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Original Article

Early Echocardiographic Findings of Pulmonary Hypertension-specific Therapy in Children

Pulmoner Hipertansiyon-spesifik Tedavinin Çocuklardaki Erken Ekokardiyografik Bulguları

Akif KAVGACI, Fatma Sedef TUNAOGLU, Serdar KULA, Ayse Deniz OGUZ, Semiha TERLEMEZ, Fatma INCEDERE

Gazi University Faculty of Medicine, Department of Pediatric Cardiology, Ankara, Turkey

ABSTRACT

Objective: Echocardiography is a very useful tool for the diagnosis and evaluation of pulmonary hypertension (PH). This study was planned to investigate whether echocardiographic (ECHO) data of patients with PH are effective in the follow-up and course of treatment.

Methods: A retrospective analysis of the data from 26 PH patients was performed. Analyses were performed on the data of the patients, including their demographics and ECHO findings. The ECHO measurements of the patients were labeled as 0 (beginning of the PH specific therapy), 1 (on the 15th day of the therapy), 2 (one month after the previous echocardiogram).

Results: The left ventricle ejection fraction (EF) (p=0.05) and fractional shortening (FS) (p=0.038) values in $ECHO_2$ were significantly higher than those in $ECHO_1$. Aortic velocity-time integral$_1$ (VTI_1) was significantly higher than aortic VTI_0 (p=0.001; p<0.01), and tricuspid annular plane systolic excursion$_2$ ($TAPSE_2$) was significantly higher than $TAPSE_0$ (p=0.046). Moreover, right ventricular ejection time$_1$ ($RVET_1$) was significantly higher than $RVET_0$ (p=0.034), and left ventricular ejection time$_1$ ($LVET_1$) was significantly higher than $LVET_0$ (p=0.003).

Conclusions: This study provides information on ECHO parameters that improve during the initial stages of therapy. Based on the results of our study, even at the beginning of treatment, there were increases in right and left ventricular filling, EF, and FS. Clinical deterioration of PH can be detected early/before the clinical status of the patient worsens with detailed examinations using echocardiography.

Keywords: Echocardiography, pulmonary hypertension, pediatrics

ÖZ

Amaç: Ekokardiyografi, pulmoner hipertansiyon (PH) tanısı ve tedavisinde çok yararlı bir araçtır. Bu çalışmada PH tanılı çocuk hastalarda ekokardiyografik (EKO) verilerinin tedaviyi izlem ve yönlendirmede etkin olup olmadığını değerlendirmeye yönelik planlanmıştır.

Yöntemler: PH tanısı ile merkezimizde takip ettiğimiz 26 hastanın verileri retrospektif olarak incelenmiştir. Hastaların demografik özellikleri ve EKO bulgularını içeren veriler üzerinde analizler yapılmıştır. EKO ölçümleri hastalara tedavi başlangıcında (EKO_0), tedavinin 15. gününde (EKO_1) ve EKO_1'den bir ay sonra (EKO_2) yapılmıştır.

Bulgular: EKO_2'deki sol ventrikül ejeksiyon fraksiyonu (EF) (p=0,05) ve fraksiyonel kısalma (FK) (p=0,038) değerleri EKO_1'dekilerden anlamlı olarak daha yüksekti. Aortik hız zaman integrali$_1$ (VTI_1), aortik VTI_0'dan (p=0,001; p<0,01) ve $TAPSE_2$, $TAPSE_0$'dan (p=0,046) anlamlı olarak daha yüksekti. Ayrıca, sağ ventrikül ejeksiyon zamanı$_1$ ($RVET_1$), $RVET_0$'dan (p=0,034) ve sol ventrikül ejeksiyon zamanı ($LVET_1$), $LVET_0$'dan (p=0,003) anlamlı olarak daha yüksekti.

Sonuçlar: Çalışmamız, tedavinin ilk aşamalarında düzelme gösteren EKO parametreler hakkında bilgi vermektedir. Tedavinin başlangıcında bile sağ ve sol ventrikül dolumu, EF ve FK'de düzelme görülmüştür. PH'nin klinik kötüleşmesi, EKO kullanılarak yapılan ayrıntılı incelemelerle hastanın klinik durumu kötüleşmeden önce/erken tespit edilebilir.

Anahtar kelimeler: Ekokardiyografi, pulmoner hipertansiyon, pediatri

Address for Correspondence: A. Kavgaci,
Gazi University Faculty of Medicine, Department of Pediatric Cardiology, Ankara, Turkey
E-mail: akifkavgaci@gmail.com **ORCID ID:** orcid.org/0000-0002-7502-765X

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INTRODUCTION

Pulmonary hypertension (PH) and pulmonary vascular disease that develop in relation to PH are characterized by right ventricular (RV) dysfunction, left ventricular (LV) compression, filling defects, and end-stage heart failure following pulmonary vascular remodeling formed by elevated pulmonary arterial pressure[1]. The early diagnosis and treatment of PH are vital in terms of the quality of life of the patient and their prognosis.

The parameters used in follow-up to determine the effectiveness of the drugs used and prognostic factors in pediatric PH patients can be evaluated with echocardiography. Transthoracic echocardiography is a widely available and non-invasive procedure that can measure cardiac output, assess the right and left ventricle functionality, identify disease morphology, and estimate pulmonary artery pressure and pulmonary resistance. In addition, echocardiography plays a significant role in the follow-up and monitoring of therapeutic effects in addition to detecting PH[2].

Although there are studies on the outcomes of PH therapy in the literature, there is limited data on the impacts on the results of echocardiography in the very early stages of treatment, such as the first 15 days and 1 month. The aim of this study was to report the changes in echocardiography that occurred in patients with PH throughout this initial stage of therapy.

MATERIALS and METHODS

Study Population

In this study, the data of 26 patients who were being followed up with PH diagnosis at the department of pediatric cardiology were retrospectively analyzed. The sample of the study included patients with PH under the age of 18 who attended their follow-ups at the required intervals.

The pulmonary vascular resistance (PVR), pulmonary capillary wedge pressures, and mean pulmonary artery pressures (mPAPs) obtained by catheterization in all patients who participated in our study were compatible with the criteria defined in the guidelines published by the American Heart Association/American Thoracic Society (AHA/ATS) in 2015. As per the biochemical parameters, catheterization results, echocardiographic (ECHO) findings at the time of diagnosis, and 6-min walk test (6MWT), all patients in our study were categorized as New York Heart Association functional class II. While the patients involved in the study were administered bosentan, inhaled iloprost, and sildenafil therapies, our study focused on patients who, according to ECHO results at the initiation of their condition, were exclusively undergoing bosentan treatment.

Written informed consent was signed by the parents of all children. This study was conducted in compliance with the "Declaration of Helsinki" and was approved by the Gazi University Clinical Research Ethics Committee (decision no: 541, date: 14.06.2021).

Echocardiographic Evaluation

Analyses were performed on the data of the patients, including their age, sex, weight, height, body mass index, and ECHO findings [morphological examinations, LV functions, RV end-systolic and end-diastolic diameters, tricuspid annular plane systolic excursion (TAPSE), mitral annular plane systolic excursion, inferior vena cava (IVC) systolic and diastolic diameters, hepatic vein and pulmonary vein flow rates, pulmonary artery acceleration time, aortic, pulmonary arterial, mitral, and tricuspid flow "velocity-time integral" (VTI), RV (RVET) and LV ejection times (LVET), and RV and LV tissue Doppler velocities].

The measurements were made in triplicates by the same practitioner using a GE Vivid 7 device (GE Ultrasound, Horten, Norway) with 3.5 and 5 MHz probes to include both inspiration and expiration.

ECHO measurements of the patients were taken at the beginning of treatment ($ECHO_0$), on the 15th day of treatment ($ECHO_1$), and one month after $ECHO_1$ ($ECHO_2$).

The cut-off date for data inclusion in the initial cross-sectional study was November 2018, when the intended number of patients had been enrolled. Therefore, for the definition of PH, we adopted the 2015 AHA/ATS recommendations. According to the AHA/ATS guidelines, PH can be diagnosed when mPAP $\geq$25 mmHg in children older than 3 months at sea level and pulmonary arterial hypertension can be diagnosed when mPAP ≥25 mmHg, pulmonary arterial wedge pressure <15 mmHg, and PVR >3 Wood unit.m^2 (WU.m^2)[3].

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum, maximum) were calculated for the data, and the normality of their distribution was analyzed using the Shapiro-Wilk test. Friedman tests were conducted to test whether there was a significant change in the ejection fraction (EF), fractional shortening (FS), RVET, LVET, TAPSE, and aortic VTI variables due to violations of parametric test

assumptions (non-normal distribution and low number cases, respectively). The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. An overall 5% type-I error level was used to infer statistical significance. Statistical significance was assessed on the basis of the levels of $p<0.017$ and $p<0.05$.

RESULTS

The mean age of the patients who participated in our study was found as 9.19±5.6 (1-18) years, while 42.3% of them (n=11) were female and 57.7% (n=15) were male. The mean height of the patients was 123.38±32.68 (62-176) cm, and their mean weight was 27.04±16.31 (4-63) kg. The mean body surface area of the patients was 0.93±0.4 (0.24-1.69) m^2 (Table 1).

Eight patients had primary PH, 17 had secondary PH, and one patient had chronic thromboembolic pulmonary hypertension. The accompanying congenital cardiac anomalies of the patients were ventricular septal defect (8 patients), transposition of the great arteries (3 patients), truncus arteriosus (3 patients), double-outlet right ventricle (1 patient), atrioventricular canal defect (1 patient), and total anomalous pulmonary venous return (1 patient), respectively (Table 2).

While the patients involved in the study were administered bosentan, inhaled iloprost, and sildenafil therapies, our study focused on patients who, according to ECHO results at the initiation of their condition, were exclusively undergoing bosentan treatment. After the period when ECHO data were obtained, iloprost was added to the treatment of 10 patients and sildenafil was added to 3 patients. When the distribution of the patient group according to treatment status was evaluated, 13 patients (50%) were receiving monotherapy and 13 patients (50%) were receiving dual therapy. Two patients were unable to participate in the 6MWT because of Down syndrome, and one patient could not cooperate because of their young age (5 years). The average distance covered in the 6MWT for the remaining 23 patients was 398.2±113.9 meters.

Table 1. Demographic data of the patients.

	X ± SD	Min-max (median)
Age (years)	9.19±5.6	1-18 (10)
Height (cm)	123.38±32.68	62-176 (128.5)
Weight (kg)	27.04±16.31	4-63 (24)
Body surface area (m^2)	0.93±0.4	0.24-1.69 (0.91)

SD: Standard deviation, min-max: Minimum-maximum

Seventy-seven different parameters were analyzed at the beginning of the treatment of the patients ($ECHO_0$), on the 15th day of the treatment ($ECHO_1$), and one month after $ECHO_1$ ($ECHO_2$); however, only significant results are shown in Table 3. A Supplementary Table is given for all parameters measured.

EF_0 was 66.95±10.6%, EF_1 was 64.71±10.02%, and EF_2 was 69.44±13.66% ($p=0.05$), while FS_0 was 36.73±7.48%, FS_1 was 35.08±6.93%, and FS_2 was 39.04±10.1% ($p=0.038$). There were significant increases in the EF and FS values of LV from $ECHO_1$ to $ECHO_2$.

The aortic VTI values were 20.09±8.36 cm in $ECHO_0$, 25.23±9.75 cm in $ECHO_1$, and 23.67±8.80 cm in $ECHO_2$, where aortic VTI_1 was significantly higher than aortic VTI_0 ($p=0.001$; $p<0.01$).

$TAPSE_0$ was 1.79±0.64 cm, $TAPSE_1$ was 1.93±0.84 cm, and $TAPSE_2$ was 2.15±0.65 cm, where $TAPSE_2$ was significantly higher than $TAPSE_0$ ($p=0.046$).

There were significant increases in LVET and RVET values, where $RVET_0$ was determined as 252.69±44.03 ms, $RVET_1$ was 280.77±56.52 ms, $RVET_2$ was 255.95±53.58 ms, and $RVET_1$ was significantly higher than $RVET_0$ ($p=0.034$). Moreover, $LVET_0$ was determined 247.58±37.46 ms, $LVET_1$ was 281.93±55.49 ms, $LVET_2$ was 246.26±45.27 ms, and $LVET_1$ was significantly higher than $LVET_0$ ($p=0.003$) (Table 3). The tricuspid tissue Doppler Myocardial performance index $(MPI)_0$ was 0.39±0.15, tricuspid tissue Doppler MPI_1 was 0.37±0.12, and tricuspid tissue Doppler MPI_2 was 0.39±0.15, with no statistically significant relationship found among them. Mitral tissue Doppler MPI_0 was

Table 2. Distributions of diagnosis.

		n	%
Diagnosis	Idiopathic pulmonary hypertension	8	30.76
	Secondary pulmonary hypertension	17	65.38
	VSD	8	30.76
	Transposition of the Great Arteries	3	11.53
	Truncus arteriosus	3	11.53
	DORV	1	3.84
	TAPVR	1	3.84
	AVCD	1	3.84
	CTEPH	1	3.84

VSD: Ventricular septal defect, DORV: Double outlet right ventricle, TAPVR: Total anomalous pulmonary venous return, AVCD: Atrioventricular canal defect, CTEPH: Chronic thromboembolic pulmonary hypertension

Table 3. Significant echocardiographic findings in the measurements of the patients at the beginning of treatment ($ECHO_0$), on the 15th day of treatment ($ECHO_1$) and in the first month after $ECHO_1$ ($ECHO_2$).

		$ECHO_0$	$ECHO_1$	$ECHO_2$
LVFS (%)[a]	Mean ± SD	36.73±7.48	35.08±6.93	39.04±10.1
LVEF (%)[b]	Mean ± SD	66.95±10.6	64.71±10.02	69.44±13.66
Aortic VTI (cm)[c]	Mean ± SD	20.1±8.36	25.23±9.76	23.68±8.8
RVET (ms)[d]	Mean ± SD	252.69±44.03	280.77±56.52	255.95±53.58
LVET (ms)[e]	Mean ± SD	247.58±37.46	281.93±55.49	246.26±45.27
TAPSE (cm)[f]	Mean ± SD	1.79±0.64	1.93±0.84	2.15±0.65

[a] $LVFS_2$ was significantly higher than $LVFS_1$ (p=0.038)

[b] $LVEF_2$ was significantly higher than $LVEF_1$ (p=0.05)

[c] Aortic VTI_1 was significantly higher than aortic VTI_0 (p=0.001)*

[d] $RVET_1$ was significantly higher than $RVET_0$ (p=0.034)

[e] $LVET_1$ was significantly higher than $LVET_0$ (p=0.003)*

[f] $TAPSE_2$ was significantly higher than $TAPSE_0$ (p=0.046)

* A p-value below 0.017 is considered statistically significant in accordance with the Bonferroni correction

LVFS: Left ventricle fractional shortening, LVEF: Left ventricle ejection fraction, VTI: Velocity-time integral, RVET: Right ventricular ejection time, LVET: LV ejection time, TAPSE: Tricuspid annular plane systolic excursion, IVS: Interventricular septum, ECHO: Echocardiographic

0,38±0.12, mitral tissue Doppler MPI_1 was 0,35±0.08 and mitral tissue Doppler MPI_2 was 0,4±0.13. No statistically significant relationship was found among the results of mitral tissue Doppler MPI. The RV flow Doppler MPI_0 was 0.32±0.13, RV flow Doppler MPI_1 was 0.34±0.14, and RV flow Doppler MPI_2 was 0.43±0.21, with no statistically significant relationship found among them. The LV flow Doppler MPI_0 was 0.33±0.11, LV flow Doppler MPI_1 was 0.29±0.08, and LV flow Doppler MPI_2 was 0.42±0.11. No statistically significant association was observed among the results of LV flow Doppler MPI. The supplemental table includes all of the patients' ECHO results.

DISCUSSION

PH is a progressive and usually fatal disease. When its symptoms become noticeable, the underlying disease causing it often has reached an advanced stage. Functional status and survival rates of patients with PH have dramatically increased as a result of recent advancements in pharmacological therapy. Because PH is a degenerative condition, it is crucial to stop its rapid advancement in afflicted children[4]. Echocardiography is an easily applicable, non-invasive, and inexpensive method that is used not only in the diagnosis of PH but also in its follow-up and for the assessment of treatment response[2].

Recent studies have shown that RV function is an important indicator of significant cardiopulmonary diseases such as PH and end-stage heart failure[5,6]. Transthoracic echocardiography is an important tool for evaluating RV dysfunction. The most significant outcomes of PH are RV "remodeling" and its effect on the left part of the heart/systemic flow[7].

In this study, it was determined that the left ventricular ejection fraction $(LVEF)_2$ values increased significantly in comparison with the EF_1 values. In parallel with this result, the FS_2 values also increased significantly compared with the FS_1 values. In a study conducted with pediatric patients with PH, Koestenberger et al.[8] reported that LVEF showed a negative correlation with increases in the pulmonary arterial systolic pressure/systemic systolic pressure ratio and the PVR index, and as the severity of the disease increased, LVEF decreased. They also stated that a significant increase in RV afterload caused RV volume overload, and this could paradoxically lower LVEF because of the direct interaction between the ventricles[8]. In our study, we noted clinically significant enhancements in the LVEF and LVFS, both falling within the normal range. The observed progress in LV function suggests that targeted therapies for PH initiate early modifications and have a positive influence on LV functions, particularly by reducing the RV afterload, preventing excessive RV volume, and enhancing the diastolic filling of the left ventricle.

In our study, the aortic VTI_1 values were significantly higher than the aortic VTI_0 values (p=0.001). An increased aortic VTI value indicates a higher flow passing through the aorta and increased stroke volume. Aortic VTI is an important indicator of the systolic function of the heart and stroke volume. The excessive increase in RV pressure in PH shifts the septum to the left and compresses the left ventricle. The improvement of LV systolic functions and

increased stroke volume showed that the negative effect of the right ventricle on the left ventricle decreased.

According to our results, $TAPSE_2$ was higher than $TAPSE_0$ (p=0.046). The most important ECHO parameter used to longitudinally estimate RV systolic functions is TAPSE. Beyond reflecting RV functions, TAPSE also has an important place in the global assessment of RV functions[9]. In PH, especially idiopathic PH and Eisenmenger syndrome, TAPSE has a significant prognostic value[10-12]. The normal value of TAPSE in adults is greater than 2 cm, but there is no clear cutoff value in children. Nevertheless, the increase in the TAPSE values of our patients was a favorable finding in terms of the improvement of RV function. In the results of our study, the reduction in TA values despite the increase in tricuspid E values may be considered acceptable in terms of showing that RV relaxation was made easier with the treatment. These results can be used as proof that the RV afterload has decreased. The negative impact of the right ventricle on LV filling reduces because of the reduction in resistance in front of the right ventricle, and the aortic VTI rises as a result.

In our study, using the tissue Doppler method, right ventricle, left ventricle, and interventricular septum (IVS) tissue Doppler measurements (S', E', A') were performed. In these measurements, while an increase was observed in the tricuspid annulus (TA) É, this increase was not significant. The IVS middle É values showed a statistically significant change. The IVS middle É2 value is significantly lower than IVS middle É0 (p=0.037). It was reported that there was a reduction in E' in pediatric PH, and E' was correlated with the mean pulmonary arterial pressure and RV end-diastole pressure in PH, but this correlation was not seen in patients with shunts[13]. Considering the age groups of the patients and their variety of underlying diseases, we believe that it would be more reasonable to compare changes in TA E' values measured in childhood separately in each age group rather than comparing them between adults and children. TA E' values less than 8 m/s were considered low in our study. However, the significant increase in TA E' values with treatment can be considered to be in favor of an improvement in the diastolic functions of the right ventricle. The positive effect of treatment on the pulmonary vascular bed can reduce the afterload of the right ventricle, thus resulting in its easier relaxation. The increase in E' velocity may be considered an indicator of this favorable development. The higher TA tissue Doppler E' values in the third and last ECHO examinations than those in the second examinations in our study showed the positive effects of the treatment on diastolic functions in the early period. When examining tricuspid and mitral tissue Doppler MPI values, although a significant numerical increase was observed between mitral tissue Doppler MPI_1 and MPI_2, no statistically significant relationship was found between mitral tissue Doppler MPI values. Similarly, although the LV and RV flow Doppler MPI_2 values were significantly higher than the flow Doppler MPI_1 values, no statistically significant difference was detected.

Our study illustrates notable increases in the LVET and RVET values. Specifically, $RVET_1$ was higher than $RVET_0$ (p=0.034), and $LVET_1$ was significantly higher than $LVET_0$ (p=0.003). RVET shortening has been documented in both adults and children with PH[14,15]. In the literature, it is thought that LVET may be associated with RV stroke volume and RV afterload, thereby being considered a significant prognostic factor indicating the patient's clinical deterioration. There is also evidence suggesting that shortened LVET is associated with a worse prognosis in pre-capillary PH with right heart failure[16,17]. Our study suggests that the elevation in RVET and LVET values positively impacts early-phase treatment for PH, aligning with findings in the existing literature.

In our study, significant increases were observed in the IVC end-systolic and end-diastolic diameters. Information on right atrial pressure values can be obtained by measuring the end-systolic and end-diastolic diameter values of the IVC. The IVC index is used in adults but not in children. Because RV functions in pediatric patients usually do not deteriorate until the advanced stages of the disease, an increase might not be observed in right arterial pressure values. In our study, no significant change was found in the IVC collapsibility index, which does not have a place in the examinations of pediatric patients.

Recent studies have shown that TAPSE/systolic pulmonary artery pressure (sPAP) is affected by RV diastolic stiffness in severe PH, as assessed by echocardiography. It has been reported that the prognosis of patients with a TAPSE/sPAP <0.31 mm/mmHg is worse than those with higher TAPSE/sPAP ratio[18]. In our investigation, the mean TAPSE/sPAP value was above 0.31 mm/mmHg in all ECHO exams, which was not statistically significant. There is a need for larger-scale investigations in which this novel metric is also employed in pediatric patients.

CONCLUSION

Early identification of the clinical symptoms of PH can be achieved through detailed ECHO examinations before the patient's clinical condition deteriorates. In our study, notable increases were observed, particularly in

LVEF, LVFS, reflecting LV systolic functions, and TAPSE, a crucial measurement indicating RV systolic functions, compared with baseline values. These ECHO findings indicate that specific treatments for PH induce early changes and positively impact specific parameters. We emphasize improvements in the early phase of therapy because the research often highlights changes in indicators 8-12 weeks after the start of treatment.

Ethics

Ethics Committee Approval: This study was approved by Gazi University Faculty of Medicine Clinical Research Ethics Committee with decision number 541 on 14.06.2021.

Informed Consent: Written informed consent was signed by parents of all children.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: A.K., F.S.T., S.K., A.D.O., S.T., F.I., Concept: F.S.T., Design: F.S.T., Data Collection and/or Processing: A.K., F.S.T., S.K., A.D.O., Analysis and/or Interpretation: F.S.T., S.K., Literature Search: A.K., F.I., Writing: A.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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Supplementary Table. Echocardiographic findings in the measurements of the patients at the beginning of treatment ($ECHO_0$), on the 15th day of treatment ($ECHO_1$) and in the first month after $ECHO_1$ ($ECHO_2$).

		$ECHO_0$	$ECHO_1$	$ECHO_2$
RVIDd (cm)	Mean ± SD	3.23±0.95	3.52±0.91	3.31±0.81
RVIDs (cm)	Mean ± SD	2.48±0.91	2.79±0.86	2.54±0.81
RV IVSd (cm)	Mean ± SD	0.69±0.21	0.74±0.22	0.7±0.28
RV IVSs (cm)	Mean ± SD	0.8±0.18	0.91±0.19	0.83±0.3
RV anterior wall Dd (cm)	Mean ± SD	0.88±0.25	0.85±0.21	0.85±0.27
RV anterior wall Sd (cm)	Mean ± SD	1.11±0.37	1.12±0.28	1.09±0.32
Tricuspid annulus diameter (cm)	Mean ± SD	2.59±0.6	2.83±0.66	2.85±0.6
Mitral annulus diameter (cm)	Mean ± SD	2.41±0.65	2.49±0.64	2.39±0.67
PA annulus diameter (cm)	Mean ± SD	2.01±0.47	1.96±0.54	2.19±0.58
Aortic annulus diameter (cm)	Mean ± SD	1.98±0.7	1.9±0.66	2.02±0.84
TAPSE (cm)	Mean ± SD	1.79±0.64	1.93±0.84	2.15±0.65
MAPSE (cm)	Mean ± SD	1.38±0.48	1.39±0.45	1.33±0.3
Aortic VTI (cm)	Mean ± SD	20.1±8.36	25.23±9.76	23.68±8.8
VKI systolic diameter (cm)	Mean ± SD	0.99±0.39	1.22±0.61	1.1±0.42
VKI diastolic diameter (cm)	Mean ± SD	0.63±0.31	0.77±0.42	0.71±0.38
Hepatic vein d (m/s)	Mean ± SD	0.49±0.16	0.55±0.25	0.52±0.18
Hepatic vein s (m/s)	Mean ± SD	0.76±0.26	0.72±0.25	0.73±0.24
Hepatic vein a (m/s)	Mean ± SD	0.48±0.16	0.47±0.18	0.50±0.23
Tricuspid E (m/s)	Mean ± SD	1.06±0.35	1.05±0.38	1±0.37
Tricuspid A (m/s)	Mean ± SD	0.85±0.28	0.86±0.26	0.74±0.17
Tricuspid S (m/s)	Mean ± SD	3.16±1.71	3.05±1.46	3.39±1.39
Tricuspid decceleration time (ms)	Mean ± SD	103.72±73.38	106.66±106.88	82.09±39.36
Tricuspid "closure to open" (ms)	Mean ± SD	349.23±58.83	352.33±67.29	352.27±60
RV ejection time (ms)	Mean ± SD	252.69±44.03	280.77±56.52	255.95±53.58
RV flow MPI	Mean ± SD	0.32±0.13	0.34±0.14	0.43±0.21
Tricuspid VTI (cm)	Mean ± SD	21.41±9.02	20.57±8.5	28.68±42.69
Tricuspid regurgitation VTI (cm)	Mean ± SD	84.58±69.21	71.64±39.57	80.43±36.62
PA systolic flow velocity (m/s)	Mean ± SD	1.52±0.58	1.53±0.55	1.62±0.68
PA diastolic flow velocity (m/s)	Mean ± SD	1.75±1.15	1.8±1.06	2.07±1.29
PA acceleration time (ms)	Mean ± SD	89.76±24.96	93.42±25.64	96.28±27.51
PA systolic VTI (cm)	Mean ± SD	26.54±12.81	29.32±12.67	27.22±13.03
PA diastolic VTI (cm)	Mean ± SD	56±50.5	47.33±42.1	45.44±44.54
Pulmoner Vein d (m/s)	Mean ± SD	0.54±0.17	0.51±0.12	0.55±0.15
Pulmoner vein s (m/s)	Mean ± SD	0.68±0.17	0.63±0.16	0.69±0.22
Pulmoner vein a (m/s)	Mean ± SD	0.51±0.18	0.55±0.3	0.54±0.21
Mitral E (m/s)	Mean ± SD	1.19±0.31	1.2±0.31	1.14±0.29
Mitral A (m/s)	Mean ± SD	0.86±0.29	0.85±0.24	0.84±0.23
Mitral "closure to open" (ms)	Mean ± SD	327.53±50.37	360.1±52.25	337.31±62.01
LV ejection time (ms)	Mean ± SD	247.58±37.46	281.93±55.49	246.26±45.27
LV flow MPI	Mean ± SD	0.33±0.11	0.29±0.08	0.42±0.11
Mitral VTI (cm)	Mean ± SD	23.05±9.47	24.5±9.7	21.4±7
LVIDd (cm)	Mean ± SD	3.45±0.99	3.94±1.27	3.77±1.44
LVIDs (cm)	Mean ± SD	2.26±0.77	2.6±1	2.40±1.17

Supplementary Table. Continued				
LVIVSd (cm)	Mean ± SD	0.96±0.31	0.98±0.33	0.96±0.36
LVPWd (cm)	Mean ± SD	0.86±0.3	0.87±0.22	0.91±0.29
LVIVSs (cm)	Mean ± SD	0.97±0.3	1.02±0.28	1.08±0.41
LVPWs (cm)	Mean ± SD	1.22±0.43	1.27±0.43	1.3±0.42
LV fractionel shortening (%)	Mean ± SD	36.73±7.48	35.08±6.93	39.04±10.1
LV ejection fraction (%)	Mean ± SD	66.95±10.6	64.71±10.02	69.44±13.66
AO PLAX diameter (cm)	Mean ± SD	1.96±0.71	1.98±0.74	2.2±0.91
LA PLAX diameter (cm)	Mean ± SD	2.43±0.71	2.55±0.74	2.65±0.81
AO/PA	Mean ± SD	0.94±0.39	0.94±0.36	0.88±0.23
Tricuspid annulus S′ (m/s)	Mean ± SD	0.12±0.04	0.12±0.04	0.13±0.04
Tricuspid annulus E′ (m/s)	Mean ± SD	0.15±0.06	0.15±0.05	0.16±0.06
Tricuspid annulus A′ (m/s)	Mean ± SD	0.12±0.05	0.11±0.06	0.14±0.05
Tricuspid middle zone S′ (m/s)	Mean ± SD	0.1±0.04	0.14±0.13	0.09±0.04
Tricuspid middle zone E′ (m/s)	Mean ± SD	0.13±0.08	0.15±0.12	0.11±0.05
Tricuspid middle zone A′ (m/s)	Mean ± SD	0.15±0.21	0.13±0.17	0.09±0.05
IVS annulus S′ (m/s)	Mean ± SD	0.06±0.02	0.06±0.01	0.07±0.02
IVS annulus E′ (m/s)	Mean ± SD	0.09±0.04	0.09±0.04	0.1±0.04
IVS annulus A′ (m/s)	Mean ± SD	0.07±0.03	0.07±0.03	0.07±0.02
IVS middle zone S′ (m/s)	Mean ± SD	0.07±0.02	0.07±0.02	0.07±0.03
IVS middle zone E′ (m/s)	Mean ± SD	0.083±0.05	0.084±0.04	0.081±0.03
IVS middle zone A′ (m/s)	Mean ± SD	0.08±0.05	0.08±0.04	0.08±0.03
Tricuspid tissue MPI	Mean ± SD	0.39±0.15	0.37±0.12	0.39±0.15
Mitral tissue S′ (m/s)	Mean ± SD	0.09±0.03	0.09±0.03	0.11±0.04
Mitral tissue E′ (m/s)	Mean ± SD	0.14±0.05	0.13±0.04	0.14±0.04
Mitral tissue A′ (m/s)	Mean ± SD	0.08±0.03	0.07±0.03	0.08±0.04
Mitral tissue MPI	Mean ± SD	0.38±0.12	0.35±0.08	0.4±0.13
Tricuspid E/A	Mean ± SD	1.3±0.41	1.24±0.38	1.37±0.43
Tricuspid tissue E′/A′	Mean ± SD	1.38±0.67	1.64±1.1	1.28±0.78
IVS middle zone E′/A′	Mean ± SD	1.56±0.82	1.45±0.65	2±0.88
AO/LA	Mean ± SD	0.81±0.16	0.78±0.2	0.8±0.2
RV fractionel shortening (%)	Mean ± SD	29.36±14.21	21.83±8.79	26.60±16.65
Tricuspid E/E′	Mean ± SD	7.71±3.26	8.35±4.06	6.94±3.27
Paact/RVET	Mean ± SD	0.37±0.12	0.34±0.09	0.39±0.08
TAPSE/sPAP	Mean ± SD	0.0353±0.031	0.0395±0.027	0.0445±0.025

Ao: Aorta, PA: Pulmonary artery, LV: Left ventricle, RV: Right ventricle, VTI: Velocity-time integral, TAPSE: Tricuspid annular plane systolic excursion, IVS: Interventricular septum, Dd: Diastolic diameter, Sd: Systolic diameter, MAPSE: Mitral annular plane systolic excursion, MPI: Myocardial performance index, LVIDd: Left ventricular internal diameter in diastole, LVIDs: Left ventricular internal dimension in systole, LVIVSd: Left ventricular interventricular septal thickness in diastole, LVIVSs: Left ventricular interventricular septal thickness in systole, LVPWd: Left ventricular posterior wall thickness in diastole, LVPWs: Left ventricular posterior wall thickness in systole, PLAX: Parasternal long axis, RVET: Right ventricular ejection time, sPAP: Systolic pulmonary artery pressure, SD: Standard deviation, ECHO: Echocardiographic