

Evaluation of Echocardiographic Parameters for the Prediction of Prognosis in Patients Diagnosed with Pulmonary Arterial Hypertension

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Abstract

Background: We aimed to determine the importance of myocardial tissue Doppler flow rates, pulmonary artery/aorta diameter (PA/Ao), pulmonary venous flow transit time (pPTT), pulmonary artery acceleration time (PAAcTc), and right atrium area index (RAAI) parameters in the prediction of prognosis patients with a diagnosis of pulmonary arterial hypertension (PAH).

Materials and Methods: This retrospective study was done on 30 patients with systemic pulmonary arterial hypertension confirmed via catheterization who had negative vascular reactivity test results (pediatric patients with primary pulmonary hypertension and secondary pulmonary hypertension due to congenital heart disease). PA/Ao diameter, PAAcTc, pPTT, and RAAI were calculated. The patients were grouped as those with PA/Ao <1, 5>, SaO₂% <90>, and pro-B-type natriuretic peptide (BNP) <100 pg/ml>, and those receiving combination therapy or monotherapy, and the parameters were compared between the groups.

Results: pPTT was shorter in the group with SaO₂ > 90%, which was attributed to the high number of patients with idiopathic PAH in this group and more severe PAH stage. PAAcTc was shorter in patients who showed no clinical improvement on monotherapy and required multidrug therapy. RAAI was significantly increased in patients with pro-BNP > 100 pg/ml. A decreased pPTT, accompanied by a lower PAAcTc in the group with PA/Ao >1.5, indicated the severity of PAH in this group.

Conclusion: When managing PAH patients, the presence of RAAI > 18 cm²/m², PA/Ao > 1.5, and PAAcTc < 80 msn indicates a higher disease severity, and suggested that the patients' treatment regimen should be re-evaluated based on these parameters. Also, the RAAI parameter shows the closest association with pro-BNP levels, which is one of the correct prognosis indicators.

Key Words: Echocardiography, Tissue Doppler, Pulmonary arterial hypertension, Right atrium area index.

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1- INTRODUCTION

Tissue Doppler echocardiography (TDI) can be used as an important prognostic factor in the estimation and monitoring of the prognosis of pulmonary arterial hypertension (PAH) patients, and previous studies have suggested that a tricuspid valve (TV) E' flow rate is correlated with a functional severity class (NYHA) in patients with idiopathic pulmonary arterial hypertension (1, 2). Pulmonary artery acceleration time (PAAcTc), and pulmonary arterial pressure (PAP) are inversely correlated, and increased pulmonary vascular resistance (PVR) as well as decreased pulmonary compliance shorten pulmonary artery acceleration time. Accordingly, pulmonary artery acceleration time values lower than 100 ms are considered in particular to be markers of poor prognosis (3). Pulmonary arteries are wider in children with pulmonary arterial hypertension than in healthy children, and a pulmonary artery/aorta diameter (PA/Ao) of > 1.3 , as demonstrated by cardiac tomography, increases the possibility of pulmonary arterial hypertension in children (4). Right atrium (RA) enlargement is an early-term marker of right ventricular (RV) diastolic dysfunction, and right atrium area index (RAAI) can be beneficial in estimating prognosis (5). Based on these data, we aimed to evaluate echocardiographic parameters for the prediction of prognosis in patients diagnosed with pulmonary arterial hypertension, which would improve decision-making in the treatment management of pulmonary arterial hypertension patients.

2- MATERIALS AND METHODS

2-1. Study design and population

This retrospective study included a total of 30 patients with systemic pulmonary arterial hypertension confirmed via catheterization who had negative

vascular reactivity test results (pediatric patients with primary pulmonary hypertension and secondary pulmonary hypertension due to congenital heart disease) in Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Pediatric Cardiology, Istanbul, Turkey. Patients with Down's syndrome and arrhythmia were excluded.

2-2. Methods

The tissue Doppler (tricuspid lateral wall, septal, and mitral lateral walls) flow rates of patients were investigated via echocardiography, and pulmonary artery/aorta diameter (PA/Ao), pulmonary artery acceleration time, pulmonary venous flow transit time (pPTT), and right atrium area index were calculated (5, 7, 8). Blood uric acid, albumin, total blood count, 5 ml, and SaO₂% measurements were obtained. Patients were classified as those with pulmonary artery/aorta diameter greater than or less than 1.5, SaO₂% greater than or less than 90%, pro-B-type natriuretic peptide (BNP) greater than or less than 100 pg/ml, and those receiving combination therapy or monotherapy, and the parameters were compared between the groups (21). The findings in the patient group that are already different from normal were already planned to be evaluated in the same patient group. Therefore, the control group was not selected.

2-3. Measuring

Echocardiography was performed by the GE, Vivid S6 system, and images were analyzed offline after the procedure.

2-3-1. Pulmonary acceleration time (PAAcTc)

Based on American Society of Echocardiography guidelines, two-dimensional (2D), and colored Doppler echocardiographic images in parasternal short-axis views were obtained while the

patients were in the left lateral position. The maximal alignment of Doppler interrogation with blood flow direction was achieved with the placement of the sample volume at the annulus of the pulmonary valve and not more proximally in the right ventricular outflow tract.

Pulmonary acceleration time was calculated from a spectral Doppler envelope as the time interval between the onset of systolic pulmonary arterial flow (onset of ejection) and peak flow velocity (**Figure. 1**), (6).

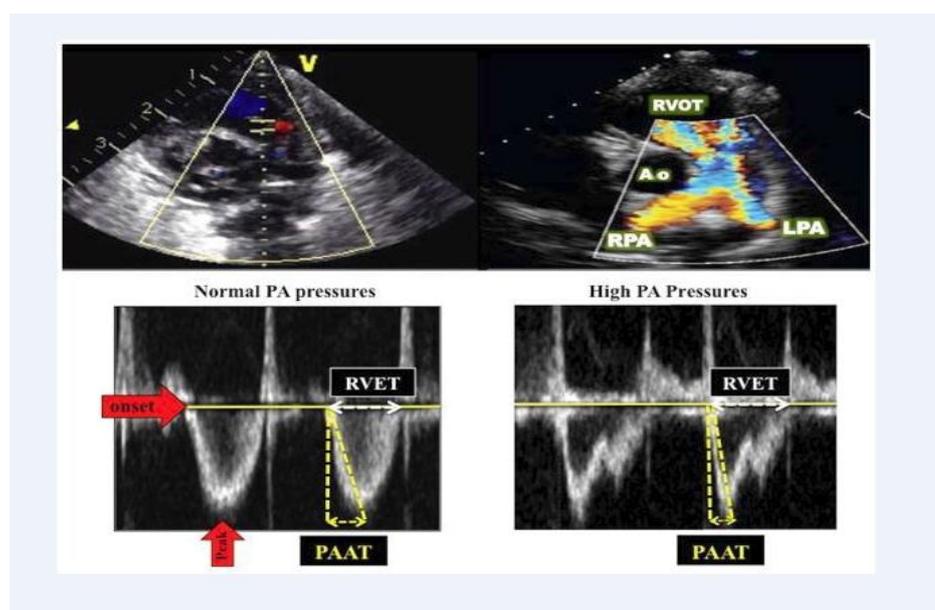


Fig. 1. A) Pulmonary artery (PA) velocity curve in a patient with normal PA pressure. PA acceleration time (PAAT) is defined as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity. Right ventricle ejection time (RVET) was measured from the interval between the onsets of RV ejection to the point of systolic pulmonary arterial flow cessation. B) PA velocity curve with a shortened PAAT in a patient with high PA pressures. Ao, aorta; RPA, right pulmonary artery; LPA, left pulmonary artery.

2-3-2. Right atrium area index (RAAI)

Right atrium enlargement has been suggested as an early sign of right ventricle diastolic dysfunction, where its increased reservoir capacity compensates for diminished right ventricle compliance. Our echocardiography protocol for right atrium size assessment includes obtaining four-chamber views with the patient in the left lateral recumbent position. Right atrium area was estimated through a planimetry tracing from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, using a GE Vivid S5. As per American

Society of Echocardiography guidelines, the measurements were performed at the end of ventricular systole (7, 8).

2-3-3. Tissue Doppler imaging (TDI)

Using a 3 MHz transducer and a tissue Doppler imaging program, the sample volume was set at 2–4 mm, the Nyquist limit was set to 15–20 cm/s⁻¹, and the gain was set such that the noise would be minimal and the obtained tissue signals would be clear. For the apical four-chamber view, the sample volume was placed at the lateral mitral annulus, the mitral septal annulus, and the lateral tricuspid annulus. Recordings were then obtained for ≥ 5 cardiac cycles while the

participants were relaxed, ensuring that flow would not be affected by respiration. The peak early (E'), late diastolic (A'), and peak systolic (S') waves were recorded from the lateral mitral annulus, the mitral septal annulus, and the lateral tricuspid annulus. The isovolumic contraction time was defined as the interval between the end of the A' wave and the onset of the S' wave; the isovolumic relaxation time was defined as the period from the end of the S' wave to the onset of the E' wave; and the ejection time was defined as the interval between the onset and end of the S' wave. The E/E' ratio was measured as a predictor of left ventricle filling pressure (9).

2-3-4. Right Pulmonary Artery distensibility index (RPADI)

The right pulmonary artery distensibility index (RPADI) was determined from a short-axis 2D-imaging view of the right pulmonary artery (RPA) (viewed from a right parasternal long-axis view optimized for the heart base/right pulmonary artery in the short axis). Right pulmonary artery distensibility index (RPADI) decreases with increasing severity of pulmonary arterial hypertension and represents the percentage change in diameter of the right pulmonary artery throughout a single cardiac cycle according to the following formula: $RPAD\ index = ([RPAS - RPAD] / RPAS)$ (10).

2-3-5. Pulmonary venous flow transit time (pPTT)

The timing of the peak late systolic pulmonary vein flow velocity may be a surrogate marker of the pathophysiological changes in the pulmonary circulation that occur in diseases associated with pulmonary hypertension and pulmonary fibrosis. In this context, the association between the pulmonary pulse transit time and other hemodynamic parameters, including the elastic properties of the pulmonary vasculature and the pulsatile

arterial load, should be explored. The mean pulmonary flow transit time is shortened in pulmonary arterial hypertension patients (11).

2-4. Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2-5. Data analysis

The SPSS for Windows 15.0 program (SPSS, Chicago, Illinois, USA) was used for statistical analysis. The results of descriptive analysis were expressed as mean \pm standard deviation (SD) for numerical variables, while the mean values of normally distributed variables were compared between the groups using Student's *t*-test, and if not normally distributed, using the Mann–Whitney U-test. The Kruskal–Wallis test was used to determine significant differences between continuous variables. If the overall P-value was significant, the Mann–Whitney U-test was applied to evaluate differences among groups. A Chi-square test was performed for each categorical variable. Significance of $p < 0.05$.

3- RESULT

The mean age of patients was 17.68 ± 7.47 years (min: 4.5–max: 35), and the mean body surface area was 1.42 ± 0.39 m² (min: 0.69–max: 2.07). Of the entire sample, 13 (43.3%) patients were female and 17 (56.7%) were male. While pulmonary arterial hypertension was present in a single ventricle physiology of six (20%) patients, 24 (80%) patients had biventricular cardiac conditions. No pre-tricuspid pathologies were noted in any of

the patients, while 11 (37%) patients had a post-tricuspid pathology (ventricular septal defect, patent ductus arteriosus), 10 (33%) had complex cardiac pathologies (atrioventricular septal defect, turuncus arteriosus, etc.), and nine (30%) had diagnoses of idiopathic pulmonary arterial hypertension. SaO₂ was < 90% in 15 (50%) patients. In total, 13 (43.3%) patients were receiving monotherapy, 17 (56.7%) were receiving multidrug therapy, and pro-BNP levels were > 100 pg/ml in 13 (43.3%) patients. Pulmonary artery/Aort diameter (PA/Ao) was measured as > 1.5 in 16 (53.3%) patients. Uric acid levels were elevated in the group with SaO₂% < 90 (**Table.1**), and this condition was associated with hypoxia. The shortened pulmonary venous flow transit time in the group with SaO₂ > 90% was associated with the higher number of patients with idiopathic pulmonary arterial hypertension in this group, which leads to

an increased severity of pulmonary arterial hypertension and a higher rate of fibrosis development in the pulmonary bed in this patient group (**Table.1**). Pulmonary acceleration time was significantly shorter in patients who showed no clinical improvement on monotherapy and required multidrug therapy (**Table.1**), while right atrium area index was significantly increased in patients with pro-BNP > 100 pg/ml. The decreased pulmonary venous flow transit time and lower pulmonary acceleration time in the group with pulmonary artery/Aort diameter (PA/Ao) > 1.5 reflected the severity of pulmonary arterial hypertension in this patient group (**Table.2**). The mitral and septal wall E' waves were also lower in the group receiving multidrug therapy, indicating a higher incidence of left ventricular involvement in this patient group when compared to patients receiving monotherapy (**Table.3**).

Table-1: Comparison of groups with saturation greater than or less than 90% and those receiving monotherapy or multidrug therapy.

Variables	Saturation <90% (n:15)	Saturation >90% (n:15)	P1	Monotherapy (n:13)	Multidrug (n:17)	P2
Albumin g/dl	4.27 ± 0.24	4.20 ± 0.41	NS	4.21 ± 0.33	4.26 ± 0.35	NS
Uric acid	6.24 ± 1.46	4.95 ± 1.39	0.02	5.28 ± 1.19	5.73 ± 1.79	NS
MPV	9.56 ± 1.66	9.54 ± 1.30	NS	9.36 ± 1.49	9.68 ± 1.46	NS
RDW	15.81 ± 3.13	14.75 ± 1.84	NS	14.74 ± 2.02	15.62 ± 2.87	NS
Pulmonary venous time (msn)	155.90 ± 53.12	117.46 ± 28.13	0.03	137.80 ± 50.07	131.38 ± 41.27	NS
Pulmonary AcTc	71.56 ± 14.73	72.89 ± 20.82	NS	84.25 ± 19.01	63.23 ± 11.66	0.004
Pro-BNP	113.94 ± 143.28	190.68 ± 285.08	NS	93.56 ± 111.26	202.44 ± 284.46	NS
RPA distensibility index	28.21 ± 9.36	23.16 ± 7.17	NS	23.55 ± 8.33	26.56 ± 8.41	NS
RAA index (cm ² /m ²)	17.67 ± 5.30	17.74 ± 4.50	NS	17.39 ± 3.72	17.91 ± 5.40	NS

P1: Comparison of groups with saturation greater than vs. P2: Less than 90%.

P2: Comparison of data of patients receiving monotherapy and multidrug therapy.

MPV, mean platelet volume; RDW, red cell distribution width; AcTc, acceleration time corrected; pro-BNP, pro-B-type natriuretic peptide; RPA, right pulmonary artery; RAA, right atrium area; NS, not significant.

Table-2: Comparison of groups with BNP higher and lower than 100.

Variables	Pro-BNP > 100 (n:13)	Pro-BNP < 100 (n:17)	P1	PA/Ao < 1.5 (n:14)	PA/Ao > 1.5 (n:16)	P2
Albumin g/dl	4.29 ± 0.38	4.25 ± 0.31	NS	4.16 ± 0.34	4.29 ± 0.34	NS
Uric acid	5.52 ± 1.23	5.54 ± 1.77	NS	5.83 ± 1.85	5.02 ± 1.28	NS
MPV	9.86 ± 1.21	9.35 ± 1.68	NS	9.90 ± 1.52	9.26 ± 1.60	NS
RDW	14.40 ± 1.08	16.04 ± 3.03	NS	15.85 ± 2.87	14.70 ± 1.81	NS
Pulmonary venous time (msn)	136.8 ± 53.5	134.4 ± 42.6	NS	140.6 ± 49.4	128.2 ± 41.4	0.05
Pulmonary AcTc	64.94 ± 13.14	78.54 ± 20.06	NS	79.90 ± 12.57	66.58 ± 20.3	0.05
RPA distensibility index	23.47 ± 7.08	25.89 ± 9.23	NS	22.36 ± 7.08	27.97 ± 9.18	NS
RAA index (cm ² /m ²)	21.88 ± 3.99	15.04 ± 3.13	0.000	15.67 ± 4.12	19.05 ± 5.34	NS

P1: Comparison of data of patients with BNP higher and lower than 100.

P2: Comparison of data between patients with PA/Ao ratio less than vs greater than 1.5.

MPV, mean platelet volume; RDW, red cell distribution width; AcTc, acceleration time corrected; pro-BNP, pro-B-type natriuretic peptide; RPA, right pulmonary artery; RAA, right atrium area; PA/Ao, pulmonary artery/aorta diameter; NS, not significant.

Table-3: Comparison of tissue Doppler imaging rates of patients receiving monotherapy and multidrug therapy.

Variables	Monotherapy (n:13)	Multidrug (n:17)	P-value
TV S'	9.17 ± 3.29	9.06 ± 2.63	NS
TV E'	11.75 ± 3.62	9.00 ± 3.58	0.05
TV A'	9.00 ± 4.41	11.29 ± 4.49	NS
Septal S'	4.50 ± 0.90	4.31 ± 0.79	NS
Septal E'	8.58 ± 2.93	6.25 ± 1.84	0.016
Septal A'	5.33 ± 2.53	5.25 ± 1.88	NS
MV S'	8.17 ± 2.44	6.94 ± 1.56	NS
MV E'	13.33 ± 3.72	10.06 ± 3.10	0.018
MV A'	7.00 ± 2.92	6.81 ± 2.68	NS

TV, tricuspid valve; MV, mitral valve; NS, not significant.

4- DISCUSSION

We aimed to evaluate echocardiographic parameters for the prediction of prognosis in patients diagnosed with pulmonary arterial hypertension and how it would improve decision-making in the treatment management of pulmonary arterial

hypertension patients. As tissue Doppler imaging provides important information relating to ventricular function and interactions between the two ventricles, it may be useful for clinicians in the optimization of heart failure treatment, the estimation of prognosis, and the monitoring of response in patients with pulmonary arterial hypertension. Tissue

Doppler imaging is impaired in children with pulmonary arterial hypertension when compared to healthy children, and the findings resemble those seen in patients with Eisenmenger's disease or idiopathic pulmonary arterial hypertension. A previous study involving children with pulmonary arterial hypertension reported decreases in tricuspid valve (TV), and septal S' and E' wave flow rates, while pulmonary acceleration time, on the other hand, had the best correlation with tricuspid valve (TV) and septal systolic tissue Doppler imaging flow rates (12). In another study, the mitral valve free wall myocardial performance index (MPI) was closely associated with poor functional class, and the authors of that study concluded that tissue Doppler imaging waves and BNP could be useful in the assessment of treatment response in pulmonary arterial hypertension patients (1). The tricuspid valve (TV) E' flow rate was found to be correlated with functional class severity in pediatric patients with idiopathic pulmonary arterial hypertension, while tricuspid valve (TV) E' was noted to be inversely correlated with BNP, right ventricle end-diastolic pressure, and mean pulmonary artery pressure, and a tricuspid valve (TV) E' of ≤ 8 cm/s was found to be a determinant of survival in those patients (2).

In the present study, mitral and septal wall E' wave rates were particularly and significantly decreased in patients undergoing multidrug therapy compared to those on monotherapy, indicating a higher rate of left ventricle involvement of the disease in this patient group. The need for medical treatment was particularly increased in those with septal E' waves below the 8 cm/s threshold. Pulmonary artery acceleration times reflect the distance from start of ejection to the peak flow rate, and the normal value in adults varies between 136 and 153 msec, being inversely correlated with pulmonary

arterial pressure (PAP). Increased pulmonary vascular resistance and decreased pulmonary compliance shorten pulmonary acceleration time, and in adults, pulmonary acceleration time and heart rate are inversely correlated. It is corrected by the RR interval. Right ventricle preload and right ventricle systolic functions affect pulmonary acceleration time (13), and in healthy adults, pulmonary acceleration time should be higher than 110 ms (3). A previous study reported that pulmonary acceleration time was directly but inversely correlated with mPAP and pulmonary vascular resistance and directly correlated with pulmonary artery compliance. A pulmonary acceleration time of < 90 ms and a PAAcTc/RVET of < 0.31 led to a pulmonary arterial hypertension diagnosis with 97% sensitivity and 95% specificity. PAAcTc/RVET is not affected by heart rate, but in the presence of a heart rate lower than 60 or higher than 100, pulmonary acceleration time should be corrected based on heart rate. In children, there is a linear relationship between pulmonary vascular resistance and pulmonary arterial pressure at heart rates between 55 and 150 (14).

Pulmonary acceleration time 100 ms had 84% specificity and 89% sensitivity for SPAP > 38 mmHg, mPAP > 25 mmHg (15). In the present study, pulmonary acceleration time (< 84 ms) was significantly shortened in patients who showed no sign of clinical improvement following monotherapy and therefore started multidrug therapy. A pulmonary artery diameter greater than 29 mm is moderately/highly specific for a pulmonary arterial hypertension diagnosis in adults, while pulmonary artery/Aort diameter (PA/Ao) > 1 is highly specific (16). Pulmonary artery/Aort diameter (PA/Ao) is reliable for pulmonary vascular resistance, and this ratio decreases with age (17). There have been studies

reporting a cut-off value determining mPAP > 20 mmHg as pulmonary artery/Aort diameter (PA/Ao) > 0.9 (18). Pulmonary arteries are wider in children with pulmonary arterial hypertension when compared to healthy children. A pulmonary artery/Aort diameter (PA/Ao) > 1.3, as demonstrated by cardiac tomography, increases the suspicion of pulmonary arterial hypertension in children. While this ratio varies among different age groups, there is no gender-based difference (4). In a previous study including 159 patients with Ejection Fraction-preserved heart failure, the pulmonary artery/Aort diameter (PA/Ao) ratio was found to be the strongest predictor of moderate and severe pulmonary arterial hypertension and showed the best correlation with mPAP values, and the pulmonary artery/Aort diameter (PA/Ao) ratio has been found to be a strong predictor of TPG > 12 mmHg (19). In a study involving 235 patients with idiopathic pulmonary fibrosis, a high pulmonary artery/Aort diameter (PA/Ao) diameter was associated with poor right ventricle (RV) function and a right-sided deviation of the QRS axis, and was considered to be an independent predictor of pulmonary arterial hypertension.

The presence of a pulmonary artery/Aort diameter (PA/Ao) ratio of < 1.1, a QRS axis of < 90, and normal right ventricle function has an 85% probability of eliminating pre-capillary pulmonary arterial hypertension (20). In the present study, a decreased pulmonary and venous flow transit time and pulmonary acceleration time in the group with pulmonary artery/Aort diameter (PA/Ao) > 1.5 indicated the severity of pulmonary arterial hypertension in this group. The right ventricle develops systolic and diastolic dysfunction as pulmonary arterial hypertension progresses, followed by hypertrophy-dilation of the right ventricle. The right atrium is also affected

by these changes. Right atrium filling pressure increases, and right atrium width is known to be a predictor of pulmonary arterial hypertension prognosis. A previous study suggested that the Right Atrium function index (RAFi) was a strong prognostic marker, along with a 6-min walking test, NT-pro-BNP levels, and right atrium area in pulmonary arterial hypertension patients (21). Another study suggested use of the Right atrium area index to estimate prognosis (5). In the present study, Right atrium area index showed the closest association with pro-BNP levels, with right atrium area index significantly increased in patients with pro-BNP levels of > 100 pg/ml. The right pulmonary artery distensibility index reflects the percentage of change in right pulmonary artery diameter. Right pulmonary artery distensibility index decreases with increasing severity of pulmonary arterial hypertension (10), while pulmonary and venous flow transit time reflects the pathophysiological changes in pulmonary circulation that occur in the presence of diseases accompanied by pulmonary hypertension and pulmonary fibrosis (11).

Right pulmonary artery distensibility index levels were not significantly different between the patient groups investigated in the present study, although a shortened pulmonary and venous flow transit time in the group with SaO₂ > 90% was associated with the higher number of patients with idiopathic pulmonary arterial hypertension in this group, leading to increased severity of pulmonary arterial hypertension and a higher rate of fibrosis development in the pulmonary bed in this patient group. In addition, a decreased pulmonary and venous flow transit time in the group with pulmonary artery/Aort diameter (PA/Ao) > 1.5 indicated the severity of pulmonary arterial hypertension in this patient group.

4-1. Study Limitations

The small number of patients represents a limitation of this study. Also, not having a control group.

5- CONCLUSION

In pulmonary arterial hypertension patients, the presence of a right atrium area index (RAAI) $> 18 \text{ cm}^2/\text{m}^2$, pulmonary artery/Aort diameter (PA/Ao) > 1.5 , and pulmonary artery acceleration time (PAAcTc) $< 80 \text{ msn}$ indicates higher disease severity, and it can thus be concluded that the patients' treatment regimen should be re-evaluated based on these parameters. In particular, the Right atrium area index parameter shows the closest association with pro-BNP levels.

6- FUNDING SOURCE

No external funding was secured for this study.

7- FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose

8- WHAT IS ALREADY KNOWN"

A previous study suggested that the 6-min walking test, NT-pro-BNP levels, were strong prognostic markers in pulmonary arterial hypertension patients.

9- WHAT THIS STUDY ADDS"

In the present study, Right atrium area index showed the closest association with pro-BNP levels, with right atrium area index significantly increased in patients with pro-BNP levels of $> 100 \text{ pg/ml}$. In particular, the Right atrium area index parameter shows the closest association with pro-BNP levels.

10- CONFLICT OF INTEREST: None.

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