

Obstructive Sleep Apnea as a Risk Factor for Coronary Artery Disease

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Abstract

Background and Objective: Obstructive sleep apnea (OSA) is frequent and in some degree it affects about 24% of male and 9% of female in middle age adults. This study aimed to assess the association between risk of OSA and CAD.

Materials and Methods: This case-control study was performed among 184 patients with a history of coronary angiography in two catheter labs at hospitals in Qom, Iran. Control group had normal or minimal coronary stenosis (<50%) and case group had 1, 2 or 3 coronary vessel disease. All the patients completed demographic and Berlin questionnaires and then data were analyzed using SPSS version 16.

Results: Mean (\pm SD) age of participants was 55.36 ± 10 years. A total of 119 (61.4%) patients were female. This study showed significant difference between risk of OSA in patients with CAD and those without CAD (OR=1.25), hypertension (OR=10.4) and non-insulin dependent diabetes mellitus (OR=2.12), but there were no correlation between risk of OSA and ejection fraction less than 45% (P value=0.582).

Conclusions: OSA can be considered as one of the important risk factors for CAD.

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway, thereby inducing apnea episodes despite persistent thoracic and abdominal respiratory effort. Obstruction of upper airway and consequently negative intrathoracic pressure during sleep result in deterioration of blood gas and considerable sleep fragmentation with excessive daytime sleepiness (1). The disease has a high prevalence in the general population. On the basis of an obstructive apnea frequency, in middle age, 24% of men and 9% of women have OSA and it is associated with accompanying daytime sleepiness which is

a complaint for approximately 3-7 percent of men and 2-5 percent of women in the general population. Men are affected more than women. Other risk factors include middle and older ages, being overweight or obese, and having a small mouth and throat (2,3).

Most of the studies in recent years have reported the coronary artery disease (CAD) as a negative consequence of OSA. Progressive and chronic arteriosclerosis in the coronary arteries may lead to intimal thickening and rupture of atherosclerotic plaque with associated platelet adhesion, thrombus formation, and eventual stenosis of the coronary arteries which result in flow limitation and a subsequent imbalance of myocardial oxygen supply, unstable angina, non-Q-wave and Q-wave myocardial infarction and sudden cardiac death (4,5).

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Although mortality because of CAD has slightly decreased in the past decade in developed countries, CAD remains the most common cause of death all over the world, with an incidence of 380 myocardial infarctions per 100,000 persons per year among people aged between 36 and 64 years (6,7).

In Iran, adult mortality due to CAD was 317 persons daily and 116 thousands per year in 2001 (7). High risk behaviors such as lack of exercise, cigarette smoking and addiction, anxiety and stress, over-use of salt and unsaturated oil were underlying causes for increasing risk of ischemic heart disease in Iran (8). In the light of high frequency of overweight and consequently OSA and considering the correlation of apnea with cardiac disease (10,9), this study was aimed to assess the association between risk of OSA and CAD.

Materials and Methods

We conducted a case-control study during a six month period. All referred to Shahid Beheshti and Vali-Asr Hospitals in Qom for coronary angiography from April-October 2012 were considered for enrollment. Patients who were older than 30 years of age, without any history of acute coronary syndrome, ventricular arrhythmia, uncontrolled hypertension (200/ 100 mmHg) or markedly positive stress test were eligible. We performed 201 coronary angiography including 108 patients with coronary stenosis and 93 cases with normal or minimal stenosis. Considering inclusion and exclusion criteria, a total of 184 patients (92 individuals in each group) were recruited in this study (8).

Participants with coronary artery stenosis over 50% in one, two or three vessels were considered as case group and others with normal or less than 50% stenosis were enrolled as control groups.

Demographic characteristics such as age, sex, body mass index (BMI), neck circumference, marital and educational status were recorded for the participants in addition to Berlin questionnaire (BQ) as risk assess-

ment for OSA through direct interview. The BQ is a validated questionnaire developed in 1996 which explores known symptoms and features of OSA. Its validity and accuracy in primary care settings has been shown previously (11).

BQ is divided into three sections. Section one addresses snoring and witnessed apnea. Those who snore are asked to rate their snoring with regard to loudness, frequency, and whether their snoring bothers other people. Section two addresses daytime fatigue and sleepiness, and frequency of falling asleep while driving, or being in the car with a driver. In section three, a positive response is defined as a self-report of hypertension or a BMI >30 kg/m². Individuals who had positive scores in sections two of the three, or all categories were considered as high risk for OSA. Individuals who did not meet the above criteria were considered as low-risk for OSA.

The high risk pre-test probability for OSA predicts a Respiratory Distress Index (RDI) of >5 with a sensitivity of 0.86, a specificity of 0.77, a positive predictive value of 0.89 and a likelihood ratio of 3.79 (11). For questionnaire validation, we used the same methodology used by Netzer et al. (12). Bilingual physicians translated the BQ from its original English version into Persian. The Persian translation was back-translated into English by other bilingual physicians to ensure it was consistent with the content of the original version. For assessment of validity, prior to be used in the study, 30 patients filled out the questionnaire. Internal consistency of the first and second categories of the BQ was calculated separately. Finally, a Cronbach's alpha coefficient of 0.74 was calculated for this questionnaire.

In this study, the criteria for non-insulin dependent diabetes mellitus (NIDDM) were two times random fasting blood sugar more than 126 mg/dl or a single measurement over 200 mg/dl (13). For hyperlipidemia (HLP), the criteria comprised having LDL > 160 mg/dl with less than two cardiovascular risk factors, LDL over 130 mg/dl with

Table 1. Demographic characteristics in case and control groups

Demographic characteristics		Case		Control		P value
		n	percent	n	percent	
Sex	Female	53	57	60	65	0.28
	Male	39	43	32	35	
Marital status	Single	11	12	16	17	0.36
	Married	81	88	76	83	
Education level	Illiterate	32	34.8	35	38	0.55
	Primary	35	38	33	37.5	
	Guidance	10	10.9	9	9.8	
	Secondary	4	4.3	4	4.3	
	Postgraduate	11	12	19	11.4	
		Mean ± SD	Mean ± SD			P value
Age (year)		56.17 ± 8.38	54.55 ± 11.46			0.27
BMI (kg/m ²)		27.82 ± 5.60	28.28 ± 5.34			0.59
Neck circumference (cm)		42.90 ± 6.24	41.70 ± 5.84			0.18

Table 2. Association between risk of OSA and CAD

Risk of apnea		Case		Control		P value	OR	95% Confidence Interval	
		n	Percent	n	Percent			Lower	Upper
		High	61	66	44			48	0.008
Low	31	34	48	52					

Table 3. Association between Risk of OSA and HTN, NIDDM, and HLP

		High Risk		Low Risk		P value	OR	95% Confidence Interval	
		n	Percent	n	Percent			Lower	Upper
		HTN*	Yes	74	74			26	26
	No	17	22.1	60	77.9				
NIDDM [†]	Yes	41	41	59	59	0.02	2.12	1.10	4.07
	No	19	24.7	58	75.3				
HLP [‡]	Yes	56	56	44	44	0.009	2.22	1.21	4.09
	No	28	36.4	49	63.6				

*: Hypertension, [†]:NIDDM: Non-insulin dependent diabetes mellitus, [‡]: Hyperlipidemia

more than two risk factors and LDL above 100 in those with CAD (14).

Descriptive statistics were used to describe demographic characteristics of participants. Differences in means of continuous variables were assessed with t-test. A *P* value < 0.05 was considered significant. Continuous data are reported as mean ± SD. For analysis of qualitative parameters, we used chi-square, t- test and if it was necessary, checked with Fisher's exact test. All data were analyzed using SPSS v. 16 software for Windows (SPSS, Inc., Chicago, IL).

Results

A total of 184 patients participated in this study. Participants' mean (±SD) age was

55.36 ± 10 years, BMI was 28.06 ± 5 kg/m², neck circumference was 42.29 ± 6 cm and 61.4% of them were female. Other demographic characteristics for case and control groups are presented in Table 1.

In this study, we found a high risk of OSA among 59% of cases and 41% of controls, therefore statistically significant association was found between risk of OSA and CAD.

Also, this study showed an association between the risk of OSA with HTN, NIDDM and hyperlipidemia (Table 3).

In addition, independent t-test showed there were significant differences between the risk of OSA with BMI and neck circumference (Table 4).

Regarding the comparison of the risk of OSA with ejection fraction (EF), no signifi-

Table 4. BMI and neck circumference in terms of high and low risk for OSA

	High Risk		Low Risk		P value
	Mean	SD	Mean	SD	
BMI (kg/m ²)	29.68	5.53	26.30	4.98	< 0.001
Neck circumference (cm)	43.65	5.86	40.54	6.07	< 0.001

Table 5. Association between risks of OSA and Ejection Fraction (EF)

	EF<45%		EF>45%		P value
	n	percent	n	percent	
High Risk	18	17.6	84	82.4	0.58
Low Risk	12	14.6	70	85.4	

cant association was observed (Table 5).

Discussion

Different studies have shown a higher prevalence of OSA in patients with CAD (15). The largest study so far included 142 men with CAD confirmed by angiography. Polysomnographic evaluation has revealed a significantly higher apnea-hypopnea index (AHI) in this patient population compared to age-matched controls. An AHI of 4-10 has been shown in 37% of the patients with CAD while, the same proportion in controls was 22% (16).

Several studies in patients with CAD have yielded similar results with a reported incidence of OSA between 31-50% (18, 17). Hung et al., investigated male patients after myocardial infarction and found a mean AHI of 13/h, whereas the AHI was only 4/h in male controls without evidence of ischemic heart disease (19). In another study, the prevalence of CAD was 25% in patients with OSA confirmed by polysomnography (PSG) (20).

In this study, prevalence of high risk for OSA in case and control groups was 66% versus 48%, respectively. The prevalence of high risk for OSA was higher in CAD group; however, there was no significant association between risk of OSA and EF <45%. Although the exact mechanism linking sleep apnea with cardiovascular disease is unknown, there is evidence that OSA is associated with a group of proinflammatory and prothrombotic factors that are also important in the development of atherosclerosis.

Some studies have shown that patients with obstructive sleep apnea have high sympathetic activity when awake, with further increases in blood pressure and sympathetic activity during sleep. These increases are attenuated by treatment with CPAP (22, 21). Obstructive apnea is associated with endothelial dysfunction, increased C-reactive protein and cytokine expression, elevated fibrinogen levels and decreased fibrinolytic activity. Enhanced platelet activity and aggregation, leukocyte adhesion and accumulation of endothelial cells are common in both obstructive apnea and atherosclerosis (23). Thus, obstructive apnea is associated with myocardial ischemia, acute coronary events, surge in sympathetic activity, blood pressure, and ventricular dysfunction.

Many studies have shown that patients with obstructive sleep apnea have an increased incidence of daytime HTN, and this syndrome is recognized as an independent risk factor for HTN (25, 24). In current investigation, we detected prominent association between HTN and risk of OSA. In some studies, there is an association between obstructive sleep apnea syndrome (OSAS) and carbohydrate metabolic disturbances. These presented the data of clinical trials that showed OSAS as a risk factor of type 2 diabetes mellitus (27,26). Present findings showed a significant association between NIDDM and risk of OSA.

Also, there were considerable relationships among HLP, BMI, and neck circumference with the risk of OSA. There is an obesity epidemic worldwide, which has been increasing in recent years especially in

Middle East and Iran. In many studies, prevalence of overweight and obesity in Iran were reported in the range of 28-41% and from 10- 26%, respectively (29,28). Obesity is a major risk for OSA as well. In general, one-third of obese patients and two-third of morbid obese patients have OSA (31,30). This evidence shows sleep related breathing problem is very common and is associated with an increased risk of cardiovascular disease.

This study has the limitation of not using PSG for OSA diagnosis. The gold standard for diagnosis of sleep apnea syndrome is based on PSG, and severity is measured with an AHI that counts the total number of apneas per hour of sleep. However, PSG in the sleep laboratory is expensive, cumbersome, and not readily available in many geographic areas despite a growing demand for this test. There are some questionnaires for screening of sleep apnea in the current study, BQ was used.

In conclusion, considering the high incidence of CAD and sleep apnea in Iran and their association with OSA, studies like this can help physicians in correct management of ischemic heart disease.

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