

# Echocardiographic Evaluation of Orthotopic Heart Transplantation: Single-Center Experience

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**Background:** In patients with advanced heart failure, significant improvement in pharmacological and non-pharmacological treatment strategies has conferred better survival rates and quality of life.

**Objectives:** This is a report on echocardiographic findings in heart transplantation (HTx) patients in their first 5 postoperative months.

**Patients and Methods:** Twenty patients undergoing HTx between September 2009 and July 2010 whose clinical and echocardiographic findings had been registered monthly for 5 months after HTx were enrolled.

**Results:** Eleven males and five females at a mean age of 33 years [range = 17-58 years] were enrolled in the study. The mean of the left ventricular ejection fraction (LVEF) was  $52 \pm 8.2\%$  and  $58 \pm 2.5\%$  on the first day and at 5 months after HTx, respectively. There was no LV enlargement at 5 months' follow-up. The right ventricle (RV) was mildly enlarged, but the reduced baseline RV function showed improvement at the 5th postoperative month (mean TAPSE was  $11.7 \pm 3.3$  mm on the first post-HTx day versus  $17.2 \pm 6.3$  mm after 5 months;  $P < 0.005$ ). The pulmonary arterial pressure was slightly elevated at baseline, and it showed no significant decrease 5 months after HTx. More than 90% of the cases showed only mild tricuspid regurgitation at 5 months' follow-up. The tissue Doppler imaging-derived velocities of the medial and lateral mitral annuli and the tricuspid annulus demonstrated a gradual increment during the follow-up and reached their highest value at 5 months' follow-up.

**Conclusions:** The cardiac grafts at 5 months' post-HTx follow-up were characterized by normal LV dimensions and EF. Also, RV dysfunction and tricuspid regurgitation were frequent findings, but they were not associated with the clinical signs of congestive heart failure, morbidity, and mortality in the majority of our patients.

**Keywords:** Heart Transplantation; Echocardiography; Indices

## 1. Background

In patients with advanced heart failure, significant improvement in pharmacological and non-pharmacological treatment strategies has conferred better survival rates and quality of life (1). However, the left ventricular (LV) function usually remains severely depressed, and long-term follow-up is not yet available on many treatment modalities. In contrast to the more recently developed therapeutic options, heart transplantation (HTx) was introduced into broad clinical use 30 years ago and might be considered the gold standard for adequately selected patients (2-7). Even so, beyond survival rates, little is known about follow-up echocardiographic findings on HTx (8-10). We herein report the echocardiographic findings on HTx patients in our center.

## 2. Objectives

This is a report on echocardiographic findings in heart

transplantation (HTx) patients in their first 5 postoperative months.

## 3. Patients and Methods

Among patients undergoing HTx at Masih-Daneshvari Heart Transplantation Center between September 2009 and July 2010, those who had regular follow-up sessions and whose clinical and echocardiographic findings had been registered monthly for 5 months after HTx were enrolled.

### 3.1. Echocardiographic Examination

All the recipients underwent standard evaluations, consisting of echocardiography, electrocardiography, and routine lab tests on each visit. Echocardiographic evaluations were performed using a SonoSite MicroMaxx ultrasound imaging system with a 2.5-MHz transducer from a standard window and views in the left lateral

position. All the echocardiographic studies were performed by a single echocardiographer. Atrial and ventricular dimensions, atrial areas, and ejection fraction (EF) were measured. Additionally, valvular competence was evaluated via color Doppler echocardiography, and the right ventricular (RV) size and function were assessed using tricuspid annular plane systolic excursion (TAPSE). Furthermore, the pulsed-wave Doppler technique was employed to measure the E,A velocity of the mitral and tricuspid valves, and tissue Doppler imaging (TDI) was used to measure the medial and lateral mitral annuli and the tricuspid annulus for the estimation of S, E, A velocity and calculation of the right and left myocardial performance index (MPI). MPI were used as a useful method for the baseline and serial follow up measurements RV the function and was calculated based on the following formula:

$$\text{MPI} = \text{TCO} - \text{ET} / \text{ET}$$

TCO (The tricuspid closure opening time) , (ET) Ejection time.

All echocardiographic measurement and calculations were done based on the latest American Society of Echocardiography guidelines. The study was approved by the institutional ethics committee, and informed consent was obtained from all the patients.

### 3.2. Statistical Analysis

All the statistical analyses were performed using IBM SPSS Statistics 19 for Windows (IBM Corp., Armonk, NY, USA). The data were assessed for normal distribution using the Kolmogorov-Smirnov test. The quantitative variables are presented as mean (standard deviation) and the categorical variables as counts and percentages. Paired t test or its non-parametric equivalent, Wilcoxon signed-rank test was used, as appropriate, to compare the quantitative variables.

## 4. Results

A total of 20 patients (65 % male) underwent HTx between September 2009 and July 2010. The mean age of the study population at the time of HTx was 33 years (range = 17-58 years), and the mean age of the donors was  $26.7 \pm 6.7$  years (range = 17-40 years). The indications for HTx were comprised of dilated cardiomyopathy in 15 (75 %) patients, ischemic cardiomyopathy in 2 (10 %), arrhythmogenic RV dysplasia in 2 (10 %), and valvular heart disease in one (5 %) (Table 1). The transplantation technique was bicaval anastomosis in all the patients, and immunosuppressive therapies were initiated and continued in accordance with the 2010 International Society of Heart and Lung transplantation guidelines (11). All the patients were continuously and closely monitored by our transplantation clinic staff. Any complications such as hypertension, renal dysfunction, and infections were registered and managed by the transplantation team in Masih-Daneshvari Heart Transplan-

tation Center. Three patients (2 females and one male) died because of disseminated intravascular coagulation and intracranial hemorrhage during the first postoperative week. Among the 20 patients, 17 patients were alive for 16 months and 16 patients had regular follow-up sessions and their clinical and echocardiographic findings were registered monthly for 5 months. During the 5-month follow-up period, none of the patients was symptomatic in terms of dyspnea. There were some complications such as asymptomatic acute cellular rejection (proven by endomyocardial biopsy), inferior vena cava stenosis, pulmonary emboli, massive pericardial effusion, diabetes mellitus, and renal failure, all of which were successfully addressed.

### 4.1. Echocardiographic Findings

#### 4.1.1. Chamber Study and Ventricular Function

Table 2 depicts the chamber study findings on the

**Table 1.** Characteristics of the Heart Transplantation Recipients

Characteristics	Descriptive Index
<b>Age, yr</b>	
Mean	33.6
Range	17-58
<b>Sex, No. (%)</b>	
Male	13 (65)
Female	7 (35)
<b>Transplantation cause, No. (%)</b>	
Dilated cardiomyopathy	15 (75)
Ischemic cardiomyopathy	2 (10)
Arrhythmogenic right ventricular dysplasia	2 (10)
Valvular cardiomyopathy	1 (5)
<b>Donor age</b>	
Mean $\pm$ SD	$26.73 \pm 6.74$
Range	17-40
<b>Early in-hospital mortality, No. (%)</b>	3 (15)
<b>Major postoperative complications<sup>a</sup></b>	6
<b>Previous implantable cardioverter-defibrillator</b>	3 (15)
<b>Transplantation technique</b>	
<b>Bicaval, %</b>	100

<sup>a</sup> Major postoperative complications include new-onset diabetes mellitus, inferior vena cava stenosis, pulmonary thromboemboli, recurrent pericardial effusion, renal insufficiency, and atrial flutter (each in one patient).

first post-HTx day and at 5 months' follow-up. The LV dimensions, i.e. left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD), were within the normal range. The mean LVEDD was  $4 \pm 0.5$  cm on the first post-HTx day and  $4.5 \pm 0.7$  cm at 5 months' follow-up ( $P > 0.05$ ). The mean LVESD was  $2.8 \pm 0.7$  on the first post-HTx day and  $3 \pm 0.6$  cm at 5 months' follow-up. The left atrial area was  $17.1 \pm 6.2$  cm<sup>2</sup> on the first postoperative day and  $22.1 \pm 7.5$  cm<sup>2</sup> after 5 months. The right atrial area was within the normal range:  $15.2 \pm 3.7$  cm<sup>2</sup> early after HTx and  $15.4 \pm 4.2$  cm<sup>2</sup> at 5 months' follow-up. The RV dimension was  $3 \pm 0.5$  cm on the first post-HTx day with no change to  $2.9 \pm 0.5$  cm at 5 months' follow-up. The LVEF, the index of the systolic function, was preserved and normal in all the patients. The RV dysfunction as assessed by TAPSE and peak S velocity was significantly reduced in the early postoperative period ( $11.7 \pm 3.3$  mm and  $5.5 \pm 0.5$  cm/sec) and showed improvement during our 5-month follow-up period ( $17.2 \pm 6.3$  mm and  $9.5 \pm 3.1$  cm/sec) (Figure 1 and 2). Pulmonary arterial pressure was only mildly elevated after HTx ( $36.4 \pm 6.6$  mmHg early and  $37.2 \pm 7.1$  mmHg at 5 months' follow-up) (Figure 3 and 4).

#### 4.1.2. Doppler and Tissue Doppler Study

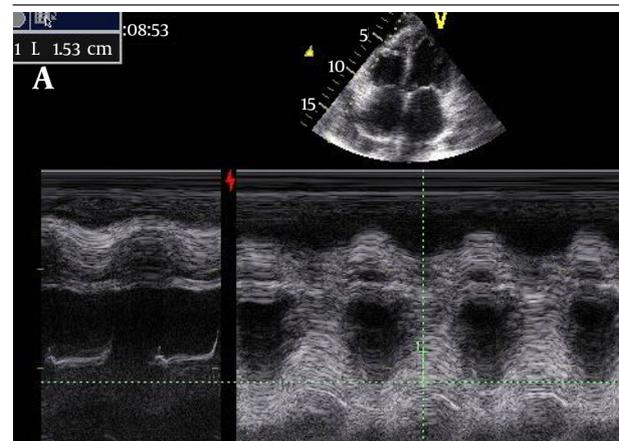
Table 3 presents the Doppler and TDI findings on the first post-HTx day and at 5 months' follow-up (12). The mean isovolumic relaxation time was  $68 \pm 32$  msec early after HTx and  $61 \pm 7.3$  msec 5 months after transplantation. The mean mitral E-wave deceleration time was  $162.7 \pm 39$  msec early after HTx and reached  $150 \pm 32$  msec 5 months later. The TDI-derived MPI was  $0.97 \pm 0.54$  early after HTx and  $0.66 \pm 0.17$  at 5 months' follow-up for the left-sided MPI, and  $0.79 \pm 0.34$  early after HTx and  $0.79 \pm 0.27$  at 5 months' follow-up for the right-sided MPI (13) (Figure 5).

#### 4.2. Valvular Function Assessment

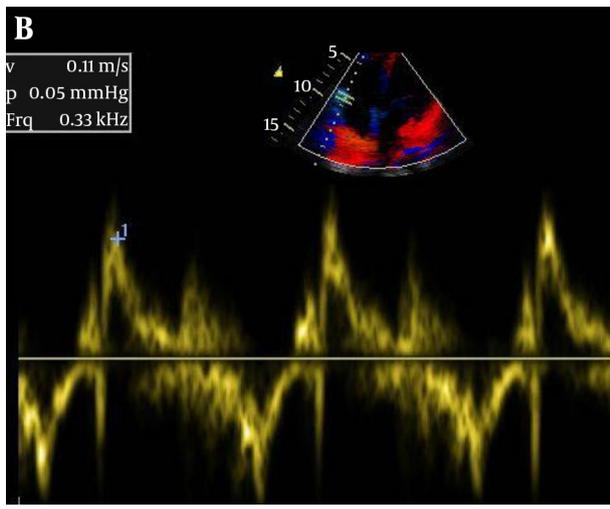
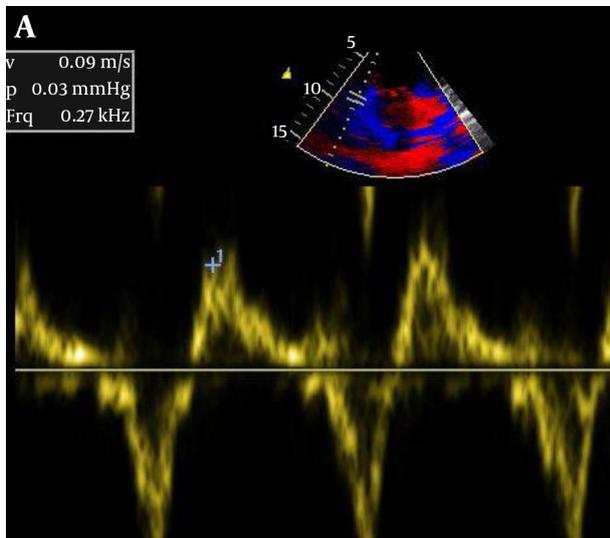
The assessment of valvular competence revealed tricuspid regurgitation > mild grade in 38.5 % of the patients on the first post-HTx day and 6.2% at 5 months' follow-up. There was no pericardial effusion (PE) in 66 % of the patients, whereas 25 % had mild PE, 9 % had moderate PE, and 0 % had large PE 5 months following HTx. The TDI-derived velocities of the medial and lateral mitral annuli and the tricuspid annulus exhibited a gradual increment during the follow-up and reached their highest value 5 months after HTx (Figure 6 and 7). The mean  $E/E'$  ratio, a marker of the LV filling pressure, was normal in the early phase and demonstrated no change at 5 months' follow-up ( $9.3 \pm 2.9$  vs.  $7.8 \pm 2.1$ ;  $P = 0.15$ ).

**Table 2.** Echocardiographic Indices Showing the Cardiac Chamber Size and Function in the Heart Transplantation Recipients at 5 Months' Follow-up

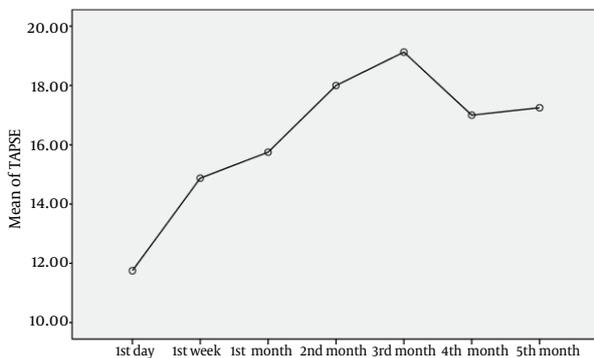
Variable	First Day	5th Month	P Value
Ejection fraction, %	$52 \pm 8.23$	$58 \pm 2.58$	0.027
End-diastolic diameter, cm	$4 \pm 0.5$	$4.55 \pm 0.79$	0.454
End-systolic diameter, cm	$2.86 \pm 0.71$	$3.08 \pm 0.67$	0.722
Left atrial area, cm <sup>2</sup>	$17.1 \pm 6.27$	$22.1 \pm 7.53$	0.463
Right atrial area, cm <sup>2</sup>	$15.2 \pm 3.79$	$15.4 \pm 4.29$	0.415
Right ventricular size, cm	$3.04 \pm 0.54$	$2.92 \pm 0.53$	0.397
Tricuspid annular plane systolic excursion, mm	$11.75 \pm 3.32$	$17.25 \pm 6.36$	0.014
Pulmonary arterial pressure, mmHg	$36.4 \pm 6.6$	$37.22 \pm 7.12$	0.385
Tricuspid S velocity, cm/sec	$5.5 \pm 0.5$	$9.5 \pm 3.1$	0.013
Moderate/Severe tricuspid regurgitation, %	38.5	6.2	0.125
Pericardial effusion, %	53.4	34	0.153



**Figure 1.** Upper: First post-Heart Transplantation Tricuspid Annular Plane Systolic Excursion, Lower: Tricuspid Annular Plane Systolic Excursion 5 Months After Heart Transplantation



**Figure 2.** Upper: first month post HTx Tricuspid systolic or S velocity, Lower: Tricuspid S velocity 5 months after HTx

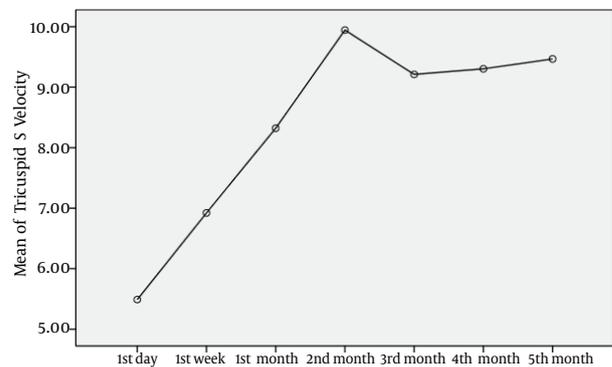


**Figure 3.** Diagram Showing Changes in Tricuspid Annular Plane Systolic Excursion during a 5-Month Follow-up period

**Table 3.** Doppler/Tissue Doppler Echocardiographic Indices in the Heart Transplantation Recipients at 5 Months' Follow-up<sup>a</sup>

Variable	First Day	5th Month	P Value
DT, msec	162.77 ± 39	150 ± 32	0.986
IVRT, msec	68 ± 32	61 ± 7.3	0.319
E/E' ratio	9.3 ± 2.9	7.8 ± 2.1	0.151
LV MPI	0.97 ± 0.54	0.66 ± 0.17	0.385
RV MPI	0.79 ± 0.34	0.79 ± 0.27	0.108
Medial mitral annulus E' velocity, cm/sec	7.7 ± 1.8	11.3 ± 4.1	0.015
Medial mitral annulus A', cm/sec	5.4 ± 2.8	9.1 ± 2.2	0.003
Medial mitral annulus S velocity, cm/sec	6.6 ± 1.8	8.8 ± 1.6	0.016
Lateral mitral annulus E' velocity, cm/sec	5.7 ± 1.8	7.7 ± 4.2	0.651
Tricuspid E' velocity, cm/sec	5.6 ± 1.3	10.5 ± 2.3	0.014
Tricuspid A' velocity, cm/sec	5.5 ± 2.4	8.5 ± 2.4	0.213

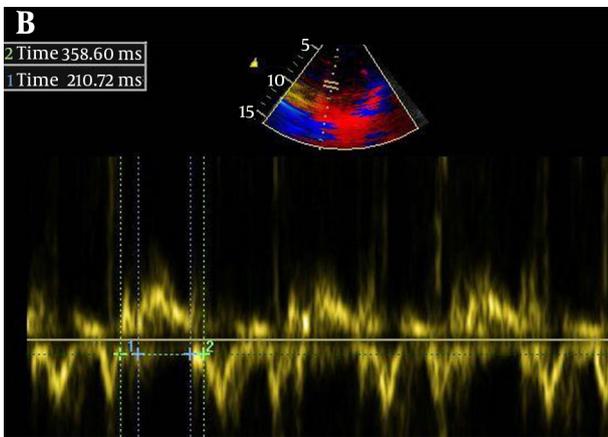
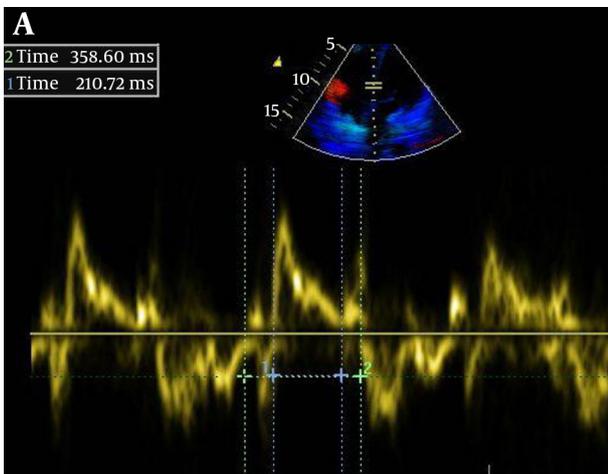
<sup>a</sup> Abbreviations: EF, Ejection Fraction; RV, Right Ventricle; LV and RV MPI, Left Ventricular and Right Ventricular Myocardial Performance Index; DT, Deceleration Time; IVRT, Isovolumic Relaxation.



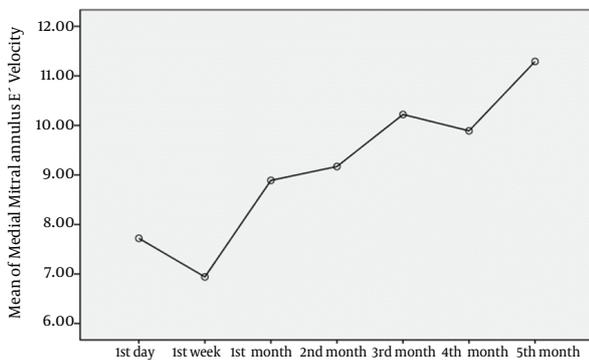
**Figure 4.** Diagram Showing Changes in Tricuspid annulus Peak Systolic velocity

## 5. Discussion

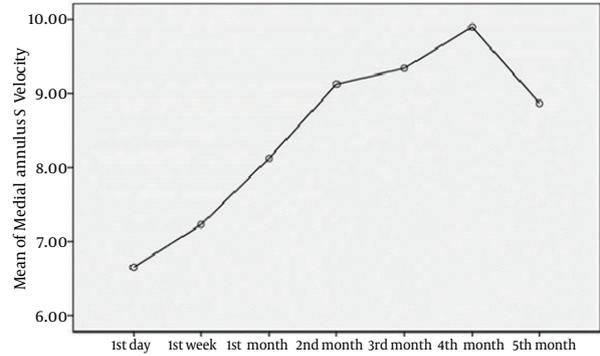
During the last two decades, HTx has been established as a satisfactorily adequate treatment modality for patients with end-stage heart failure (2-4). With the increasing success of HTx programs, the number of long-term survivors is growing continuously (5-7). The present study was focused on a single-center experience at a follow-up period of 5 months at Masih-Daneshvari Heart Transplantation Center. Twenty consecutive HTx recipients were followed up regularly for up to 5 months, and 16 of these patients fulfilled the regular outpatient visits in our HTx clinic. In the short-term HTx survivors, acute rejection (14, 15) and infection play a dominant role in the mortality (16, 17), while the main causes of complications in the long-term survivors are chronic rejection and the side effects



**Figure 5.** Upper: Early post-Heart Transplantation Myocardial Performance Index (MPI = 0.70) Lower: Myocardial Performance Index 5 Months after Heart Transplantation (MPI=0.59)



**Figure 6.** Diagram Showing Gradual Improvement in the Medial Mitral Annulus Early Diastolic (E') Velocity



**Figure 7.** Diagram Showing Gradual Improvement in the Mitral Annulus Systolic (S) Velocity

of immunosuppressive medications. Moreover, reduced graft function may occur owing to the denervation of the graft and rhythm disturbances (2, 3). Consequently, echocardiographic evaluation remains mandatory for the continuously growing number of patients surviving HTx (4-7). All the HTx operations were performed via bicaval anastomosis in our center, precluding a comparison between the effects of the different techniques (bicaval vs. biatrial) on echocardiographic findings (18). One of the gravest late complications of HTx is graft-associated coronary artery vasculopathy, which is primarily observed in the first postoperative year. Our short-term follow-up of the study population showed no such complication (19, 20); nonetheless, a longer-term follow-up of our patients might have yielded a different outcome as regards this complication. As was expected, mild RV enlargement and systolic dysfunction and mild pulmonary arterial hypertension were observed in the early postoperative period, but all of them improved gradually overtime. A rise in the RV volume shortly after HTx is an adaptive mechanism to pulmonary hypertension, which is generally present in the recipients due to chronic heart failure and congested pulmonary circulation. Previous research has demonstrated a regression in such changes within a few months after HTx (21). Otherwise, elevated pulmonary vascular resistance and pulmonary hypertension could ensue the pretreatment of the organ donor, ischemic damage, and reperfusion injury in the wake of prolonged ischemia and the perioperative use of cardiopulmonary bypass (heart-lung machines), blood transfusion and protamine administration, and pulmonary vasoconstriction secondary to hypoxia, which can be modified by adjusting the setting of the ventilator and optimal positive end-expiratory pressure. The echocardiographic assessment of our study population at 5 months' follow-up revealed the following major findings:

- 1) All the patients had a well-preserved LV systolic function.
- 2) The whole study population had normal LVEDD and LVESD.

3) There was mild and nonsignificant left atrial enlargement in the majority of the patients despite the use of the bicaval anastomosis technique in all the cases. This finding is consistent with a study by Lauerma et al. (22), who performed HTx on 10 patients via the classic biatrial anastomosis technique and reported mild left atrial enlargement ( $3.7 \pm 8.9$  cm) according to cardiac magnetic resonance imaging, and also with a study by Traversi et al. (23), who compared the two anastomosis techniques in terms of the right and left atrial volumes and functions using detailed echocardiography and reported smaller atrial volume and better function in the bicaval technique.

4) There was mild RV enlargement in the majority of our patients early after HTx. This finding chimes in with a study by Hosenpud et al. (24), who performed HTx on 10 patients and reported mild RV enlargement in the first postoperative week ( $3.4 \pm 0.6$  cm) and at 3 months' follow-up ( $3.9 \pm 0.6$  cm), which was considered normal findings early after HTx.

5) There were intact left-sided heart valves as opposed to tricuspid regurgitation in the majority of the grafts: 38% > mild tricuspid regurgitation in the early post-HTx period and 6.2% moderate/severe grade tricuspid regurgitation at 5 months' follow-up. This finding is concordant with a study by Rees and Sivarajan (25, 26), who performed HTx on 48 patients and reported tricuspid regurgitation in 41 (trivial tricuspid regurgitation in 23, mild in 12, and moderate in only 6; other valvular lesions such as mitral and aortic regurgitation were not common), and with a study by Chan et al. (27-30), who reported that 92.2% of their HTx recipients were free of severe tricuspid regurgitation at 5 years' follow-up.

6) There was a gradual improvement in the RV systolic function as assessed by TAPSE and TDI-derived peak S velocity during our 5-month follow-up period. This finding is in line with a study by Fyfe et al. (31), who performed HTx on 21 pediatric patients and reported some degree of RV dysfunction with reduced tricuspid systolic velocity ( $5.8 \pm 1.4$  cm/sec), which failed to normalize even 5 years after transplantation.

7) There was a gradual increase in the TD-derived velocities of the medial and lateral mitral annuli ( $E^{\circ}$ ,  $A^{\circ}$ ) during our 5-month follow-up period. This finding tallies with another study by Fyfe et al. (32), who performed HTx on 53 pediatric patients at a mean age of 10 years and reported reduced tricuspid systolic velocity (2 to 2.9 cm/sec), reduced tricuspid early diastolic velocity (1.9 to 3.7 cm/sec), and mitral systolic velocity of up to 1.5 cm/sec. The authors suggested that TDI be conducted two to three times each year to survey graft impairment because only in HTx patients with graft failure is a higher rate of reduction in velocities noticed at early follow-up.

8) There was an unchanged mean LV filling pressure as measured with the  $E/E^{\circ}$  ratio.

9) There was a prolonged MPI after HTx with a nonsignificant reduction at 5 months' follow-up. Frea et al. (33)

performed HTx on 152 patients and reported a higher rate of adverse cardiac events in cases with a prolonged MPI > 0.45 at a follow-up period of 5 years.

This study underscores the feasibility of echocardiography in the postoperative evaluation of HTx patients. Future studies with larger populations and longer follow-up periods are required to shed further light on the morphological changes of heart grafts and the role of echocardiography.

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