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Obstructive sleep apnea syndrome is associated with impaired pulmonary artery distensibility and right ventricular systolic dysfunction

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Background/aim: We investigated whether obstructive sleep apnea syndrome (OSAS) has any impact on pulmonary artery distensibility (PAD) and right ventricular (RV) function.

Materials and methods: Subjects were categorized according to apnea–hypopnea index (AHI) as follows: controls (n = 17 and AHI < 5), mild-to-moderate OSAS (n = 22 and AHI = 5–30), and severe OSAS (n = 29 and AHI > 30). All subjects underwent transthoracic echocardiography after polysomnography to assess PAD and RV function. PAD was recorded as M-Mode trace of the right pulmonary artery and was defined as (PAmax –PAmin/PAmin) × 100. S' was measured by means of TDI of the lateral annulus of the RV using apical four-chamber view.

Results: Patients with severe OSAS demonstrated impaired RV longitudinal systolic function (S') compared to the other groups ($P < 0.05$). Impaired pulmonary vasculature elastic properties as reflected by decreased PAD were more prevalent in severe OSAS (26.2 ± 5.7%) compared to the controls (29.9 ± 4.6%; $P < 0.05$) and mild-to-moderate OSAS (29.0 ± 4.1%; $P < 0.05$). An inverse relation between PAD ($P < 0.05$), RV myocardial performance index (MPI) ($P < 0.05$), and AHI was demonstrated. S' also correlated with PAD ($P < 0.05$).

Conclusion: PAD is a significant tool to evaluate pulmonary vasculature stiffening and is well correlated with disease severity in OSAS. Further, impaired PAD may lead to RV systolic dysfunction.

Key words: Echocardiography, obstructive sleep apnea syndrome, pulmonary artery distensibility, apnea–hypopnea index, myocardial performance index

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disorder characterized by repetitive episodes of airflow cessation termed as apnea, or reduction termed as hypopnea despite persistent thoracic and abdominal respiratory effort during sleep (1). Clinical and epidemiological data suggest an independent association between OSAS and systemic arterial hypertension, pulmonary hypertension, coronary artery disease, cardiac arrhythmias, heart failure, and sudden cardiac death (2). Meanwhile many studies have also shown an association between OSAS and impaired arterial distensibility (3). It is considered an early manifestation of adverse structural and functional changes in the vessel wall (4). Previous studies have mainly focused on the properties of aortic arterial distensibility, showing that it is an important predictor of cardiovascular morbidity and mortality in both the general population and in patients with OSAS (5). However, currently, only limited data exist for pulmonary artery distensibility in OSAS patients and its impact on right ventricular function. Hypoxia, such as occurs in OSAS, is thought to be responsible for endothelial dysfunction in the pulmonary vascular bed with consequent vasoconstriction and vascular remodeling (6). Impaired distensibility of the pulmonary arterial bed with subsequently increased load on the right ventricle may lead to right ventricular dysfunction and altered blood flow patterns throughout the lungs (7). Transthoracic echocardiography, which is noninvasive, can be used repeatedly with low medical cost and is one of the best methods to assess proximal pulmonary artery stiffness and the overall condition of the heart.

The purpose of this prospective study was to evaluate whether OSAS in different severities had any impact

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on pulmonary vasculature stiffening represented by pulmonary artery distensibility measured by transthoracic echocardiography. Further, we tried to elucidate the association between pulmonary artery stiffness symbolized by pulmonary artery distensibility measurement and right ventricular function.

2. Materials and methods

2.1. Study design and patient population

The present study enrolled 68 of 92 consecutive subjects who underwent their initial polysomnography with a complete transthoracic echocardiogram within 1 week of their sleep study between January 2010 and January 2011. Twelve subjects were excluded because of inadequate image quality; 9 patients met the eligibility criteria but decided not to participate; 3 participants could not complete the full-night polysomnography and so their data were not evaluated. Data on the demographic characteristics, medical history, medications, laboratory values, and anthropometric measures were obtained before polysomnography. Height and weight were recorded at the time of polysomnography and were used to calculate the body mass index (weight in kilograms divided by height in square meters). Clinical information included a history of hypertension, defined as documented diagnosis, treatment such, or whether the recorded blood pressure was ≥140/90 mmHg. Dyslipidemia was defined according to the European Dyslipidemia Guidelines of 2016, as the use of lipid lowering therapy or documented diagnosis of dyslipidemia. Diabetes was defined as a fasting glucose level ≥ 126 mg/dL or receiving therapy with insulin and/or oral hypoglycemic agents. Coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary bypass graft surgery. Smoking status was classified as current, past, or never. Exclusion criteria were defined as follows: participants under 18 years, patients with left ventricular dysfunction (left ventricular EF < 50%), cardiac surgery (valve and coronary artery bypass grafting) or coronary artery disease, presence of a permanent pacemaker, moderate-to-severe valvular heart disease, cardiomyopathies, and pulmonary hypertension due to identifiable causes. Further, subjects with previous use of continuous positive airway pressure treatment, cancer and/or other important comorbidities with an expected survival under 2 years, morbid obesity (BMI ≥ 40 kg/m^2), heart rhythm except sinus rhythm, and suboptimal echocardiographic images for measurements were excluded from the study. To assess whether OSAS affects pulmonary artery stiffness independently of pulmonary pressure, we excluded patients with an estimated pulmonary systolic pressure > 40 mmHg and who had severe chronic obstructive pulmonary disorder. Informed consent was obtained from the subjects. This cross-sectional study was approved by the Institutional Review Board of our institution.

2.2. Polysomnography

Standard overnight polysomnography was performed in all subjects by Embla Flaga N7000. Polysomnography included the following variables: electro-oculogram, six electroencephalogram channels, bipolar surface electromyograms of submentalis and bilateral anterior tibialis muscles, and position sensors to record body position and movements. Respiratory monitoring consisted of oro-nasal thermistor and nasal cannula, tracheal microphone, thoracic and abdominal respiratory effort (Piezo belts), finger pulse-oxymetry, and electrocardiogram, as well as simultaneous video recording. Sleep staging was performed according to the guideline (8). Apnea was defined as a complete cessation of airflow for at least 10 s. Hypopnea was defined as an at least 50% decrease in baseline in airflow accompanied by 3% desaturation and/or associated with arousal, or 30% drop of nasal pressure baseline signal accompanied by 4% desaturation lasting at least 10 s. Apnea–hypopnea index was defined as the number of apneas and hypopneas per hour of sleep. The groups were defined as control subjects (AHI, <5), mild-to-moderate OSAS (AHI = 5–30), and severe OSAS (AHI ≥ 30).

2.3. Echocardiographic measurements

All echocardiographic measurements were performed by a single experienced cardiologist who was unaware of the clinical and laboratory variables of the patients. The intra-observer variability was 7.2%, representing acceptable accuracy and reproducibility of data. The echocardiographic examination was performed with subjects in the left lateral decubitus position using a commercially available ultrasound system with a 2.5–3.5 MHz transducer (ie33, Phillips Medical System, Bothell, WA, USA). Left ventricular ejection fraction (EF) was estimated using Simpson's biplane method. The right pulmonary artery was evaluated from the suprasternal view by echocardiography. An M-mode cursor was oriented along the right pulmonary artery diameter. M-mode traces were recorded at a speed of 100 mm/s. Maximum (PAmx) and minimum (PAmin, at the R peak) right pulmonary artery diameters were measured. The leading edge to leading edge method was used for measurements. Right pulmonary artery distensibility was defined as follows: (PAmx – PAmin/PAmin) × 100 as previously described (Figure 1) (9). The pulmonary artery systolic pressure (sPAP) was calculated by adding the pressure gradient through the tricuspid valve obtained

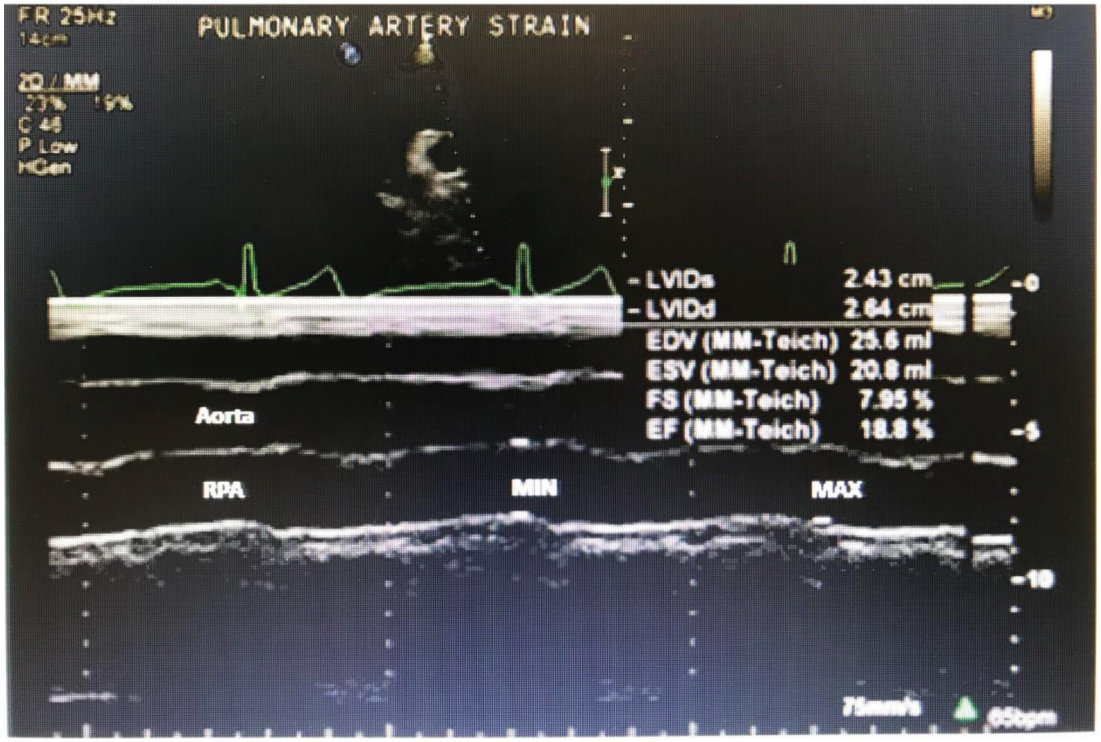

Figure 1. Transthoracic echocardiographic view showing measurement of pulmonary artery distensibility. RPA, right pulmonary artery; min, minimal diameter; max, maximal diameter.

by tricuspid regurgitation to right atrial pressure. Right ventricular fractional area change (FAC) was measured (10). Although it excludes the right ventricular outflow tract it is a simple surrogate marker of right ventricular ejection fraction. Tissue Doppler imaging was used to obtain the right ventricular myocardial velocities (S') in the apical four-chamber view with a sample volume placed at the lateral segment of the tricuspid annulus. The parameters necessary for calculation of MPI were obtained by tissue Doppler in the apical four-chamber view (11). Tricuspid annular plane systolic excursion (TAPSE) represents the distance of systolic excursion of the right ventricular annular plane towards the apex and is measured as the maximum apical excursion of the lateral tricuspid annular plane as previously described (7).

2.4. Statistical analysis

To assess baseline difference across the study groups, we used one-way analysis of variance of continuous variables and the chi-squared test for categorical variables. Pearson's correlation coefficient was used for determining the correlation between different laboratory and clinical parameters. Correlation analysis was performed using univariate clinical and laboratory variables. The statistical boundary was accepted as 0.05. Statistical analysis was performed using a statistical software package (SPSS, Inc., Chicago, IL, USA).

3. Results

We studied a total of 68 subjects (17 control subjects, 22 mild-to-moderate OSAS, 29 severe OSAS). Table 1 presents the demographic characteristics of the patients included in the study. These characteristics did not show any significant differences among the groups except for beta-blocker usage and AHI. Table 2 compares the echocardiographic parameters. There was no difference regarding left ventricular EF between the groups. In regard to right ventricular systolic function, right ventricular FAC and TAPSE did not differ between the groups. However, longitudinal right ventricular systolic function was impaired in severe OSAS as reflected by S'. Furthermore, right ventricular MPI did not differ as a marker of global right ventricular systolic and diastolic function. Pulmonary vasculature was assessed by sPAP and it was shown that there was a significant trend to increase with disease severity compared to the controls. Pulmonary artery distensibility was shown to be significantly decreased in patients with severe OSAS (Figure 2). Only AHI and MPI had a significant correlation with pulmonary artery distensibility (Table 2; Figures 3 and 4). Furthermore, correlation analysis was performed, and AHI, S', and MPI showed a significant correlation with pulmonary artery distensibility ($P < 0.05$) (Table 3). There was also a significant correlation between S' and pulmonary artery distensibility ($p<0.05$) (Table 4).

Table 1. Clinical characteristics and laboratory findings of study population.

Variable	Controls n = 17	Mild-to-moderate OSAS n = 22	Severe OSAS n = 29	P-value
AHI	2.6 ± 1.1	16.6 ± 8.6[1]	56.2 ± 19.2[1,2]	<0.05
Male (%)	64.7 (11)	63.6 (14)	55.2 (16)	0.756
Age (years)	42.9 ± 13.1	41.4 ± 12.6	43.1 ± 11.1	0.885
Hypertension (%)	52.9 (9)	72.7 (16)	58.6 (17)	0.406
Diabetes mellitus (%)	5.9 (1)	13.6 (3)	27.6 (8)	0.147
Hyperlipidemia (%)	47.1 (8)	50.0 (11)	41.4 (12)	0.821
Smoking (%)	41.2 (7)	45.5 (10)	43.8 (14)	0.897
RAAS-Inhibitors (%)	47.1 (8)	45.5 (10)	51.7 (15)	0.897
Beta-blocking agents (%)	5.9 (1)	50.0 (11)[1]	24.1 (7)[1]	0.008
Calcium channel blocking agents (%)	17.6 (3)	9.1 (2)	20.7 (6)	0.528
BMI (kg/m^2)	26.3 ± 1.4	27.2 ± 1.4	27.5 ± 2.2	0.347
Systolic BP (mmHg)	130.8 ± 10.6	132.5 ± 9.8	135.6 ± 9.2	0.243
Diastolic BP (mmHg)	80.8 ± 6.7	81.8 ± 8.8	84.6 ± 12.0	0.398
Resting HR (beats/minute)	74.3 ± 4.3	76.0 ± 7.2	76.3 ± 6.0	0.542

Abbreviations: AHI, apnea–hypopnea index; RAAS, renin–angiotensin–aldosterone system; BMI, body mass index; HR, heart rate
[1]: P < 0.05 vs. control group; [2]: P < 0.05 vs. mild-to-moderate OSAS

Table 2. Echocardiographic parameters of the study population.

Variable	Controls n = 17	Mild-to-moderate OSAS n = 22	Severe OSAS n = 29	P-value
LV EF, %	63.4 ± 2.5	63.6 ± 2.8	62.2 ± 4.4	0.294
RV FAC, %	52.0 ± 4.0	50.1 ± 4.2	49.5 ± 3.0	0.082
TAPSE, mm	22.6 ± 0.7	22.4 ± 1.0	22.3 ± 0.7	0.455
RV MPI	0.41 ± 0.03	0.44 ± 0.06	0.45 ± 0.06	0.126
S', cm/s	12.3 ± 1.2	11.5 ± 1.2	11.0 ± 1.0[1]	<0.05
PAmax, mm	27.4 ± 3.2	25.8 ± 2.6	26.9 ± 3.0	0.231
PAmin, mm	19.2 ± 3.0	18.3 ± 2.3	19.8 ± 2.4	0.143
PAD, %	29.9 ± 4.6	29.0 ± 4.1	26.2 ± 5.7[1,2]	<0.05
sPAP, mmHg	25.5 ± 4.0	29.7 ± 4.3[1]	30.5 ± 4.7[1]	<0.05

Abbreviations: LV EF, left ventricular ejection fraction; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; PAD, pulmonary artery distensibility; sPAP, systolic pulmonary artery pressure
[1]: P<0.05 vs. control group
[2]: P<0.05 vs. mild-to-moderate OSAS

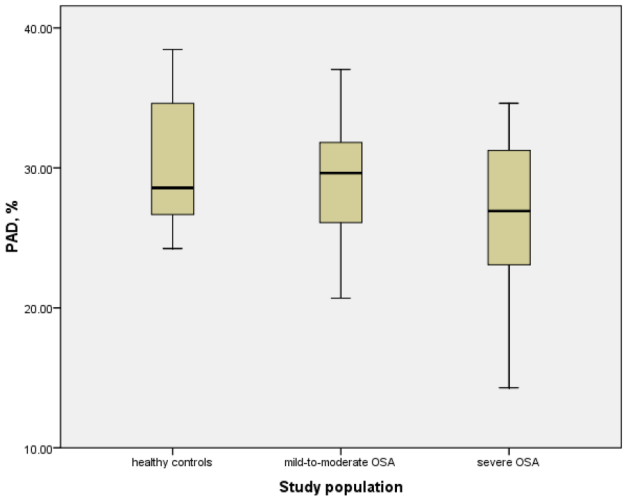

Figure 2. Relationship between pulmonary artery distensibility and obstructive sleep apnea severity.

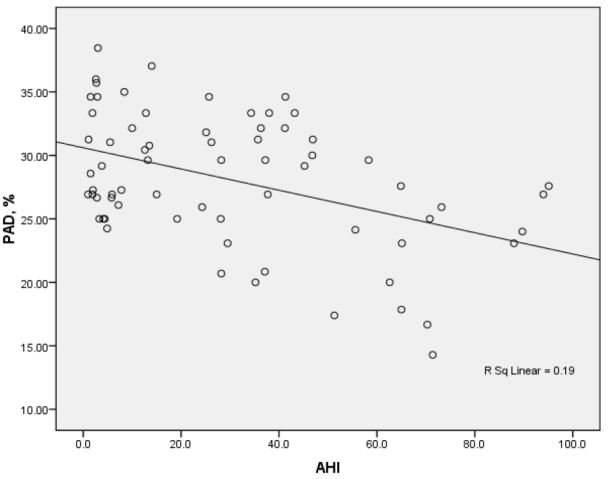

Figure 3. Correlation between pulmonary artery distensibility and apnea–hypopnea-index.

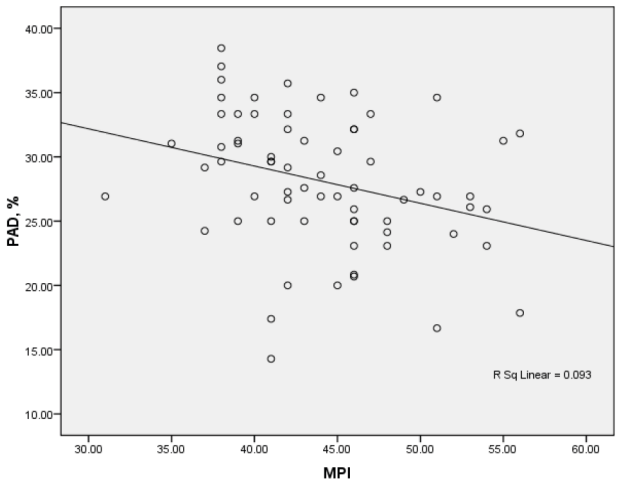

Figure 4. Correlation between pulmonary artery distensibility and right ventricular myocardial performance index.

4. Discussion

In the present study we demonstrated that the pulmonary artery becomes less distensible in patients with OSAS. Further, pulmonary artery distensibility deteriorated with increasing severity of OSAS. The second main finding was impaired longitudinal systolic function (S') of the right ventricular in severe OSAS patients.

The pulmonary artery is a low pressure, high distensibility system that acts to transform the high pulsatile right ventricular output into near steady flow at the capillary level (12). Pulmonary artery distensibility is a new index that can be used to evaluate the elastic properties of pulmonary arterial vasculature (13). Currently it is the best predictor of mortality from right ventricular failure (14). Arterial distensibility is mainly determined by structural and functional components of elastic properties. Since elastic fibers are the main load-bearing components of the arterial wall, disruption of the elastic properties could be responsible for arterial stiffness (15). It was reported that hypoxia, such as occurs in OSAS, may lead to such alterations by decreasing glycosaminoglycan and collagen (16). Another explanation is that intermittent nocturnal hypoxia may cause pulmonary arterial endothelial dysfunction, which in turn leads to vasoconstriction and vascular remodeling (6). In a previous study, Akdag et al. assessed aortofemoral distensibility in OSAS patients with a different parameter than ours by means of echocardiography. They used aortic velocity propagation and reported a significantly decreased value of this parameter for this patient group (3). Again the principle of nocturnal hypoxemia with consequent endothelial dysfunction was considered the main cause of vascular stiffness. A further study conducted by Kasikcioglu et al. demonstrated impaired aortic distensibility in patients with OSAS. They observed not only decreased aortic distensibility but also diastolic deterioration of the LV (17). In this context the aorta was not only considered a conduit delivering blood. Its elastic properties also affect left ventricular function with a possible remodeling of the left ventricle (18). Similar findings obtained for the aorta in OSAS patients were also reported for the pulmonary vascular bed. In patients with OSAS, Altıparmak et al. revealed significantly impaired pulmonary artery distensibility that was also positively correlated with AHI (19).

Direct measurement of main pulmonary artery distensibility requires pressure measurements, which

Table 3. Correlation with PAD of the study population.

Variables	r	P-value
AHI	–0.436	<0.05
S’	0.397	<0.05
RV MPI	–0.305	<0.05
sPAP	–0.223	0.081

Abbreviations: AHI, apnea–hypopnea index; RV MPI, right ventricular myocardial performance index; sPAP, systolic pulmonary artery pressure

Table 4. Correlation with S’ of the study population.

Variables	r	P-value
AHI	–0.417	<0.05
PAD	0.396	<0.05
sPAP	–0.273	0.086

Abbreviations: AHI, apnea–hypopnea index; PAD, pulmonary artery distensibility; sPAP, systolic pulmonary artery pressure

can currently only be achieved by invasive right heart catheterization. Using alternative noninvasive metrics of stiffness would be desirable for the clinically indicated frequent follow-ups or screening tests or the assessment of treatment responses. In this context we chose echocardiography as a preferable method for evaluating the right pulmonary artery distensibility. Beside its noninvasiveness, it has high accuracy and speediness in assessing the overall condition of the heart. Although right pulmonary artery distensibility and main pulmonary artery distensibility may theoretically not be comparable, we decided to take the right pulmonary artery for measurement because of two reasons. First, the window takes advantage of the superior resolution of M-mode echocardiography in comparison to two-dimensional echocardiography. Second, because of similar arterial wall architecture, the elastic properties of the right and main pulmonary artery would not be expected to differ (20).

The second important finding of our study was an impaired right ventricular systolic function, which was evaluated by means of longitudinal right ventricular basal movement S’. This parameter has been validated against radionuclide angiography and has been shown to be an accurate reproducible parameter of right ventricular systolic function (21). Further, there was a correlation between right ventricular MPI and pulmonary artery distensibility. The pulmonary artery plays an important role in facilitating the transition from right ventricular pulsatile flow to the nearly steady flow at the capillary level with minimal energy expenditure. The preservation of this right ventricular-PA coupling is fundamental to the maintenance of right heart hemodynamics and of pressure function relationships throughout the pulmonary vascular tree (22). The pulmonary artery elasticity is an important factor governing this relationship, with increased stiffness leading to higher right ventricular pulsatile work load, decreased contractile performance, and enhanced energy transmission to smaller pulmonary vessels, resulting in further vascular damage (23–25). A recent study by Altıparmak et al. demonstrated also that pulmonary artery distensibility is associated with right ventricular systolic and diastolic parameters (19). They used right ventricular MPI, which is a global parameter of cardiac function combining both systole and diastole. This index was considerably higher in OSAS patients with impaired pulmonary artery distensibility compared to controls showing right ventricular distension, overload, and dysfunction. A further study by Mahfouz et al. evaluated the impact of pulmonary artery distensibility on right ventricular function and tricuspid regurgitation (TR) after successful percutaneous balloon mitral valvuloplasty (PBMV). They reported that pulmonary artery distensibility was an independent predictor of TR regression and sustained right ventricular functional improvement after successful PBMV (9).

With the recognition of the prognostic importance of pulmonary artery distensibility, its impact on right ventricular function and its contributory role in the development and progression of distal vessel small-vessel proliferative vasculopathy, pulmonary artery distensibility is an attractive target for the treatment of

the underlying disease. However, there is currently scarce literature showing that improvement of pulmonary artery distensibility might be linked to better clinical outcomes.

4.1. Conclusion

We demonstrated impaired values for pulmonary artery distensibility in patients with OSAS. These values are well correlated with the severity of the disease. Further, impaired pulmonary artery distensibility may lead to right ventricular systolic dysfunction. In this context, assessment of proximal pulmonary artery distensibility by means of echocardiography could be an early and simple determinant of right ventricular dysfunction and a routine part of clinical evaluation.

4.2. Limitations

The first limitation is the rather small number of OSAS patients in each subgroup, which limits the power of comparison. Further studies with larger numbers are needed to assess the effects of OSAS on pulmonary artery distensibility and right ventricular function. Another major limitation is the lack of biochemical determination of cardiac loading conditions by brain natriuretic peptides, which have good correlation with diastolic and systolic abnormalities. Further, optimal assessment of pulmonary circulation is difficult with echocardiography due to short penetration depth and difficulties in obtaining appropriate acoustic position. Lastly, the possible effect of beta-blockers on the pulmonary artery system cannot be excluded.

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