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Cardiac function and cognitive function in patients with obstructive sleep apnea

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Abstract

Objectives: This study was designed to evaluate echocardiographic findings in patients with obstructive sleep apnea (OSA) with cognitive impairment and compare it with the control group.

Methods: Sixty-seven OSA patients and 52 group of healthy controls were evaluated prospectively by Mini-Mental State Examination questionnaire and trans-thoracic echocardiography.

Results: The cognitive impairment and diastolic dysfunction were 19.6% ($P = .002$) and 18.4% ($P = .016$) more prevalent in OSA group compared to the control group. The mean tricuspid regurgitant gradient, pulmonary artery size, and transmitral *A* velocity were higher, but mean right ventricular peak systolic velocity, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), transmitral *E/A* ratio, and annular *E'* velocity were lower in the OSA group than the control group. Comparing the patients with and without cognitive disorders, showed significant differences regarding the size of right atrium, TAPSE and FAC ($P < .05$).

Conclusions: OSA patients need accurate cardiac examinations, early diagnosis, and interventions to prevent the progression of cardiac dysfunction, especially older male patients with higher BMI and impaired cognition. Further studies are needed to determine the exact link between the OSA, obesity, and cardiac physiology.

Keywords: Sleep apnea, Polysomnography, Echocardiography, Heart, Cognition

Introduction

Sleep disturbance due to respiratory disorders is a common disorder that increases with age and usually remains undiagnosed (Young et al. 2002; Khazaie et al. 2011). Obstructive sleep apnea (OSA) is the most common form of these disorders, characterized by stopping breathing or periods of shallow breathing. Various studies have reported a prevalence of 9 to 24% in the age range of 30–60 years (Young et al. 2002). OSA is a clinical disorder result from recurrent sleep apnea with symptoms of snoring, respiratory pause, sudden and frequent awaking following a respiratory interruption, morning headaches, fatigue, and daytime sleepiness (Young et al. 2002; Khazaie et al. 2011). OSA patients are also at risk for cardiovascular disease and stroke due to hypoxia and hypercapnia (Al-Khadra et al. 2018; Li et al. 2018; Hui et al. 2019). Although polysomnography is the gold standard for the diagnosis of obstructive sleep apnea, history and physical examination are the simplest and most cost-effective way to detect the possibility of OSA (Khazaie et al. 2011). Since polysomnography is time-consuming and requires special measures, most OSA cases are left undiagnosed and untreated (Young et al. 2002). OSA is a known predictor for cardiovascular disease and its related mortality. It is two to five times more common in patients with coronary artery disease compared to the general population (Tuleta et al. 2011). In the study of Konecny et al., 30–90%, and in the study of Bradley et al., 99% of patients with myocardial infarction had OSA (Bradley and Floras 2009; Konecny et al. 2010). Respiratory disruptions and decreased oxygen saturation due to OSA increase sympathetic system activity, endothelial dysfunction, inflammatory reactions, and platelet activity. Moreover, OSA could cause metabolic

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disorders that may induce and aggravate cardiovascular diseases and arrhythmia (Khazaie et al. 2011; Evans et al. 2014). OSA is also associated with modifiable cardiovascular risk factors. Fifty percent of hypertensive patients have OSA. Repeated hypoxia causes hyperaldosteronism to increase sympathetic tone, endothelial dysfunction, and inflammatory process, which intensifies the process of atherosclerosis and hypertension. About 83% of type two diabetic patients have OSA (Khazaie et al. 2011). OSA disrupts glucose metabolism, increases the chance of developing type two diabetes, impaired glucose tolerance, insulin resistance, and dyslipidemia (Evans et al. 2014). Failure to control and treat OSA in patients with myocardial infarction increases the risk of coronary artery occlusion and increases cardiovascular morbidity and mortality (Bozbas et al. 2017).

Due to the negative impact of OSA on cognitive functioning in daily life, the psychological evaluation of these patients became more prominent, recently (Tudorache et al. 2019). Studies in OSA patients showed some degrees of impaired cognitive function, memory, executive function, and motor abilities (Daurat et al. 2016; Tudorache et al. 2019). This study was designed to evaluate echocardiographic findings in patients with obstructive sleep apnea with cognitive impairment and compare it with the control group.

Methods and materials

Study population

OSA patients referred to the polysomnography unit of Baqiyatallah hospital during the years 2018–2019 were considered as the sampling frame. The polysomnography was done for all patients and the apnea-hypopnea index (AHI) was measured. Moderate (AHI = 15–30) and severe (AHI ≥ 30) OSA patients were included inti the study as OSA group if they had consented to participation. Patients with AHI < 15 were enrolled into study as control group. Apnea and hypopnea were defined according to the Chicago criteria (a > 50% reduction in airflow, or a ≤ 50% decrease in airflow associated with an oxygen desaturation of ≥ 3% or arousal) (Quan et al. 1999). Patients were excluded if they had known cardiac disorders (e.g. heart failure, myocardial infarction, arrhythmia, and cardiomyopathy), history of stroke, psychological and neurological disorders, and in case of using sedative drugs. Patients were also excluded if they had severe left-sided valvular diseases and decompensated failure of the left heart.

Subjects' evaluations

After giving informed consent, the subjects' demographic data (e.g. age, gender, and body mass index), history, physical examination findings, and polysomnography results were registered in their checklist.

Echocardiography was done for all patients and healthy controls by a single physician in a unique center with the same equipment. The echocardiographic parameters of left ventricular ejection fraction (LVEF), right atrium (RA) diameter, right ventricle (RV) mid diameter, tricuspid regurgitant gradient (TRG), right ventricular peak systolic velocity (RVSM), tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), existence of patent foramen ovale (PFO), inferior vena cava (IVC) diameter, right ventricular outflow tract (RVOT), pulmonary artery (PA) size, transmitral early diastolic velocity (*E*), and mitral annular early diastolic velocity (*E'*) were measured in all OSA and control subjects. Echocardiograms and tissue Doppler images were obtained by the Vivid-7 ultrasound machine (GE Medical Systems, Milwaukee, Wis) using the M4S probe in the left lateral decubitus position based on the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (Galderisi et al. 2017). An interview was done for OSA and control subjects to assess their cognitive function using a validated Persian version of the Mini-Mental State Examination (MMSE) questionnaire (Ansari et al. 2010).

Ethical consideration

The study protocol was approved by the local institutional review board and Ethics Committee of Baqiyatallah University of Medical Sciences and was in line with the Declaration of Helsinki guideline. All the patients and the control group were enrolled voluntarily by giving written informed consent. Echocardiography, polysomnography, and other para-clinic evaluations were free of charge for the participants of both groups. All data were kept secure and anonymous.

Statistical analysis

Data analysis was done by statistical package for the social sciences software (SPSS version 21, IBM Co., Armonk, NY, USA) for Microsoft Windows. The normality of distribution in quantitative variables was checked by the one-sample Kolmogorov-Smirnov (K-S) test. Independent samples t-test was used to compare normally distributed and the Mann-Whitney *U* test for non-normally distributed quantitative variables between the two groups. Chi-square and Fisher's exact tests were used to compare the categorical variables between the two groups. A binary logistic regression test with the forward stepwise (Wald) method was used to compare the independent effect of variables between the two groups. A two-sided *P* value of less than 0.05 was considered statistically significant.

Results

Comparing the OSA and control groups

One-hundred and nineteen people with a mean age of 49.74 ± 12.24 years and a mean body mass index (BMI) of 29.17 ± 5.29 kg/m^2 were evaluated (64 OSA patients and 52 healthy controls). The apnea was severe in 50 patients and moderate in 17 patients. There was no significant difference regarding the subjects' gender between the OSA and control groups, but the subjects' age and BMI were significantly more in OSA patients compared to the controls.

The MMSE score was significantly more in healthy controls compared to OSA patients ($P = .002$). Considering the cut-off point of ≤ 23 for the existence of cognitive disorder, 25.4% of OSA patients and 5.8% of healthy controls had impaired cognitive function ($P = .004$).

The existence of diastolic dysfunction was significantly more in the OSA group compared to the control group (29.9% vs. 11.5%, $P = .016$), but there was no significant difference regarding LVEF between the two groups.

The echocardiography parameters of mean TRG, PA size, transmitral *A* velocity, and frequency of enlarged IVC were significantly more in OSA patients compared to the healthy subjects. The mean RVSM, TAPSE, FAC, transmitral *E/A* ratio, septal and lateral annular *E'* velocities were significantly more in the control group compared to the OSA group. There were no significant differences between the OSA and control groups regarding mean RA and RV size, proximal and distal RVOT, transmitral *E* velocity, and frequency of PFO existence (Table 1).

Multivariate analysis using binary logistic regression showed independent differences in subjects' age, gender, BMI, impaired cognitive function, and transmitral *E/A* ratio between the OSA patients and healthy controls ($R^2 = 0.662$, $P < .001$).

Table 1 Comparing the patients with and without obstructive sleep apnea (OSA) [a, b]

Variable	OSA (*N* = 67)	Control (*N* = 52)	*P*
Age, years	54.29 ± 10.60	43.87 ± 11.78	< 0.001
BMI, kg/m^2	31.57 ± 5.44	26.01 ± 2.81	< 0.001
Gender, male/female	36/31	28/24	0.990
MMSE score	25.98 ± 2.92	27.57 ± 2.32	0.002
Cognitive disorder	17 (25.4)	3 (5.8)	0.004
LVEF, %	53.13 ± 2.59	53.86 ± 2.36	0.115
Diastolic dysfunction	20 (29.9)	6 (11.5)	0.016
RA diameter, mm	13.84 ± 3.53	13.68 ± 2.94	0.789
RV mid diameter, cm	3.12 ± 0.36	3.10 ± 0.37	0.750
TRG, mmHg	23.55 ± 5.71	20.17 ± 4.41	0.001
RVSM, cm/sec	12.22 ± 2.21	13.17 ± 2.11	0.019
TAPSE, mm	19.81 ± 4.42	22.72 ± 3.89	< 0.001
FAC, %	40.48 ± 9.57	45.06 ± 9.01	0.009
PFO	8 (11.9)	11 (21.2)	0.174
Enlarged IVC	8 (11.9)	0 (0.0)	0.008
RVOT proximal diameter, cm	2.86 ± 0.45	2.86 ± 0.45	0.981
RVOT distal diameter, cm	2.17 ± 0.43	2.01 ± 0.81	0.228
PA size, mm	2.26 ± 0.87	2.01 ± 0.33	0.032
Transmitral *E* velocity, m/sec	0.70 ± 0.17	0.75 ± 0.19	0.169
Transmitral *A* velocity, m/sec	0.75 ± 0.21	0.62 ± 0.16	< 0.001
Transmitral *E/A* ratio	0.98 ± 0.28	1.25 ± 0.38	< 0.001
Septal annular *E'* velocity, cm/sec	8.09 ± 1.10	9.29 ± 2.84	0.011
Lateral annular *E'* velocity, cm/sec	10.15 ± 2.13	11.36 ± 3.12	0.018

[a] Data are presented as mean ± standard deviation or frequency (frequency percent)

[b] Abbreviations: *BMI* Body mass index; *km* Kilograms; *m* Meter; *MMSE* Mini-mental state examination; *LVEF* Left ventricular ejection fraction; *RA* Right atrium; *RV* Right ventricle; *TRG* Tricuspid regurgitant gradient; *RVSM* Right ventricular peak systolic velocity; *TAPSE* Tricuspid annular plane systolic excursion; *FAC* Fractional area change; *PFO* Patent foramen ovale; *IVC* Inferior vena cava; *RVOT* Right ventricular outflow tract; *PA* Pulmonary artery; *E* Transmitral early diastolic velocity; *E'* Mitral annular early diastolic velocity

Comparing the OSA patients with and without cognitive impairment

OSA patients with cognitive impairment had more RA size and less TAPSE and FAC compared to OSA patients without impaired cognitive function. There were no significant differences regarding the subjects' age, BMI, gender, LVEF, diastolic dysfunction, RV size, TRG, RVSM, PFO, RVOT, PA size, and transmitral *E and A* and annular *E'* velocities between the OSA subjects with and without cognitive impairment. Table 2 compares the OSA patients with and without the cognitive disorder.

Discussion

Obesity as a confounding factor

In our study, the BMI of OSA patients was higher than the control group, which could affect the subjects' cardiovascular function. Obesity was an independent risk factor for right atrial enlargement in OSA patients of Al-Khadra et al.'s study (Al-Khadra et al. 2018). Hui's investigation also showed that obesity and OSA are two independent risk factors for cardiac dysfunction (Hui et al. 2019). The subjects' BMI was also higher in the OSA group than the control group in previous studies (Buonauro et al. 2017). Our study tried to remove the effect of obesity and other confounders on the results by multivariable analysis. Only five variables of age, male gender, BMI, cognitive impairment, and transmitral *E/A* ratio were significantly different between the two groups in multivariable analysis.

Table 2 Comparing OSA patients with and without cognitive impairment

Variable	Cognitive impairment		*P*
	Yes (*N* = 17)	No (*N* = 50)	
Age, years	57.12 ± 12.6	53.34 ± 9.8	0.207
BMI, kg/m^2	29.87 ± 5.0	32.15 ± 5.5	0.136
Gender, male/female	10:7	26:24	0.626
LVEF, %	52.35 ± 3.1	53.40 ± 2.4	0.151
Diastolic dysfunction	6 (35.3)	14 (28.0)	0.570
RA diameter, mm	15.89 ± 3.8	13.14 ± 3.2	0.005
RV mid diameter, cm	3.16 ± 0.35	3.11 ± 0.36	0.574
TRG, mmHg	24.88 ± 5.4	23.10 ± 5.8	0.269
RVSM, cm/sec	12.75 ± 2.3	11.86 ± 1.7	0.162
TAPSE, mm	18.18 ± 4.6	20.65 ± 4.1	0.043
FAC, %	33.71 ± 10.2	42.78 ± 8.2	0.003
PFO	2 (11.8)	6 (12.0)	0.674
RVOT proximal diameter, cm	2.84 ± 0.61	2.87 ± 0.39	0.806
RVOT distal diameter, cm	2.31 ± 0.45	2.11 ± 0.41	0.114
PA size, mm	2.40 ± 0.45	2.22 ± 0.97	0.461
Transmitral *E* velocity, m/sec	0.75 ± 0.22	0.69 ± 0.15	0.168
Transmitral *A* velocity, m/sec	0.85 ± 0.31	0.72 ± 0.16	0.138
Septal annular *E'* velocity, cm/sec	8.82 ± 1.74	8.18 ± 2.09	0.529
Lateral annular *E'* velocity, cm/sec	10.24 ± 2.25	9.88 ± 1.79	0.555

Cardiac function of OSA patients compared to the controls

A decreased RA function in OSA patients compared to the control group was reported by Li and colleagues, which had a direct relationship with the apnea severity (Li et al. 2018). The right ventricular diameter and pulmonary artery systolic pressure were higher and right ventricular global longitudinal strain (GLS) was lower in OSA patients than in the control group in a study by Buonauro and colleagues. They showed no significant difference between the OSA and control groups in terms of TAPSE, RVEF, transmitral *E/A* ratio, RV end-diastolic volume, RV end-systolic volume, RV stroke volume, and RV cardiac output (Buonauro et al. 2017). Our study showed similar results regarding the patients' LVEF but not about their RV size, TAPSE, and transmitral *E/A* ratio. Bozbas and colleagues reported a decreased coronary reserve flow in OSA patients compared to the control group (Bozbas et al. 2017).

Some previous studies showed the increased transmitral *E/A* ratio and annular *E'* velocity and reduced transmitral *A* velocity in OSA patients compared to the healthy subjects (Sascău et al. 2018). Some studies showed lower LVEF and E velocity in OSA patients compared to the controls (Sascău et al. 2018).

A meta-analysis showed the higher RV diameter, RV free wall thickness, and myocardial performance index and lower RV annular systolic velocity, TAPSE, and FAC in OSA patients compared to the control group (Maripov et al. 2017). The lower amounts of TAPSE, FAC, and RVSM in OSA patients compared to the controls were also observed in our study, but there was no significant difference in RV size between our groups.

Effect of OSA treatment on patients' cardiac function

Adenotonsillectomy increased the RV myocardial performance index in children with sleep apnea induced by adenotonsillar hypertrophy (Kim et al. 2018). PFO closure in OSA patients did not significantly change the AHI and oxygen desaturation index but improved their quality of life and Epworth's score (Hoole et al. 2017). Treatment with continuous positive airway pressure (CPAP) can decrease the IVC diameter and tricuspid regurgitation(Au et al. 2018) and can increase annular *E'* velocity and pulse wave velocity (Shim et al. 2018).

The relationship between cognitive function and cardiac function in OSA

The number of patients with impaired cognitive function was more and the mean MMSE score was lower in the

OSA group than in the control group. Previous studies showed the negative impact of OSA on patients' cognitive function (Daurat et al. 2016; Tudorache et al. 2019). We compared OSA patients in two groups with and without impaired cognitive function. In patients with cognitive impairment, the size of RA was higher, and FAC and TAPSE were lower than in patients without impaired cognitive function. The relationship between cognition and dynamic cardiac change is fascinating. Hence, future studies could evaluate the potential link between RA size and FAC/TAPSE with cognitive function.

This study had some limitations. The MMSE score seems to be not enough for evaluating the cognitive function in OSA patients. Future studies could use the Montreal Cognitive Assessment (MOCA) or other cognitive tests to reach more accurate results. This study was not able to follow the patients for a period. Future studies could evaluate the effect of OSA treatment on the patients' cardiac function.

Conclusion

The results showed an impaired cardiac function of OSA patients compared to the control group regarding diastolic function, TRG, RVSM, TAPSE, IVC size, pulmonary artery size, FAC, transmitral *A* velocity, *E/A* ratio, and annular *E'* velocity. Obstructive sleep apnea and obesity were two dependent risk factors for patients' cardiac dysfunction, but obstructive sleep apnea had only an independent effect on transmitral *E/A* ratio. The results also indicated a higher prevalence of cardiac dysfunction in patients with cognitive impairment compared to those with normal cognitive function. Given the results of this study and the presence of cardiac dysfunction in OSA patients, it is recommended that these patients be examined more closely to prevent cardiac dysfunction with early interventions. Multiple risk factors together would be a potential target of the patients' evaluation for early intervention along with older and higher BMI men. Further studies are needed to determine the exact link between the OSA, obesity, and cardiac physiology.

List of Abbreviations

AHI: Apnea-hypopnea index; BMI: Body mass index; CPAP: continuous positive airway pressure; *E*: Trans-mitral early diastolic velocity; *E'*: mitral annular early diastolic velocity; EF: Ejection fraction; FAC: Fractional area change; GLS: Global longitudinal strain; IVC: Inferior vena cava; LV: Left ventricle; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; OSA: Obstructive sleep apnea; PA: Pulmonary artery; PFO: Patent foramen ovale; RA: Right atrium; RV: Right ventricle; RVOT: Right ventricular outflow tract; RVSM: Right ventricular peak systolic velocity; TAPSE: Tricuspid annular plane systolic excursion; TRG: Tricuspid regurgitant gradient

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Authors' contributions

Idea development: EV; AK, Study design: EV; AK; TB, Data collection: EV; AK; RA; TB, Data analysis: AK, Manuscript draft: EV; AK; RA; TB, Study supervision: EV; AK. The author(s) read and approved the final manuscript

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Availability of data and materials

The raw data will be available by the corresponding author upon request.

Ethics approval and consent to participate

The Ethics Committee of Baqiyatallah University of Medical Sciences approved the study protocol. All the patients and the control group were enrolled voluntarily by giving written informed consent.

Consent for publication

Written informed consent was obtained for the publication of the subjects' data anonymously.

Competing interests

Authors declared no conflict of interests.

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