Obstructive sleep apnea, detected by the *Berlin Questionnaire*: an associated risk factor for coronary artery disease

Risco de apneia obstrutiva do sono detectado pelo *Questionário de Berlim* está associado com doença arterial coronariana

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Abstract

Obstructive sleep apnea (OSA), a risk factor for coronary artery disease, remains under diagnosed. We investigated if OSA identified by the Berlin Questionnaire *(BQ) is associated with the risk of coronary artery disease. Cases were patients referred for elective coronariography. The cases were classified with significant coronary lesions (stenosis ≥ 50% in an epicardial coronary) or without significant coronary lesions. Controls were selected from a population-based sample. Positive BQ results were identified in 135 (41.2%) of 328 cases, in contrast with 151 (34.4%) of 439 control subjects (p = 0.03). In a multinomial logistic analysis, the risk for OSA identified by the BQ was independently associated with coronary artery disease in cases with lesions of at least 50% (OR = 1.53; 95%CI: 1.02-2.30; p = 0.04). The risk from OSA identified by the BQ was higher in younger subjects (40-59 years) (OR = 1.76; 95%CI: 1.05-2.97; p = 0.03) and in women (OR = 3.56; 95%CI: 1.64-7.72; p = 0.001). In conclusion, OSA identified by the BQ greatly increases the risks of coronary artery disease in patients having significant coronary artery lesions indicated by anangiogram, particularly in younger individuals and in women.*

Coronary Artery Disease; Obstructive Sleep Apnea; Questionnaires

Obstructive sleep apnea (OSA) is highly prevalent in persons [1] with coronary artery disease, a leading cause of morbidity and mortality [2]. OSA has been identified as an independent risk factor for coronary artery disease in some [3,4] but not all studies [5]. OSA and coronary artery disease share several risk factors, and it is still disputed if OSA is a direct risk for vessel damage [6] and cardiovascular disease at all [7,8]. Angiographic analyses have suggested that OSA may contribute to the severity of coronary artery disease [9,10]. OSA may trigger the rupture of vulnerable plaques, leading to acute myocardial infarction [11,12]. OSA has been identified as an independent predictor of angiographic and clinical outcomes in coronary artery disease, such as cardiac death, myocardial infarction and reinfarction or revascularization after percutaneous coronary intervention [13,14].

Polysomnography (PSG) is the gold standard for OSA diagnosis [15]. Nonetheless its availability is still limited worldwide. To circumvent this limitation, questionnaires have been developed to screen for OSA [16]. They are easily administered, inexpensive, applicable in large surveys, and useful for screening a diagnosis of OSA. The *Berlin Questionnaire* (BQ) was designed to identify individuals at higher risk of having OSA in primary care. The BQ includes questions on obesity, hypertension, snoring, daytime sleepiness and fatigue [17]. We demonstrated that a positive response to the questionnaire was independently associated with resistant hypertension [18].

We hypothesized that an association between OSA and coronary artery disease can be detected by the BQ. As of this date, this method has not yet been employed in this setting.

Methods

This is a case-control study. Cases were patients referred for elective coronary angiography for diagnostic purposes. Patients had class I to II stable angina or had an evidence of ischemia in non-invasive testing. Patients with prior treatment of coronary artery disease by angioplasty or surgery, current or previous malignancies, chronic disabling disease, or major surgery in the last two years were excluded. Cases were additionally classified according to severity of coronary artery disease by quantitative digital angiography in patients with or without significant lesions, defined as ≥ 50% stenosis in major epicardial vessels or their branches.

Controls were selected from a population-based study that investigated 1,858 adult residents randomly selected from the city of Porto Alegre, Rio Grande do Sul State, Brazil. Details of this study are described elsewhere [19]. Among 1,210 individuals aged 40 years or older, a random sample of 439 individuals matched to the cases, by age and gender, were selected. Controls with history of cardiovascular disease (defined by a medical history of myocardial infarction, artery failure, stroke or coronary artery bypass grafting and self-reported *angina pectoris*) were excluded.

Procedures

Cardiovascular risk factors, socioeconomic and demographic characteristics were assessed using the same standardized questionnaire both in the control group and case individuals. Interviews were conducted by certified investigators. Skin color was defined by the referred race of the ascendants [20]. Smokers were characterized by lifetime consumption of at least 100 cigarettes, and pack-years of smoking were calculated by multiplying the daily number of packs smoked and number of years of smoking [21]. Abusive consumption of alcoholic beverages was defined by an average daily intake ≥ 30g of ethanol for men and ≥ 15g ethanol for women [22].

Blood pressure was measured with an OMRON device, model CP-705 (OMRON Co. Ltd., Dalian, China), with the patient sitting, and the average of three measurements was used in the analyses. Hypertension was defined as systolic pressure ≥ 140mmHg, diastolic pressure ≥ 90mmHg or use of blood pressure-lowering medications. Diabetes mellitus was defined by a history of a physician's diagnosis of diabetes or use of antidiabetic agents.

Anthropometric assessment was performed with the participant wearing light clothing without shoes. The average of two or three measurements was used in the analysis. Weight and height were measured in a scale to the nearest 100g with a scale (model TINN 00088; Plenna S.A., São Paulo, Brazil), and height (cm) was measured maintaining the Frankfurt plane, to the nearest 0.1cm. Waist circumference was measured at the midpoint between the lower costal rib and superior iliac crest. Body mass index (BMI) was calculated as [weight (kg)/height (m)^2].

Berlin Questionnaire (BQ)

Controls were interviewed during a home visit, as part of a larger study [19]. Case patients answered the BQ, read by the investigators, after catheterization. When possible, wives and husbands of the case patients and the controls helped to answering the questions.

The BQ is composed of three categories of symptoms, five questions are related to snoring and cessation of breathing in category 1, four questions are related to daytime sleepiness in category 2; there is a question about high blood pressure and also a question about the BMI in category 3. In category 1 and 2, high risk was defined as persistent symptoms (> 3-4 times/week). In category 3, high risk was defined by the presence of hypertension (≥ 140/90mmHg or use of medication) or a BMI ≥ 30kg/m^2. Patients and control subjects were classified as having high risk for OSA if scores were positive on two or more categories.

Coronary angiography

Coronary angiography was performed by transfemoral access, according to the Seldinger technique, using Axion Artis equipment (Siemens, Munich, Germany) by experienced interventional cardiologists. The diagnosis of significant lesions was established by quantitative analysis of the major epicardial vessels – branch, anterior descending artery, circumflex and right coronary artery – and branches with a diameter ≥ 3mm – obtuse marginal arteries, posterolateral, first diagonal, diagonal second, apical and posterior descending. Evaluation of the images was done independently by two cardiologists and disagreements were settled by a third interventional cardiologist. Stenosis was detected, as well as the percentage of stenosis in relation to the diameter, through digital quanti-

tative analysis. Significant coronary artery disease was defined as stenosis ≥ 50% in at least one epicardial coronary artery.

Statistical analysis

The sample size was calculated to detect an odds ratio (OR) of at least 2.0 with p α = 0.05 and 80% power, assuming a prevalence of BQ positives of 35% in the controls and 50% in the cases, with a ratio between controls and cases of 2.5:1. Thus, the required sample size was 126 cases and 315 controls. In order to maintain the power in the multivariate analysis, the sample size was increased to 328 cases and 439 controls. The differences between means were compared using Student's t-test. Chi-square test was used to compare proportions. T-test and ANOVA were employed to test for differences between the cases classified with significant and non-significant coronary lesions, and controls. Odds ratios and confidence intervals for significant lesions in the high-risk BQ were calculated in a multinomial regression analysis, adjusting for age, gender, skin color, education, smoking, alcohol beverage consumption and diabetes mellitus. This method enables calculating odds ratios of a dependent-variable with more than two categories. The categories were cases with significant and non-significant lesions in the coronary angiography. Analyses were conducted using the Statistical Package for Social Sciences (version 16.0; SPSS Inc., Chicago, USA).

The study was approved by the Ethics Committee of Porto Alegre Clinics Hospital (Hospital das Clínicas de Porto Alegre) which is accredited by the Office of Human Research Protections as an Institutional Review Board. All participants signed an informed consent form.

Results

The flow chart of the selection of cases and controls is presented in the Figure 1. A total of 328 individuals referred for coronary angiography, aged 36 to 82 years, were characterized as cases and classified by the presence or absence of significant stenosis. The reasons for coronary angiography included; angina pectoris in 54.9% of cases, a previous acute myocardial infarction (15.2%), chest pain with positive exercise testing (16.5%) or positive nuclear myocardial perfusion scan (2.1%), dyspnea precipitated by exertion (3.3%), atypical chest pain (0.8%), abdominal pain on exertion (0.4%) and other indications (6.5%). Of the 328 cases, 167 had no significant lesions (< 50% stenosis) and 161 had significant lesions (≥ 50% stenosis) in at least one epicardial coronary artery.

Demographics and other characteristics of cases and controls are showed in Table 1. There were no significant differences between groups in distribution of gender and smoking. Cases had higher systolic and diastolic blood pressure, age, BMI, waist circumference and prevalence of hypertension and diabetes. Cases had fewer years of formal education. The proportion of individuals with a positive BQ was higher in the cases than in the controls (41.2% *vs*. 34.4%; p = 0.03).

In stratified analyses, the risk for OSA detected by the BQ was higher in individuals aged 40-59 years and in women (Table 2). Table 3 shows the OR for coronary artery disease when OSA is identified by the BQ, stratified by age and gender. In both crude and adjusted multinomial regression analysis, patients 40-59 years old and women identified as high risk by the BQ were more likely to have significant coronary lesions.

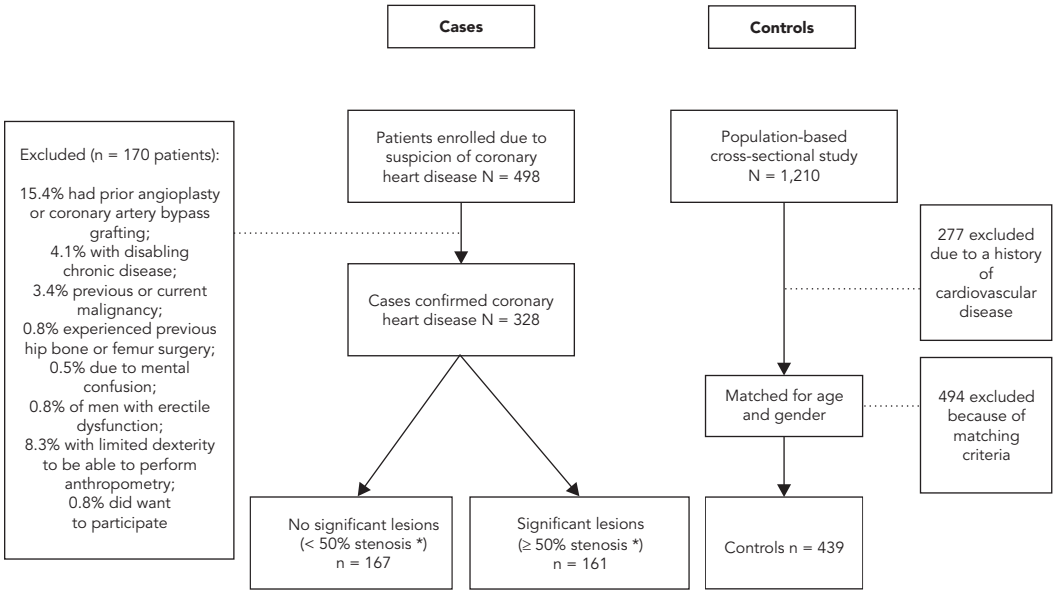
In Table 4, multinomial logistic analysis showed that individuals with a BQ positive result for OSA had an OR (71% higher risk) of displaying significant coronary lesions. Adjusting for age, gender, skin color, education, smoking, alcohol beverage consumption and diabetes, the effect of a positive BQ for risk of coronary lesions was still significant (OR = 1.53, p = 0.04). Hypertension and excess of adiposity, associated with OSA in the univariate analysis, were not included in the model because they are part of the BQ. Individuals without significant lesions had odds ratios not significantly different from that of the controls in any model (Table 4).

Discussion

In this case-control investigation, OSA identified by the BQ was associated with a significant risk of coronary artery disease, independent of age, gender, and other confounding factors. The association was stronger among younger individuals and women. To the best of our knowledge, this is the first demonstration of the performance of the BQ to identify the association between OSA and coronary artery diseaseas confirmed by coronary angiography. The risk of coronary artery disease associated with OSA identified by the BQ was not a factor in cases that didn't have significant coronary lesions, weakening the intensity of the association and suggesting that these individuals are similar to individuals of the same age and gender living in communities without an indication for coronary angiography. On the other hand, the risk in individuals with significant lesions has clinical implications, since the

Figure 1

Flow diagram of subject recruitment.



* In at least one epicardial coronary artery.

use of the BQ could optimize the referral rate for full polysomnography, an exam that is not broadly available worldwide. The confirmation of OSA would lead to treatment to prevent coronary artery disease [23,24] and the occurrence of early signs of atherosclerosis [25].

The association between OSA and coronary artery disease has been reported in several contexts. OSA is associated with coronary risk factors [26,27,28,29,30,31] and with known symptomatic coronary artery disease identified by angiography [32]. OSA was present in 9 of 10 patients with nocturnal *angina pectoris* [33] and in 37% of men and 30% of women with coronary artery disease [34]. After the first acute myocardial infarction, 65.7% of patients had an apnea-hypopnea index ≥ 15/h [35]. In other studies, the prevalence of OSA in patients with artery heart disease ranged from 43 to 66.4% [36,37,38,39]. The prevalence of a high risk of coronary artery disease associated with OSA in our survey was within these estimates. We had recently showed, in a post-hoc analysis of a smaller case-control study, that high risk for coronary artery disease associated with OSA had an odds ratio of 4.5 (1.03-19.25) for coronary artery disease [40].

The BQ has been utilized to identify OSA risk factors in samples of individuals with other cardiac diseases and its prevalence has been similarly high. Chilukuri et al. [41] reported a high risk factor of coronary artery disease associated with OSA identified by the BQ in 44% of patients with atrial fibrillation. Patients with OSA had a greater recurrence rate of atrial fibrillation after catheter arrhythmia ablation than patients without OSA. The prevalence of a high risk factor of coronary artery disease associated with OSA identified by the BQ was 80% in patients with resistant hypertension versus 44% in patients with controlled hypertension [18]. Drager et al. [42] found similar performance of the BQ in the hypertensive population.

The high risk factor of coronary artery disease associated with OSA identified by the BQ was 34.4% in the control group and was similar to reports of the high risk factor of coronary artery disease associated with OSA identified by the BQ that ranged between 26 and 37.5% [17,26,43,44]. In contrast, the prevalence of OSA identified by the BQ in our control population was lower than the reported by Tufik et al. [1], using PSG, in a sample of the general population (49.3%).

Women are less likely than men to report typical snoring and symptoms of apnea [45]. There is also a tendency to delay suspicion and diagnosis of coronary artery disease in women [46]. The

Table 1

Demographics and other characteristics of control individuals and case patients.

	Controls (n = 439)	Cases (n = 328)	p-value *
Gender			0.762
Male	274 (62.4)	209 (63.7)	
Female	165 (37.6)	119 (36.3)	
Age (years)	56.3 ± 9.5	58.3 ± 9.2	0.004
Skin color			0.006
White	327 (74.5)	214 (65.2)	
Education (years)	8.9 ± 5.1	6.2 ± 4.1	< 0.001
Alcohol consumption			< 0.001
Non-abusive	282 (64.2)	301 (91.8)	
Abusive	157 (35.8)	27 (8.2)	
Smoking (packs/years)			0.653
Absent or < 20	165 (37.6)	129 (39.3)	
≥ 20	274 (62.4)	199 (60.7)	
Systolic blood pressure (mmHg)	131.6 ± 23.2	139.6 ± 22.2	< 0.001
Diastolic blood pressure (mmHg)	80.6 ± 12.8	82.6 ± 13.3	0.034
Hypertension			< 0.001
Yes	210 (47.8)	263 (80.2)	
No	229 (52.2)	65 (19.8)	
Diabetes mellitus			0.001
Yes	51 (11.6)	65 (19.9)	
No	388 (88.4)	261 (80.1)	
BMI (kg/m²)	26.9 ± 4.86	28.5 ± 4.9	< 0.001
Waist circumference	92.5 ± 13.3	95.4 ± 11.2	0.002
High risk in BQ	151 (34.4)	135 (41.2)	0.033

BMI: body mass index; BQ: *Berlin Questionnaire*.

Note: data are presented as number (%) or mean ± standard deviation.

* The differences between means and differences in proportions were compared using Student's t-test and chi-square test respectively.

Table 2

Comparison of obstructive sleep apnea syndrome risk estimated using *Berlin Questionnaire* (BQ) in cases and controls, stratified by gender and age-groups.

High risk	Controls (n = 439)	Cases (n = 328)		p-value
		No significant lesion (n = 167)	Significant lesion (n = 161)	
	n (%)	n (%)	n (%)	
Age (years)				
40-59	85 (29.8)	37 (39.4)	48 (49.5)	0.015
60-90	66 (42.9)	22 (30.1)	28 (43.8)	0.07
Gender				
Men	110 (40.1)	46 (36.2)	36 (43.9)	0.5
Women	41 (24.8)	13 (32.5)	40 (50.6)	< 0.001

Note: no significant lesion: < 50% stenosis in at least one epicardial coronary artery; significant lesion: ≥ 50% stenosis.

Table 3

Odds ratios (OR) and 95% confidence intervals (95%CI) in multinomial regression analysis of risk of *Berlin Questionnaire* (BQ) associated with coronary artery disease.

	Unadjusted OR (95%CI)		Adjusted OR (95%CI)	
	No significant lesion	**Significant lesion**	**No significant lesion**	**Significant lesion**
40-59 years (n = 476)				
Low risk	1.00	1.00	1.00 *	1.00 *
High risk	1.53 (0.94-2.48)	2.31 (1.44-3.70)	1.21 (0.73-2.02)	1.76 (1.05-2.97)
p-value	0.09	0.001	0.5	0.03
60-90 years (n = 291)				
Low risk	1.00	1.00	1.00 *	1.00 *
High risk	0.58 (0.32-1.04)	1.04 (0.58-1.87)	0.59 (0.29-1.08)	1.28 (0.65-2.51)
p-value	0.07	0.9	0.08	0.5
Men (n = 483)				
Low risk	1.00	1.00	1.00 **	1.00 **
High risk	0.85 (0.55-1.31)	1.17 (0.71-1.92)	0.74 (0.47-1.18)	1.08 (0.64-1.82)
p-value	0.5	0.5	0.2	0.8
Women (n = 284)				
Low risk	1.00	1.00	1.00 **	1.00 **
High risk	1.46 (0.69-3.08)	3.10 (1.76-5.46)	1.66 (0.64-3.30)	3.56 (1.64-7.72)
p-value	0.3	< 0.001	0.3	0.001

Note: no significant lesion: < 50% stenosis in at least one epicardial coronary artery; significant lesion: ≥ 50% stenosis.

* OR adjusted for: gender, skin color, education, smoking, alcohol consumption and diabetes;

** OR adjusted for: age, skin color, education, smoking, alcohol consumption and diabetes.

Table 4

The association of *Berlin Questionnaire* (BQ) with coronary artery disease according to confounding factors.

	Controls (n = 439)	**Cases**			
		No significant lesion (n = 167)		**Significant lesion (n = 161)**	
	OR (95%CI)	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
BQ (risk, 1)	1.00	1.04 (0.72-1.51)	0.8	1.71 (1.18-2.46)	0.004
Model 1: BQ + age (years)	1.00	1.01 (0.69-1.47)	1.0	1.69 (1.17-2.45)	0.005
Model 2: Model 1+ male gender	1.00	0.96 (0.66-1.41)	0.9	1.77 (1.22-2.57)	0.003
Model 3: Model 2 + skin color (white)	1.00	0.96 (0.65-1.40)	0.8	1.76 (1.21-2.56)	0.003
Model 4: Model 3 + education (years)	1.00	0.93 (0.63-1.36)	0.7	1.62 (1.10-2.38)	0.01
Model 5: Model 4 + smoking (pack-years)	1.00	0.93 (0.63-1.36)	0.7	1.62 (1.10-2.39)	0.01
Model 6: Model 5 + alcoholic consumption (abusive)	1.00	0.88 (0.59-1.31)	0.5	1.53 (1.02-2.30)	0.04
Model 7: Model 6 + diabetes mellitus	1.00	0.87 (0.58-1.31)	0.5	1.53 (1.02-2.30)	0.04

OR: odds ratio; 95%CI: 95% confidence interval.

Note: no significant lesion: < 50% stenosis in at least one epicardial coronary artery; significant lesion: ≥ 50% stenosis.

lower suspicion of OSA identified by the BQ in women, was associated with the higher prevalence of abnormal angiograms in women (85.9 *vs.* 73.7% in men) and may explain the higher risk for coronary artery diseasein women with a positive BQ than that identified in this survey. The gender difference in OSA prevalence is negligible after the age of 60 years [2,47]. The OSA identified by the BQ and suspicion of higher risk for significant coronary artery disease in individuals aged 40-59 years age group suggests that OSA is more important in younger individuals. At older ages, other risk factors for coronary heart disease may prevail in the causation of atherosclerosis,making the risk added by OSA in elderly individuals undetectable by the BQ.

Our study has limitations that deserve attention. The BQ is a screening test for the high risk of OSA and should not replace a full OSA investigation [48]. On the other hand, the use of the BQ as screening for OSA is feasible and may help to increase the diagnosis of OSA in patients with suspected coronary artery disease [49]. Since controls were not submitted to coronary angiography, the possibility they had subclinical coronary atherosclerosis remains and could be a measurement bias. Nonetheless, this possibility is unlikely, since controls never had a suspicion of having coronary artery disease (the main criterion for being a case in our investigation). The lack of evaluation of lipid profile in cases and controls is a potential source of bias, but there was no reason to suspect that the prevalence of lipid disorders was any different between individuals with and without OSA. The case-control design precludes establishing the temporal association. OSA may be the cause of coronary artery disease and vice-versa. The bulk of evidence, including longitudinal studies, suggests that the first option is more plausible.

In conclusion, the high risk factor of coronary artery disease associated with OSA identified by the BQ predicts significant coronary artery lesions, particularly in middle-aged patients and in women. The use of the BQ in patients with suspicion of coronary artery disease may increase the diagnosis and treatmentof OSA, preventing the clinical manifestations of disease.

Resumo

Síndrome da apneia obstrutiva do sono (SAOS), fator de risco para doença arterial coronariana, permanece subdiagnosticada. Investigou-se se o risco de SAOS pelo Questionário de Berlim *(QB) associa-se com doença arterial coronariana. Casos foram pacientes encaminhados para coronariografia eletiva, classificados em casos com lesão significativa (estenose ≥ 50%) ou sem lesões significativas. Controles foram selecionados em amostra populacional. QB foi positivo em 135 (41,2%) de 328 casos, em contraste com 151 (34,4%) de 439 controles (p = 0,03). Em análise logística multinomial, o risco de SAOS identificado pelo QB associou-se com doença arterial coronariana exclusivamente nos casos com lesões de pelo menos 50% (OR: 1,53; IC95%: 1,02-2,30; p = 0,04). Em indivíduos com lesões significativas, o risco de SAOS pela QB foi maior entre os que têm 40-59 anos (OR: 1,76; IC95%: 1,05-2,97; p = 0,03) e em mulheres (OR: 3,56; IC95%: 1,64-7,72; p = 0,001). Em conclusão, alto risco para a SAOS identificados pela QB associa-se a risco de lesões coronarianas significativas na angiografia, particularmente em indivíduos mais jovens e em mulheres.*

Doença da Artéria Coronariana; Apnéia do Sono Tipo Obstrutiva; Questionários

Contributors

D. Massierer coordinated data collection, collaborated with the data analysis and prepared the first draft of this manuscript. J. P. Ribeiro and M. V. Wainstein performed the angiographies, participated in the interpretation of results and preparation of this manuscript. L. B. Moreira participated in the analysis of results and preparation of this manuscript. P. P. Pellin, M. S. Garcia, I. F. Antunes and A. L. Zacharias were responsible for data collection, prepared draft versions of this manuscript and gave final approval for this version of the manuscript. S. C. Fuchs, D. Martinez and F. D. Fuchs designed the study, supervised the analysis and prepared the draft and final versions of this manuscript.

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