Influence of obstructive sleep apnea on right heart structure and function

Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder associated with increased cardiovascular morbidity and mortality. This study aimed to investigate heart structure and function and their correlation with the degree of OSAS and sleep indexes in patients diagnosed with OSAS.

Materials and methods: A cohort of 77 patients (48 males, aged 58.1 ± 11.0 years, body mass index [BMI] = 32.4 ± 6.2) admitted to the hospital due to suspected OSAS was examined using echocardiography and polysomnography.

Results: Patients with moderate-to-severe OSAS compared to patients without diagnosed OSAS or with mild OSAS had greater right ventricular outflow tract (RVOT) dimensions (32.6 ± 3.6 vs 30.9 ± 2.4 mm; p < 0.05), larger right atrial area (RAA; 21.1 ± 4.8 vs 17.2 ± 3.2 mm; p = 0.002), greater right ventricular mid-cavity diameter (RVD; 35.5 ± 7.0 vs 32.2 ± 4.7 mm; p = 0.02), and diminished tricuspid annular plane systolic excursion (TAPSE, 21.9 ± 4.5 vs 25.8 ± 4.4 mm; p = 0.04), while there were no significant differences in tissue doppler imaging (TDI) parameters (S’ and E’) and in valvular regurgitation gradient for both groups. Moreover, significantly greater RVOT dimensions (31.6 ± 2.6 vs 30.9 ± 3.0 mm, p = 0.04), RVD (39.3 ± 7.0 vs 32.7 ± 5.2 mm, p = 0.003), and RAA (21.4 ± 4.4 vs 18.1 ± 4.2 mm, p = 0.02) as well as reduction in TAPSE (20.9 ± 5.3 vs 25.0 ± 4.3 mm, p = 0.01) were observed in patients having ≥10 episodes of obstructive apnea (OA) per hour.

Conclusions: In moderate-to-severe OSAS patients, right ventricular (RV) enlargement was observed together with RV dysfunction as measured by TAPSE. Examination using TDI is not superior to standard echocardiography for the detection of heart pathology in OSAS patients. Right heart pathology is present predominantly in patients with obstructive apnea.

Key words: sleep apnea, CPAP, polysomnography, echocardiography, right ventricle

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Introduction

Obstructive sleep apnea syndrome (OSAS) is the most common type of sleep-related breathing disorder caused by repetitive airway collapse during sleep, affecting approximately 2–10% of the middle-aged global population [1, 2]. It is characterized by daytime sleepiness; however, serious complications such as hypertension, ischemic heart disease, diabetes, and stroke have also been linked to OSAS [3–6]. Moreover, breathing disturbances may alter pulmonary circulation, resulting in the deterioration of right heart function and structure. As current studies emphasize the influence of RV function on outcomes, accurate RV assessment is essential in OSAS patients [7]. Obstructive sleep apnea syndrome has been linked to alterations in cardiac structure, but the pathophysiologic mechanisms between these cardiac abnormalities and OSAS are not completely understood [8]. It is now considered that recurrent hypoxia in OSAS leads to oxidative stress and increased sympathetic tone, consequently raising the levels of circulating inflammatory markers leading to endothelial dysfunction and elevated blood pressure, which eventually promotes blood-clotting disturbances [9]. As chest pressure becomes highly negative during respi-
ration in OSAS patients, the decreased pressures according to the respiratory cycle have a negative effect on pulmonary and systemic hemodynamics, mainly by increasing afterload [10]. The relationship between OSAS and RV wall thickness as well as right heart dimensions was previously reported; however, analysis of the data has been inconclusive [11].

The aims of this study were (I) to evaluate heart structure and function in patients diagnosed with OSAS; (II) to assess the influence of the degree of OSAS on changes in the structure and function of the right heart, and finally; (III) to assess the correlation between sleep indexes and right heart structure and function.

Materials and methods

Patients
A cohort of 77 consecutive patients admitted to the Department of Diagnostic Medicine due to suspected OSAS was examined using echocardiography and polysomnography. Patients were eligible if they were over 18 years of age and were able to give informed consent. The exclusion criteria were as follows: inability to perform the testing procedures or to self-operate a continuous positive airway pressure (CPAP) device, severe or moderate valvular disease, heart failure of any etiology, diminished ejection fraction (< 50%), congenital heart disease, pulmonary hypertension, history of pulmonary embolism, uncontrolled arterial hypertension, uncontrolled or severe asthma, chronic obstructive pulmonary disease (COPD) or any other pulmonary disease, other untreated or uncontrolled diseases (diabetes mellitus, hypo/hyperthyroidism, renal failure, hepatic failure), patients treated previously with CPAP or any other effective treatment for OSAS. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. All subjects gave their written informed consent to participate in the study (Jagiellonian University Ethics Committee approval number 112.6120.2.2016) (Table 1).

Sleep study
The occurrence and severity of daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS). All patients enrolled in this study underwent an overnight sleep study. A standardized recording sleep-monitoring system (Embletta MPR, type III according to American Academy of Sleep Medicine, AASM) was used to perform a nocturnal sleep study in all patients and control subjects. Standard recommendations of sleep scoring criteria were used [12]. Electrocardiography, airflow analysis, and pulse oximetry were performed. Ventilatory flows, at both the nose and mouth, were measured with airflow cannulas. Respiratory movements of the chest and abdomen were monitored using inductive plethysmography belts. Body position was determined using a built-in gyro and position sensor, providing the following position outputs: supine, right, left, prone, or upright. Arterial oxygen saturation (SpO₂) was measured transcutaneously with a finger pulse oximeter.

Respiratory events were scored using the 2012 AASM criteria [13]. Obstructive apnea (OA) was defined as a ≥ 90% reduction in the respi-

### Table 1. Baseline demographic characteristics of the study cohort

|                      | Patients without OSAS and with mild OSAS (n = 27) | Patients with moderate and severe OSAS (n = 50) |
|----------------------|-------------------------------------------------|-----------------------------------------------|
| Age                  | 53.9 ± 11.0                                     | 60.3 ± 10.3                                    |
| Sex                  |                                                 |                                               |
| Male                 | 16 (20%)                                        | 32 (42%)                                       |
| Female               | 14 (18%)                                        | 15 (20%)                                       |
| BMI [kg/m²]          | 29.1 ± 5.3                                      | 34.1 ± 6.0                                     |
| NT-proBNP [pg/ml]    | 75.1 ± 70.9                                     | 98.8 ± 120.3                                   |
| Hypertension         | 16 (59%)                                        | 41 (82%)                                       |
| Diabetes mellitus    | 2 (7%)                                          | 15 (30%)                                       |
| Prediabetes          | 7 (26%)                                         | 12 (24%)                                       |
| Dyslipidemia         | 19 (70%)                                        | 42 (84%)                                       |
| Active smoker        | 3 (11%)                                         | 9 (18%)                                        |
| Prior smoker         | 12 (44%)                                        | 15 (30%)                                       |
| Hypothyroidism       | 5 (19%)                                         | 12 (24%)                                       |
| Medication           |                                                 |                                               |
| ACEi/ARB             | 9 (33%)                                         | 30 (60%)                                       |
| β-blockers           | 7 (26%)                                         | 31 (62%)                                       |
| CCB                  | 5 (19%)                                         | 18 (36%)                                       |
| Insulin              | 0 (0%)                                          | 5 (10%)                                        |
| Diuretics            | 8 (29%)                                         | 18 (36%)                                       |
| Statin               | 10 (37%)                                        | 24 (48%)                                       |

ACEI — angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; BMI — body-mass index; CCB — calcium channel blockers; NT-proBNP — N-terminal part of the propeptide of BNP; OSAS — obstructive sleep apnea syndrome. The values for moderate and severe OSAS group do not differ significantly as compared to no and mild OSAS group.
ratory airflow amplitude lasting at least 10 seconds. Hypopnea (H) was defined as a 30–89% reduction in the respiratory airflow amplitude lasting at least 10 seconds and accompanied by a decrease of at least 3% in oxygen saturation. Apnea was described as central (CA) in the absence of thoracoabdominal motion. Mixed apnea (MIX) was defined as an event which met apnea criteria and was associated with absent respiratory effort in the initial part of the event, followed by resumption of respiratory effort in the second part of the event. The average number of episodes of apnea and hypopnea per hour was defined as the apnea-hypopnea index (AHI). Obstructive sleep apnea syndrome was defined as an AHI of > 5 per hour, when clinical symptoms were present. Desaturation was defined as a decrease in the SpO\textsubscript{2} of 3% or more from baseline, and oxygen desaturation index (ODI) was calculated as the total number of desaturation episodes per hour. Subjects were classified into 4 groups according to AHI: patients without OSAS (AHI < 5/h), patients with mild OSAS (AHI 5–14/h), patients with moderate OSAS (AHI 15–29/h), and patients with severe OSAS (AHI ≥ 30/h).

**Echocardiography**

All patients underwent transthoracic echocardiography using a Philips IE33 device (transducer X5-1; 1.3 to 4.2 MHz). Two-dimensional (2-D) echocardiographic imaging in standard views was conducted, including conventional 2-D, Doppler, Color-Doppler and Tissue Doppler imaging (TDI). Examinations were performed in the left lateral decubitus and supine positions. Echocardiograms were recorded from standard parasternal, suprasternal, subcostal, and apical images. The RV and right atrial (RA) parameters were measured from the right ventricular-focused 4-chamber view. Tissue Doppler imaging was performed from the apical 4-chamber view with the pulse wave directed towards the lateral tricuspid annulus, aligned parallel to the motion of the free lateral wall towards the apex. Assessment of TDI parameters included peak systolic (S’) tricuspid annular velocity and peak early (E’) diastolic tricuspid annular velocity. The same position was used to assess tricuspid annular plane systolic excursion (TAPSE). Tricuspid valve flow pattern was obtained, determining the regurgitant flow velocity [14]. All echocardiographic measurements were obtained by an observer blinded to sleep test data and other patient characteristics (Figure 1).

**Statistical analysis**

The Shapiro-Wilk test was used to determine if variables were normally distributed. Continuous variables are presented as means and standard deviations. The Student’s t-test for continuous variables was performed to assess for differences between the groups. Chi-square test was used to examine differences in proportion. The accepted statistical significance threshold was established as a p-value of < 0.05.

**Results**

**Patient characteristics**

The group consisted of more males (48 patients, 62%) than females and the mean age was 58.1 ± 11.0 years. The average body-mass index (BMI) was 32.4 ± 6.2. Among the patients, 57 (74%) had hypertension, 17 (22%) had diabetes mellitus type 2, 19 (25%) had prediabetes, 61 (79%) had hypercholesterolemia, 5 (6%) had a history of deep vein thrombosis, and 7 (9%) had superficial venous thrombosis in the past. Asthma was present in 5 (6%) patients, while 12 (16%) patients were active smokers and 27 (35%) were ex-smokers. The following were the most frequently used drugs in the study group: beta-blockers in 38 (49%) patients, statins in 34 (44%) patients, ACE-inhibitors in 23 (30%) patients, ARBs in 16 (21%) patients, and diuretics in 26 (34%) patients. Baseline demographic data for moderate and severe OSAS group did not differ significantly as compared to no and mild OSAS group.

**Sleep study**

After an overnight complete sleep study, comprising at least 4 hours of sleep, 50 patients were classified as having moderate-to-se-
vere OSAS (AHI ≥ 15/h), while the other 27 patients were classified as having mild or no OSAS (AHI < 15/h) and served as control subjects. Sleep study variables acquired from both groups are shown in Table 2.

Association between OSAS and echocardiographic evaluation

The general quality of echocardiographic images was high (Table 3). All individuals had normal left ventricular (LV) systolic function. Furthermore, the patients did not have significant valvular heart disease, according to the exclusion criteria. Mild mitral regurgitation was present in 63 (81%) patients, mild tricuspid regurgitation was present in 59 (77%) patients, 3 (4%) patients had moderate tricuspid regurgitation, 2 (3%) patients had moderate mitral regurgitation, while mild aortic regurgitation was present in 1 (1%) patient. Additionally, transvalvular gradients measured across the aortic, mitral, tricuspid, and pulmonary valves were within the normal range (Table 4).

Patients with a diagnosis of moderate-to-severe OSAS had greater RVOT dimensions when compared to patients without diagnosed OSAS or patients with mild OSAS. A similar relationship between the examined groups was demonstrated regarding the RAA and RVD dimensions. The analysis of RV systolic function revealed a significant difference in the mean TAPSE, with moderate-to-severe OSAS patients having a decreased TAPSE. There were no significant differences in TDI parameters (S' and E') when comparing moderate-to-severe OSAS patients to mild OSAS patients or those without OSAS. Similarly, between the two groups there was no significant difference in valvular regurgitation gradient (Table 5).

In order to examine the impact of OSAS on cardiac function, the association between sleep study variables and several echocardiographic parameters as measured by 2-D, M-mode, and TDI were analyzed. A statistically significant difference in RVOT dimension was demonstrated for patients with severe OSAS (AHI ≥ 30/h), indicating RV enlargement. Significantly greater RVOT dimensions, RVD, and RAA were observed in patients with ≥ 10 OA episodes per hour, while no significant differences in these parameters were observed depending on the degree of CA and H. Interestingly, the occurrence of at least 1 MIX episode during sleep was associated with a lower

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**Table 2. Sleep study results**

|                        | Patients without OSAS and with mild OSAS (n = 27) | Patients with moderate and severe OSAS (n = 50) | P-value |
|------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| ESS                    | 7.5 ± 4.2                                        | 9.3 ± 6                                          | ns      |
| AHI (h⁻¹)              | 9 ± 3.5                                          | 37.4 ± 19.2                                      | < 0.0001|
| OA (h⁻¹)               | 2 ± 1.9                                          | 17.1 ± 17.7                                      | < 0.0001|
| CA (h⁻¹)               | 0.5 ± 0.7                                        | 1.3 ± 2.6                                        | 0.03    |
| MIX (h⁻¹)              | 0.1 ± 0.2                                        | 3.4 ± 6.3                                        | 0.03    |
| H (h⁻¹)                | 6.5 ± 2.9                                        | 15.8 ± 8.5                                       | < 0.0001|
| SpO₂ (%)               | 93.5 ± 18                                        | 90.7 ± 3.7                                       | 0.0004  |
| ODI (h⁻¹)              | 9 ± 4                                            | 38.8 ± 3.3                                       | < 0.0001|
| Advised CPAP treatment | 0                                                | 38                                               |         |

ESS — Epworth Sleepiness Scale score; AHI — apnea-hypopnea index; OA — obstructive apnea; CA — central apnea; MIX — mixed apnea; H — hypopnea; mean SpO₂ — mean blood oxygen saturation; ODI — oxygen desaturation index; CPAP — continuous positive airway pressure; OSAS — obstructive sleep apnea syndrome

**Table 3. Echocardiographic image quality in obstructive sleep apnea syndrome (OSAS) patients**

| Patients with optimal image quality, n (%) |
|--------------------------------------------|
| RVOT                                      | 75 (97%)                                   |
| RVD                                       | 70 (91%)                                   |
| RAA                                       | 72 (94%)                                   |
| S’                                         | 73 (95%)                                   |
| E’                                         | 73 (95%)                                   |
| TAPSE                                      | 76 (99%)                                   |
| TRPG                                      | 64 (83%)                                   |

E’ — peak early diastolic tricuspid annular velocity; RAA — right atrial area; RVD — right ventricular diameter; RVOT — right ventricular outflow tract; S’ — peak early systolic tricuspid annular velocity; TAPSE — tricuspid annular plane systolic excursion; TRPG — tricuspid regurgitant peak gradient
Moreover, patients with mean saturation levels < 95% during the overnight sleep study had a significantly larger RAA.

Discussion

The main finding of our study was the presence of RV enlargement and dysfunction in OSAS patients, which was diagnosed by standard 2-D echocardiography with M-mode function. We evaluated patients with various stages of OSAS who had symptoms of daytime sleepiness, but not having other significant cardiac or pulmonary diseases, or other comorbidities affecting the pulmonary circulation.

Analysis of individual parameters from the sleep study revealed a significant relationship between OA and right heart structure remodeling, and a reduction in longitudinal RV systolic function presented as TAPSE. This suggests the potential influence of OA episodes on the morphology and function of right heart structure.
contrast, no difference between the frequency of H and CA in both groups suggests that these types of disorders have no significant correlation with the severity of OSAS and its effects on heart structure. This has been confirmed by several studies, which showed that OA may lead to more severe SpO₂ desaturation when compared to hypopneic episodes [15, 16]. It has been argued that because apneic episodes arise as the result of complete upper airway collapse, they may have a more serious pathophysiologic impact than hypopneas, which are a consequence of partial upper airway collapse. Indeed, apneas should be regarded as more significant than hypopneas when assessing the severity of OSAS and its related impact on long-term cardiac risk.

Numerous studies evaluating right heart structure and function, based on echocardiographic measurements, showed significant changes in both RV morphology and efficiency in OSAS patients [17]. It has recently been demonstrated, that 3-dimensional (3D) echocardiography and speckle tracking echocardiography revealed lower 3D RV ejection fraction and global RV strain in patients with moderate and severe OSAS compared with controls [18]. This is in complete agreement with Shivalkar et al. [19], who found that among 43 patients with severe OSAS there was RV dilatation. Contrary to results reported in our study, they also showed reduced TDI systolic and diastolic velocities in the left and right ventricles. However, several researchers did not demonstrate any differences in RV structure and function, while conventional echocardiography remained the main method of evaluation [20, 21].

Karamanzanis et al. [1] described the correlation between OSAS severity and the degree of RV systolic dysfunction, which was reflected in TAPSE values. Similar conclusions can be drawn from a study by Tugcu et al. [22], which evaluated newly diagnosed OSAS patients. The most commonly used parameter in the quantification of RV function is TAPSE, owing to its ease of interpretation and the fact that the tracing can be acquired quickly [23]. Assessment of TAPSE is based on one-dimensional measurement, and therefore, represents only a part of global RV function. However, this may represent the majority of total RV function, because longitudinal contraction accounts for up to 80% of shortening of the chamber. Anatomically, this can be explained by the arrangement of muscle fibers, which run mostly longitudinally and obliquely. A potential disadvantage of TAPSE is the fact that it is angle- and load-dependent. In addition, there remains controversy regarding cut-off values and prognostic value in the prediction of cardiovascular events [24].

On the other hand, TAPSE is a reliable echocardiographic tool as it correlates well with RV ejection fraction as determined by radionuclide angiography or cardiac magnetic resonance (CMR) [25]. The other advantage of TAPSE, which is confirmed by our study, is the possibly of being derived in the vast majority of patients, regardless of difficulties in acquiring high-quality images of the entire RV free wall. Furthermore, TAPSE is considered to have strong predictive power in various diseases. For example, it is associated with a lower cardiac index and worse survival in patients with several diseases. However, there is a lack of long-term studies examining the impact of this parameter in OSAS patients [26, 27]. Despite its simplicity and some limitations mentioned above, our study shows that TAPSE links sleep study variables to RV systolic function disturbances and appears to confirm the effect of OSAS on RV function.

In contrast, Gulay et al. [28] did not detect a significant correlation between TAPSE and polysomnographic variables when studying a group of 60 OSAS patients, although the mean AHI (24.5/h; 6–98) in this study was lower than our observed values. Similarly, Hammerstingl et al. [29] observed in a group of 82 patients that RV functional parameters such as TAPSE and RV-MPI were not significantly decreased in patients with increased AHI at baseline and after 6 months of CPAP treatment.

Other echocardiographic techniques frequently used for assessing RV function include the measurement of myocardial strain by two-dimensional speckle tracking echocardiography (STE) and fractional area change (FAC). Strain evaluation requires specialized software. In addition, RV STE assessment should take into account the differences resulting from the various myocardial tracking algorithms used by software producers [30]. On the other hand, conventional measures of RV longitudinal contractility, such as TAPSE or TDI derived S’, reflect RV basal function, whereas RV strain and FAC account for a greater area of RV free wall deformation and are not prone to the errors that can occur due to translational motion. However, both of these techniques require good visibility of endocardial borders and may constitute a challenge in the assessment of RV function in patients with OSAS, especially in those who are obese.
Surprisingly, our study showed no significant difference in the assessment of TDI parameters. Similarly, the components of TDI evaluation are susceptible to comparable limitations as those of TAPSE. By analogy, S’ measures only a small region of the RV and it cannot be used in patients with regional wall-motion abnormalities. Moreover, it is not dependent on the presence of optimal image quality. S’ belongs to the most common parameters describing RV functionality, although there exists much controversy in the literature related to its utility in OSAS patients. Altekin et al. [31] assessed the relationship between AH1 and RV function, expressed as S’. In their study, which included a similar group of 79 patients with various stages of OSAS, no correlation was found between those parameters. Similarly, in a study conducted by Zhou et al. [32], assessment of S’ revealed no significant difference between healthy subjects and patients with OSAS. On the other hand, they observed regional RV systolic dysfunction and a diminished inflow EF and global EF as measured by real-time 3-D echocardiography in moderate and severe OSAS patients. Additionally, Kepez et al. [33] did not show a difference in S’ values, but they noted that the regional pattern of RV dysfunction correlated with the severity of OSAS, when assessed with strain analysis.

Our study has some limitations. No other measurement of right heart structures was attempted. It should be remembered that CMR imaging is a reference standard for the assessment of cardiac function and structure. However, echocardiographic techniques do have some advantages over CMR, including wider availability, lower cost, less patient distress related to claustrophobia, and the ability to examine patients with contraindications to CMR, such as those with implanted pacemakers or defibrillators. Moreover, our study population was relatively small but proportional to comparable studies performed in OSAS patients.

Conclusions
In summary, RV enlargement along with RV dysfunction, as measured by TAPSE, was observed in moderate-to-severe OSAS patients. Examination with TDI is not superior to standard echocardiography in the detection of heart pathology in OSAS patients. Right heart pathology is present predominantly in patients with obstructive apnea. Further prospective studies using echocardiography are needed to demonstrate the impact of observed changes on the long-term prognosis of OSAS patients.

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Conflict of interest
The authors declare that they have no conflict of interest.

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