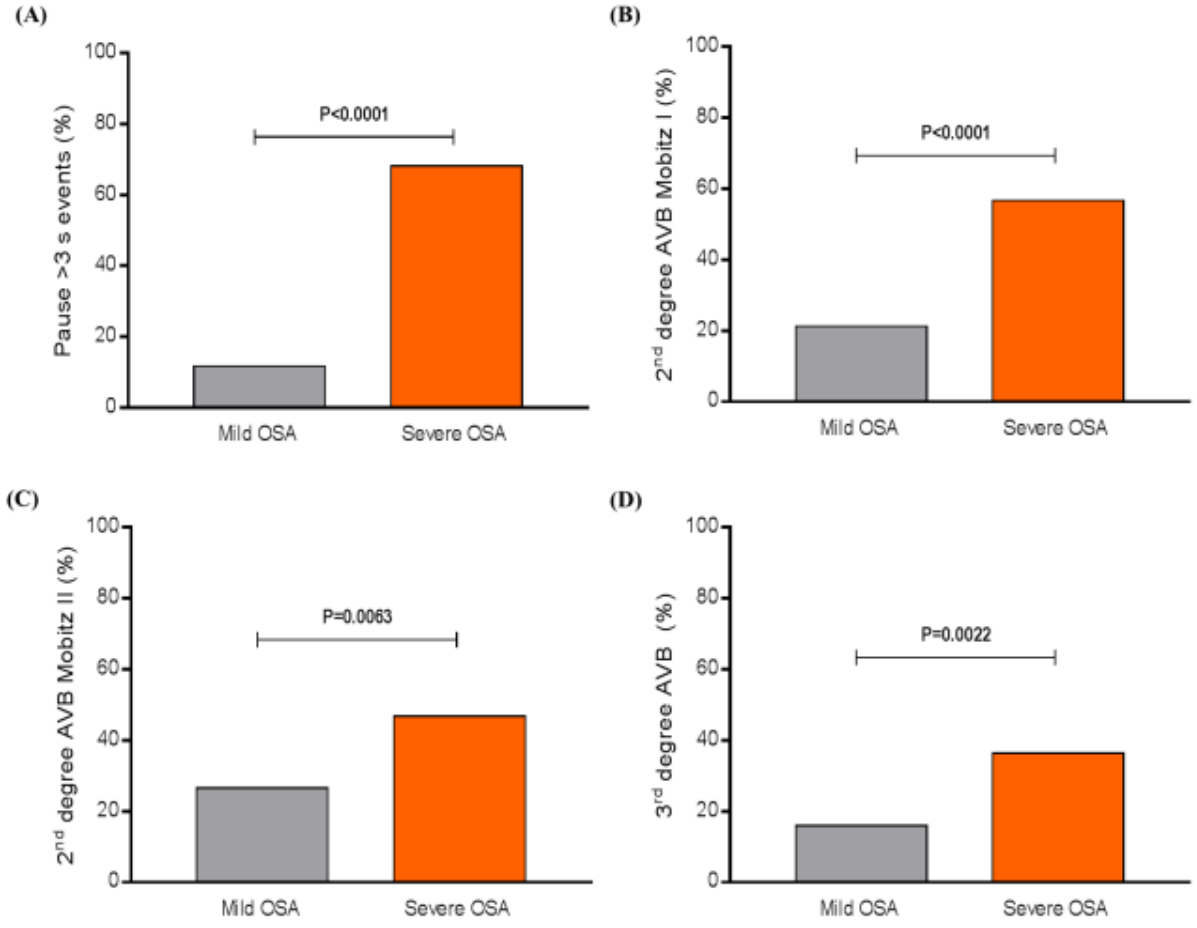

Relative risk for bradyarrhythmic events evaluated by Fisher's exact test in CKD patients

Severe *vs.* Mild OSA	Relative Risk	95% Confidence Interval	P value
Pauses > 3 seconds	4.826	2.876 – 8.502	<0.0001
2nd degree AVB Mobitz I	2.313	1.600 – 3.486	<0.0001
2nd degree AVB Mobitz II	1.600	1.152 – 2.305	0.0063
3rd degree AVB	1.834	1.227 – 2.926	0.0022

AVB, atrioventricular block; OSA, obstructive sleep apnea

Figure 1. Percentage and Relative Risk of bradyarrhythmias occurrence recorded by the 24-hour-Holter monitoring: (A) pause >3 seconds, (B) 2nd degree AVB Mobitz I, (C) 2nd degree AVB Mobitz II, and (D) 3rd degree AVB. AVB, atrioventricular block; OSA, obstructive sleep apnea; Mild OSA, n=94; Severe OSA, n=88.

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Table 1. General features of patients at baseline.

	Mild OSA	Severe OSA	P value
N	94	88	---
Age, years	58.0±15.1	62.3±16.6	0.0689
Body mass index, kg/m^2	28.3±5.5	30.6±4.8	0.0031
Male sex (%)	70 (74%)	63 (72%)	0.4495
White ethnicity (%)	60(64%)	51 (58%)	0.5378
Type 2 Diabetes *Mellitus* (%)	33 (35%)	42 (45%)	0.2334
Coronary artery disease (%)	20 (21%)	28 (33%)	0.0945
Creatinine, mg/dL	1.60±0.30	1.53±0.56	0.2904
eGFR, mL/min/1.73m² (CKD-EPI)	47.0±12.1	48.3±20.5	0.6003
Albumin: creatinine ratio, mg/g	76.5±19.4	73.0±10.6	0.1364
Hypertension (%)	94 (100%)	88 (100%)	1.0000
Mean 24-hour ABPM, mmHg	137.0±6.2/89.3±8.5	138.0±8.8/92.7±7.2	0.3743/0.9181
Apnea/hypopnea index, events/hour	10.5±6.4	55.2±10.1	<0.0001
Antihypertensive Agents			
ACE inhibitors/ARB	94 (100%)	88 (100%)	1.0000
Diuretics	70 (74%)	75 (85%)	0.0966
DHP Ca^{++} channel blockers	94 (100%)	88 (100%)	1.0000

Values are presented as Mean ± SD or %; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DHP, dihydropyridine;eGFR, estimated glomerular filtration rate; HR, heart rate; N, number of patients; OSA, obstructive sleep apnea.

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