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The correlation of ECHO findings of right cardiac pathologies with BNP, uric acid, and CRP in OSAS

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Background/aim: Right cardiac pathologies develop in patients with obstructive sleep apnea syndrome (OSAS) and in most patients there are no symptoms in the early stages of right cardiac disorders. We aimed to evaluate a possible relationship between B-type natriuretic peptide (BNP), blood uric acid, C-reactive protein (CRP), and the right cardiac pathologies in patients with OSAS, and the role of these parameters in the management of patients with OSAS.

Materials and methods: A total of 98 subjects, 31 (31.6%) controls and 67 (68.4%) with OSAS, were included in the study. All the subjects underwent polysomnography, and standard and tissue Doppler echocardiography (ECHO) examinations. BNP, CRP, and blood uric acid levels were measured in all patients.

Results: Upon evaluating the relationship between BNP and ECHO parameters, BNP levels were found to positively correlate with such ECHO parameters as pulmonary artery pressure. As for the association between CRP and ECHO findings, RV diameter exhibited a statistically significant positive correlation with them. Moreover, uric acid was found to statistically correlate positively with right atrium dimensions.

Conclusion: BNP, CRP, and blood uric acid levels can be used as adjunctive parameters in the early diagnosis and follow-up of right heart pathologies in patients with OSAS.

Key words: OSAS, echocardiography, right cardiac pathologies, BNP, uric acid, CRP

1. Introduction

Obstructive sleep apnea syndrome (OSAS), a syndrome characterized by partial or total obstruction in the upper airways, has an incidence of 2%–4% in the population and it may lead to morbidity and mortality (1,2). Right cardiac pathologies develop in patients at different rates, and most patients do not show clinical signs relevant to right cardiac pathology (3,4). Patients that have clinical symptoms related to right cardiac pathologies can be diagnosed early and treated. However, if patients with OSAS who do not have symptoms associated with right cardiac pathology could be diagnosed early, the progress of the disease could be delayed.

Enormous progress has recently been made in understanding the impact of OSAS on the cardiovascular system and the associated comorbidities. Although the exact mechanisms governing these associations are poorly understood, the accumulated evidence implicates oxidative stress and inflammation as 2 basic mechanisms associated with OSAS (5). There is increasing evidence that intermittent hypoxia plays an important role in the development of cardiovascular risk in OSAS through the activation of pulmonary inflammation pathways (6). It is also known that an increase in sympathetic activity induced by apnea and hypopnea episodes during the night may cause systolic and diastolic dysfunction of both right and left ventricles (7–9). The patient becomes subject to injuries caused by hypoxia and other events secondary to hypoxia such as sympathetic discharge during the episodes and ischemia-reperfusion and production of reactive oxygen species during reoxygenation (10). The effect of the events may be evaluated by measuring serum C-reactive protein (CRP) (11) and blood uric acid levels (12). Although there are some studies showing increased CRP levels in OSAS (6), CRP levels correlate well with adipose tissue mass and obesity rather than OSAS (13).

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CRP levels have been shown to be higher in patients with OSAS together with cardiovascular diseases compared to those who have OSAS without cardiovascular diseases (14). B-type brain natriuretic peptide (BNP) production from the heart is induced because of the hypoxia and sympathetic discharge. Elevated BNP levels are associated with left ventricular hypertrophy, left ventricular diastolic dysfunction, and impaired functional capacity (15–17).

There is not a sufficient number of studies to predict clinically asymptomatic right cardiac pathologies in patients with OSAS. In order to assist with early diagnosis and understand their role in the management of patients with OSAS, we aimed to evaluate the possible relationship between BNP, blood uric acid, CRP, and right cardiac pathologies in patients with OSAS.

2. Materials and methods

2.1. Study population

A total of 156 OSAS patients and controls were evaluated between January 2010 and December 2011. Fifty-eight patients were excluded due to hypertension, chronic left heart failure, valvular heart disease, coronary artery disease, pericardial disease, diabetes mellitus, chronic renal disease, pulmonary disease, a history of smoking 1 pack/year or more, or any infections at the time of the study or within 2 weeks prior to the study. Additionally, patients who had left heart pathologies with ECHO were excluded. A total of 67 consecutive (47 (70.1%) male and 20 (29.9%) female) patients with OSAS, and 31 (22 (70.9%) male and 9 (29.1%) female) age- and sex-matched controls were included in the study. Polysomnography was performed and subjects with an AHI < 5 were defined as the control group (group 1) while those with AHI ≥ 5 and excessive daytime sleepiness (EDS) were defined as the OSAS group (group 2) (18).

2.2. Measurements

After an initial clinical evaluation, a questionnaire was used to obtain information about snoring history, witnessed apnea, and EDS. The Epworth Sleepiness Scale (ESS) was used to evaluate sleepiness. A detailed physical examination was done and anthropometric measurements, including neck and waist circumference, height, weight, and body mass index (BMI), were obtained. Their chest X-rays, pulmonary function tests, electrocardiograms, and echocardiograms were also obtained.

Hypertension was defined as an average blood pressure of ≥140/90 mmHg, according to the National Heart Lung and Blood Institute criteria, or the current use of antihypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dL. Obesity was defined as a BMI of ≥25.

A venous blood sample was obtained in the morning after the completion of PSG. Blood CRP levels (range 0–5 mg/L), blood uric acid levels (range 3.5–7.5 mg/dL), arterial blood gases, and B-type natriuretic peptide levels (range 0–100 pg/mL) were measured. Blood uric acid level was determined by use of a cobas 8000 modular analyzer series (USA). Blood CRP analysis was conducted using nephelometry (Database Siemens Germany). Blood samples were drawn into appropriate tubes for measurement of BNP levels. BNP analysis was performed using the fluorescence immunoassay method (Biosite, San Diego, CA, USA). Arterial blood samples were drawn from the patients included in the study from the radial artery, using specially designed heparinized injectors for arterial blood gas analysis. PaO_2, $PaCO_2$, pH, and SaO_2 measurements were performed according to the ion-selective electrode method via a blood gas analyzer (cobas b 221, Mannheim, Germany).

2.3. Sleep study

Full PSG monitoring was performed with the Compumedics E-series Sleep System (Compumedics Sleep, Melbourne, Australia). Electroencephalography (EEG, C3/A2, C4/A1, O1/A2, and O2/A1), electrooculography (EOG), electromyography (EMG), and electrocardiography were performed simultaneously. Surface electrodes were used to record EEG channels, right and left EOGs, and submental EMG. Ventilatory flow, either at the nose or at both the nose and mouth, was measured with airflow. Respiratory movements of the chest and abdomen and body position were monitored by inductive plethysmography bands. The arterial oxygen saturation was measured transcutaneously with a finger oximeter. Apnea was defined as a continuous cessation of airflow for ≥10 s, and hypopnea was defined as at least a 50% reduction of airflow for ≥10 s with an oxygen desaturation of ≥3% or an EEG arousal from sleep. Apneas were classified as obstructive, central, or mixed according to the standard criteria of the American Academy of Sleep Medicine (19).

2.4. Echocardiography

All patients underwent conventional 2D and Doppler echocardiographic investigation in addition to tissue Doppler imaging by a Vivid 7 (GE, Norway) echocardiography (ECHO) device using a 2.5 MHz transducer. In the left lateral decubitus position, echocardiograms were recorded on standard parasternal and apical images. The images were viewed and recorded at end inspiration and end expiration in the patients on normal ventilation. For each patient, M-mode, B-mode, color flow mapping, and pulse-wave Doppler records were obtained.

Left ventricle diastolic diameter (LVDD), left ventricle systolic diameter (LVSD), left ventricle end diastolic volume (LVEDV), left ventricle end systolic volume (LVESV), fractional shortening (FS), left atrium diameter (LA), right atrium diameter (RA), right ventricle diameter (RV), and

interventricular septum thickness (IVS) were determined with a parasternal long-axis view. Left ventricular ejection fraction (LVEF) was calculated using a modified version of Simpson's method (20). Systolic pulmonary arterial pressure was calculated by adding estimated right atrial pressure onto the regurgitation gradient through the tricuspid valve. The dilatation of RA (over 46 mm), RV (over 45 mm), and elevation of PAP (over 36 mmHg) were defined as right heart pathologies.

Regarding the standard and tissue Doppler, a pulsed Doppler evaluation of the left ventricular inflow was performed by placing the sample volume at the tips of the mitral valve in apical 4-chamber view. The following measurements were performed in order to evaluate the global diastolic functions of the left ventricle: peak E and A wave velocities (m/s) and E/A ratio; E wave deceleration time (DT) (ms); isovolumetric relaxation time (IVRT) (ms) (time period between the end of the systolic flow wave and the onset of transmitral E wave, which is measured by placing the pulsed wave sample volume between the left ventricular outflow tract and the mitral valve). All the measurements were obtained based on the standard proposed by the American Echocardiography Society (21).

All patients were informed about the study and provided their consent to participate. The study was planned according to the ethics guidelines of the Helsinki Declaration, and the study protocol was approved by the local ethics committee (B.30.2.ATA.0.01.00/05).

2.5. Statistical analysis

Data were expressed as mean ± SD and percentage. Statistical analysis was performed using SPSS for Windows (Version 19.0; SPSS Inc., Chicago, IL, USA). The significance of the differences between groups was assessed using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U post hoc test. Spearman's correlation analyses were used for ECHO parameters between BNP, CRP, and blood uric acid. ROC curves of BNP, CRP, and uric acid were obtained for pulmonary arterial pressure. The sensitivity, specificity, and positive and negative predictive values were calculated according to their upper cut-off values. Statistical significance was accepted as P values less than 0.05.

3. Results

A total of 98 subjects, 31 (31.6%) controls and 67 (68.4%) OSAS patients, with a mean age of 49.8 ± 10.9 years and 49.7 ± 12.7 years, were included in the study. Demographic characteristics and laboratory findings of the groups are shown in Table 1. PSG and ECHO findings of the groups are shown in Tables 2 and 3.

BNP was found to show a statistically significant positive correlation with such ECHO parameters as PAP (P = 0.03, r = 0.277). As for the association between CRP and

Table 1. Demographic characteristics of all groups, their pulmonary function tests, and laboratory findings

	Group 1 (n = 31)	Group 2 (n = 67)	P value
Age (years)	49.8 ± 10.9	49.7 ± 12.7	0.032
BMI	29.5 ± 7.3	34.6 ± 8.3	0.037
NC (cm)	36.5 ± 4.2	40.6 ± 4.2	0.012
WC (cm)	98 ± 15.4	111.3 ± 14.6	0.017
ESS	3 ± 2	10 ± 4	0.001
FVC (% pred)	108 ± 13.8	105.7 ± 16.9	0.709
FEV_1 (% pred)	103.8 ± 13.6	98.2 ± 17.5	0.381
FEV_1/FVC	82.4 ± 6.7	78.1 ± 7.5	0.075
CRP	0.85 ± 0.3	2.87 ± 0.7	0.035
Uric acid	4.1 ± 0.6	9 ± 0.8	0.001
BNP	12.7 ± 4.5	35.8 ± 4.4	0.003
PaO_2	76.6 ± 11.3	69.2 ± 7.3	0.880
$PaCO_2$	33.5 ± 4.6	34.3 ± 5.1	0.703
$SatO_2$	95.2 ± 2.7	93.3 ± 4.1	0.805

Data are presented as mean ± SD. BMI: body mass index, NC: neck circumference WC: waist circumference, ESS: Epworth sleepiness scale, FVC (% pred): force vital capacity, FEV_1 (% pred): forced expiratory volume in 1 s, FEV_1/FVC: forced expiratory volume in 1 s/forced vital capacity ratio, CRP: C - reactive protein, BNP: B - type brain natriuretic peptide, PaO_2: partial pressure of oxygen, $PaCO_2$: partial pressure of carbon dioxide $SatO_2$: oxygen saturation.

Table 2. Cardiorespiratory polysomnography results of all groups

	Group 1 (n = 31)	Group 2 (n = 67)	P value
AHI	1.5 ± 1.4	52.6 ± 32.3	0.001
MD	4.3 ± 2.5	8.1 ± 4.9	0.002
DT90	26.7 ± 53	118.7 ± 98.3	0.001
MOD	84 ± 10.5	70.9 ± 4.9	0.002
AHT	1.98 ± 2.4	29.3 ± 13.8	0.001
MAHR	171.5 ± 58	200.8 ± 70.2	0.378
MHR	66.9 ± 8.2	75.6 ± 11.4	0.013
LHR	22.6 ± 17.3	19.1 ± 9.4	0.795

Data are presented as mean ± SD. AHI: apnea-hypopnea index, MD: mean desaturation, DT90: desaturation time under 90 (min), MOD: maximum oxygen desaturation, AHT: apnea-hypopnea time (min), MHR: mean heart rate, LHR: lowest heart rate, MAHR: maximum heart rate.

Table 3. Echocardiographic measurements of all groups.

	Group 1 (n = 31)	Group 2 (n = 67)	P value
LVDD (mm)	45.6 ± 4.1	46.9 ± 4.7	0.310
LVSD (mm)	27.8 ± 3.8	29.3 ± 4.5	0.367
LVEDV (mm)	92.8 ± 8.8	96.6 ± 21.7	0.263
LVESV (mm)	60.2 ± 11.5	60.8 ± 16.4	0.745
FS (%)	36.8 ± 4.2	37.6 ± 5.7	0.494
LA (mm)	36 ± 2.6	37.1 ± 3.1	0.344
RA (mm)	36 ± 2.9	48.1 ± 5.3	0.269
RV (mm)	35.7 ± 2.5	48.9 ± 5.6	0.010
IVS (mm)	9.8 ± 1.4	10.8 ± 1.2	0.039
PAP	25.3 ± 7.5	41.2 ± 12.9	0.012
DT (ms)	184.3 ± 26.4	180 ± 37.7	0.499
IVRT (ms)	81.5 ± 7.3	82.1 ± 6.6	0.676
E/A ratio	1.02 ± 0.2	0.99 ± 0.1	0.623
LVEF (%)	63.3 ± 3.2	64.2 ± 4.1	0.017

Data are presented as mean ± SD. LVDD: left ventricle diastolic diameter, LVSD: left ventricle systolic diameter, LVEDV: left ventricle end diastole volume, LVESV: left ventricle end systole volume, FS: fractional shortening, LA: left atrium diameter, RA: right atrium diameter, RV: right ventricle diameter, IVS: interventricular septum, PAP: pulmonary artery pressure DT: mitral deceleration time IVRT: isovolumic relaxation time, E/A: ratio of early and lately mitral flow velocity, LVEF: left ventricular ejection fraction.

ECHO findings, the RV diameter exhibited a statistically significant positive correlation with them (P = 0.004, r = 0.322). Uric acid levels were positively correlated with ECHO findings like RA diameter (P = 0.006, r = 0.310). All 3 parameters (BNP, CRP, and blood uric acid) were documented to have a statistically significant relationship with AHI ((P = 0.002, r = 0.350), (P = 0.032, r = 0.242), (P = 0.001, r = 0.441), respectively).

When adjusted for age and BMI, in particular, the statistically significant correlation between PAP and BNP was observed to persist. In the present study a statistically significant correlation between BNP level and all the ECHO parameters indicates the involvement of the left heart, except for LVEDV. The age- and BMI-adjusted levels of BNP, CRP, and blood uric acid, and ECHO right heart findings are presented in Tables 4 and 5.

ROC curves of BNP, CRP, and uric acid obtained for pulmonary arterial pressure are shown in Figures 1a–1c. The sensitivity, specificity, and positive and negative predictive values calculated according to their upper cut-off values are summarized in Table 6.

4. Discussion

Right cardiac pathologies are detected in different rates in OSAS patients (3,4) and there are frequently no clinical symptoms. Blood BNP, uric acid, and CRP levels can be of predictive value for right cardiac pathologies in patients with OSAS.

Primary pulmonary changes due to chronic intermittent hypoxia and apnea arousals, besides many coexisting factors, such as obesity, systemic hypertension, and coronary artery disease, may cause deterioration in the RV in patients with OSAS (22). Most studies reported that concomitant chronic pulmonary disorders were required for OSAS to cause RV dysfunction. Severe impairment of pulmonary hemodynamics occurs in patients with concomitant lung disease and morbid obesity. However, the pulmonary hemodynamics is also likely to be disrupted on the sole basis of hypoxia and sympathetic discharge induced by OSAS, without coexistent pulmonary disease and other problems (3,23,24). Accordingly, PAP was found to be elevated in our patients with OSAS (group 2) despite the absence of additional disease. However, BMI was higher in OSAS patients than it was in the control group.

In various conditions, including left cardiac disorders and many others out of the left cardiac disorders, BNP can increase. Fernandez Fabrellas et al. reported in their study a relationship between BNP and echocardiographic parameters like increased ventricular septal thickness, left ventricular posterior wall thickness, or left ventricular end-diastolic diameter (25). Arias et al. also reported a

Table 4. Echocardiographic measurements with BNP, CRP, and blood uric acid between correlations adjusted to age.

	Group 1			Group 2		
	CRP (P/r)	BUA (P/r)	BNP (P/r)	CRP (P/r)	BUA (P/r)	BNP (P/r)
RA	(0.001/–0.185)	(0.001/–0.545)	(0.001/–0.283)	(0.02/0.360)	(0.001/0.308)	(0.001/0.371)
RV	(0.308/0.048)	(0.001/–0.564)	(0.510/0.031)	(0.001/0.104)	(0.001/0.180)	(0.001/0.152)
PAP	(0.008/–0.147)	(0.001/0.250)	(0.001/–0.448)	(0.001/0.275)	(0.001/0.457)	(0.001/0.251)

RA (mm): right atrium diameter, RV (mm): right ventricle diameter, PAP (mmHg): pulmonary artery pressure, CRP: C - reactive protein, BNP: B - type brain natriuretic peptide, BUA: blood uric acid.

Table 5. Echocardiographic measurements with BNP, CRP, and blood uric acid between correlations adjusted to BMI.

	Group 1			Group 2		
	CRP (P/r)	BUA (P/r)	BNP (P/r)	CRP (P/r)	BUA (P/r)	BNP (P/r)
RA	(0.001/–0.215)	(0.001/–0.483)	(0.001/–0.297)	(0.009/0.050)	(0.001/0.318)	(0.001/0.271)
RV	(0.466/0.041)	(0.001/–0.484)	(0.652/0.025)	(0.001/0.134)	(0.001/0.190)	(0.001/0.174)
PAP	(0.001/–0.204)	(0.001/–0.460)	(0.001/–0.452)	(0.001/0.253)	(0.001/0.236)	(0.001/0.238)

RA (mm): right atrium diameter, RV (mm): right ventricle diameter, PAP (mmHg): pulmonary artery pressure, CRP: C - reactive protein, BNP: B - type brain natriuretic peptide, BUA: blood uric acid.

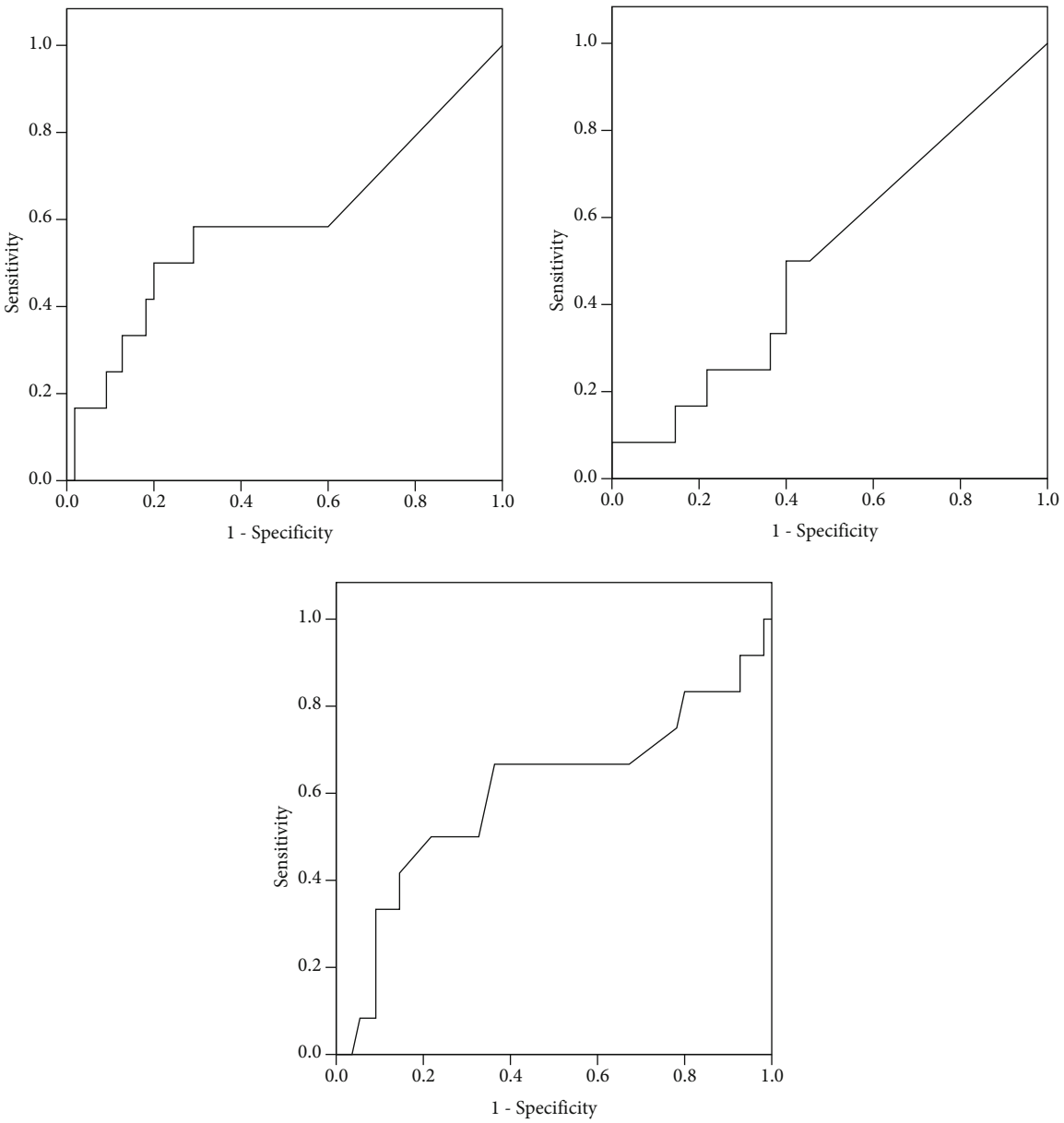

Figure 1a. ROC curves of B - type brain natriuretic peptide for pulmonary artery pressure. **b.** ROC curves of C - reactive protein for pulmonary artery pressure. **c.** ROC curves of blood uric acid for pulmonary artery pressure.

Table 6. The sensitivity, specificity, and positive and negative predictive values calculated according to their upper cut-off values.

	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BNP	0.589	16.7	98.2	66.7	84.4
CRP	0.509	8.3	98.2	50	83.4
Uric acid	0.603	0	96.4	0	81.5

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, BNP: B-type brain natriuretic peptide, CRP: C - reactive protein.

correlation between PAP and the severity of the disease in the presence of LV diastolic dysfunction (26). In the present study we documented a statistically significant correlation between BNP levels and all the ECHO parameters indicating the involvement of the left heart, except for LVEDV. Our study documented a positive correlation between the severity of OSAS and BNP levels. Although the former study reported a weak relationship between the left ventricle and BNP, we found a prominent relationship between BNP and age-adjusted parameters indicative of left ventricle functions and morphology. In addition to acting as an indicator of left heart involvement, BNP level was found in our study to have a statistically significant positive correlation with right cardiac functions and morphology. We find it remarkable that a robust correlation existed between elevation in PAP and BNP level, especially in the patients in group 2.

It is known that increases in CRP level in OSAS patients were due to increased inflammation. CRP is documented to be one of the proinflammatory proteins and an elevated CRP level is an important risk factor in atherosclerosis (27). However, a rise in CRP levels has been shown to be significant in patients with OSAS with cardiovascular diseases compared to those who have OSAS without cardiovascular diseases (14). We showed that high CRP levels are correlated with asymptomatic right cardiac pathologies in OSAS patients as well as in those with other cardiovascular diseases.

Each airway obstruction episode inducing hypoxemia causes episodes of ischemia-reperfusion injury. Such damage has mainly been attributed to the generation of reactive oxygen species during reoxygenation (28). This damage causes increased blood uric acid levels and uric acid excretion (29,30). Increased hypoxemia affects PAP and the right heart (31). Consequently, blood uric acid level, which is an indicator of hypoxemia, can be used to anticipate right cardiac pathologies in OSAS patients. Our study revealed statistically positive correlations between uric acid levels and right cardiac echo parameters. Uric acid levels in the blood may provide an idea regarding right cardiac echo parameters.

In conclusion, BNP, CRP, and blood uric acid levels can be used as adjunctive parameters in the early diagnosis and follow-up of right heart pathologies in patients with OSAS.

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