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Speckle Tracking Echocardiography before and after Surgical Pulmonary Valve Replacement in Tetralogy of Fallot Patients: Can STE Elucidate Early Left Ventricular Dysfunction?

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ABSTRACT

Background: Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. Most studies have focused on Right Ventricular (RV) dysfunction, while the left ventricle has received less attention in patients with TOF.
Objectives: This study aimed to investigate the Left Ventricular (LV) function after surgical Pulmonary Valve Replacement (sPVR) in patients with repaired TOF (rTOF) by Speckle Tracking Echocardiography (STE).
Methods: This single-center, observational, cross-sectional study was conducted on 58 volunteers (age: 15 - 31 years) divided into three groups as follows: 22 PVR patients (mean age: 18.96 ± 7 year), 16 patients with rTOF, and 20 healthy controls who were matched regarding the PVR age range. 2D echocardiography (including Doppler and M-Mode indices of the right and left ventricles) and Speckle Tracking Echocardiography (STE) (Global Longitudinal Strains (GLS) and 18 segment analyses) were performed for all patients. All analyses were done using the SPSS software and $P < 0.05$ was considered to be statistically significant.
Results: 2D echocardiography showed normal LV Ejection Fraction (LVEF) in all study groups (64% in sPVR, 60% in rTOF ($P = 0.127$), and 62.5% in the control group). However, the mean GLS of the left ventricle significantly reduced in both sPVR (-17.5 ± 2.5%) and rTOF (-17.1 ± 4.7%) patients in comparison to the control group (-20.2 ± 0.7%) ($P = 0.003$). Yet, no significant difference was observed between the rTOF and sPVR groups regarding the GLS ($P = 0.9$).
Segmental analysis of the Longitudinal Strain (LS) indicated a significant decrease in the sPVR and rTOF groups in basal anterior, basal septal, basal anterolateral, mid-anterior, and anterolateral segments. Except for the lower LS in the apical-anteroseptal segment, this level was mostly spared in both sPVR and rTOF patients.
Conclusion: LVEF was within the normal range among the sPVR patients, but the pattern of impaired segmental LS and GLS did not change compared to the rTOF group. In conclusion, sPVR might not have a significant effect on the improvement of LV function assessed by STE in patients with rTOF. LV damage occurring during the surgical correction of TOF might have a permanent deteriorating effect on LV function.

1. Background

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart diseases, which requires multiple operations, including Pulmonary Valve Replacement (PVR), in some cases due to progressive pulmonary regurgitation and Right Ventricular (RV) failure (1-5). PVR has been suggested as an effective option to improve and ameliorate the volume overload resulting from pulmonary valve regurgitation (3, 6, 7). Left ventricular

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(LV) dysfunction has been reported as a major determinant of clinical outcome in these patients (4, 8-10). Although some studies have stated the importance of LV function and size in patients with repaired TOF (rTOF), its usage as prognostic value is not adequate (4). In the recent years, assessing the myocardial motion strain by using Speckle Tracking Echocardiography (STE) has been an emerging echocardiographic technique increasingly used in heart disease diagnosis and management. It is useful for detecting subtle and early cardiac dysfunctions that cannot be discovered by conventional 2D echocardiography (11).

2. Objectives

This study was focused on LV parameters aiming at identification of systolic myocardial deformation patterns in patients with rTOF after surgical PVR using 2D STE to assess LV function and remodeling that might be undetectable by conventional 2D echocardiography.

3. Patients and Methods

This single-center, observational, cross-sectional study was approved by the local Ethics Committee of Shiraz University of Medical Sciences and written informed consent forms were obtained from all participants or their guardians before recruitment. The assessment of ventricular function was done by LV speckle tracking and conventional 2D transthoracic echocardiography using the Vivid S6 GE ultrasound machine. The study population was selected from the local database of TOF patients and was divided into three groups, including patients with rTOF after surgical PVR, patients with rTOF without PVR, and healthy individuals (Table 1). Regarding age-sex matching, there were some limitations due to the small number of cases in the PVR group and the number of patients with rTOF who were age-matched with the PVR patients. The control group participants were matched with the PVR cases based on their age range. The inclusion criteria for the rTOF group were age > five years, any form of TOF like double outlet right ventricle + severe pulmonary stenosis, total surgical correction without homograft, and acceptance to participate in the study. For the PVR group, the cases with TOF or TOF-like lesions with mechanical or biological valves who were willing to cooperate were selected. It should be noted that the total number of these cases was limited. The following exclusion criteria were applied for all groups: any history of Kawasaki or coronary artery abnormalities, history of uncontrolled tachyarrhythmia, significant residual shunt, inadequate imaging for off-line analysis, transposition of great arteries, and implanted pacemakers.

From April 2015 to May 2017, 58 volunteers with the mean age of 19.47 + 7.3 (15 – 31) years were enrolled into this study; 22 patients with surgical PVR after rTOF, 16 patients with rTOF, and 20 healthy individuals as the control group.

Two-dimensional images were obtained in the left lateral decubitus position using an S1-5 probe (1-6 MHz) at a frame rate of 60 – 90 frames/s. The guidelines of the American Society of Echocardiography, including Left Ventricular Ejection Fraction (LVEF) (Teichholz formula), RV Fractional Area Change (RV FAC) (RV FAC (%) = (RV EDA – RV ESA) / RV EDA x 100), and Tricuspid Annular Plane Systolic Excursion (TAPSE) were used for chamber measurements. Longitudinal STE was done in LV four- and two-chamber and long-axis views using the semiautomatic Automated Function Imaging (AFI) method. After three-point selection, endocardial, myocardial, and epicardial borders were adjusted by the user and then, the Echo machine started the automated process of STE. The data were presented in the 18-segment model. It should be mentioned that the apical segment is not usually visualized completely and tracking in this area is faced with many limitations. Care was taken and multiple clips were gathered for each view to minimize low-quality tracing (11, 12).

All statistical analyses were done using IBM SPSS, version 16. The data were described using mean ± Standard

Table 1. Demographic Features of All Groups

Baseline and Demographic Characteristics	rTOF + sPVR	rTOF	Normal	P-value
Number (%)	22	16	20	
Male/female, n (%)	12/10 (55%/45%)	8/8 (50%/50%)	12/8 (60%/40%)	0.803
Age at the time of study (year) (rang)	18.9 ± 7 (15 - 31)	20.6 ± 7.4 (16 - 25)	19.1 ± 7.8 (16 - 27)	0.760
Weight	52.2 ± 18	46 ± 13.3	51.8 ± 17.8	0.501
Age at operation (rang)	14.8 ± 6.6 (6-29)	3.2 ± 1.3 (1.5 - 5)	Not applicable	
Studied after PVR and repaired TOF (year)	4.2 ± 3	17.4 ± 8		
Diagnosis	-	-		
TOF preserved valve	6 (25%)	4 (25%)		
TOF-TAP	12 (55%)	9 (56%)		
DORV-VSD-PS-TAP	1 (5%)	3 (19%)		
TOF-absent LPA	1 (5%)	-		
DORV-VSD-PS-AP window-severe AI-dilated aortic root and AAO	1 (5%)	-		
TOF-absent pulmonary valve syn.	1 (5%)	-		
Type of prosthetic valve, n (%)		-		
Biological	16 (72.7%)			
Mechanical	6 (27.3%)			
Number of surgeries before PVR				
One surgery	12 (55%)	12 (75%)		
Two and more	10 (45%)	4 (25%)		

Abbreviations: DORV, double outlet right ventricle; D-TGA, d-loop transposition of the great arteries; IVS, intact ventricular septum; PA, pulmonary atresia; PR, pulmonary regurgitation; PS, pulmonary stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; TAP, transannular patch.

Deviation (SD), median, and range, as appropriated. Categorical variables were described using number and percentage. ANOVA using post-hoc tests (Tamhane) was used to compare different groups and P < 0.05 was considered to be statistically significant.

4. Results

Demographic characteristics of all three groups have been presented in Table 1. In the PVR group, there were 12 males (55%) and 10 females (45%). Surgical PVR was performed at the mean age of 14.8 ± 6.6 years (range from 6 to 29 years) and total correction of TOF at the mean age of 3.2 ± 1.3 years. In the PVR group, 14 patients were on antiplatelet and anti-coagulation medications. In the rTOF group, however, only three patients were on medications, including digoxin, captopril, and furosemide. In the surgical PVR group, 16 cases (72.7%) had a bioprosthetic valve and six (27.3%) had a mechanical valve. In the PVR group, 12 patients (55%) had one operation prior to surgical PVR (total correction of TOF), eight (36%) had two operations (modified Blalock Taussig shunt + total correction of TOF), and the remaining two (9%) had more than two operations.

Standard echocardiographic parameters have been presented in Table 2. Color Doppler and continuous wave Doppler analyses revealed moderate or greater pulmonary regurgitation in all patients with rTOF, but only mild pulmonary valve regurgitation in the surgical PVR group. The PVR group had a higher RV Outflow Tract Peak Gradient (RVOT PG) compared to the rTOF group (18.6 ± 12 mmHg vs. 12.7 ± 8 mmHg; P = 0.021). However, the two groups had no significant residual stenosis regardless of the surgical or interventional approach. Furthermore, the right ventricle dimensions were significantly lower in the surgical PVR group in comparison to the rTOF group, as shown in Figure 1 and Table 2. Moreover, both TAPSE and FAC% were significantly higher after the surgical PVR compared to the rTOF group (Table 2).

Although there was a significant difference in the RV 2D echocardiographic parameters, the RV 2D echocardiographic parameters showed no significant abnormalities in either the rTOF or the PVR group (Table 2). Interestingly, 2D echocardiography revealed normal EF (> 55%) in both rTOF and PVR groups.

The mean global longitudinal systolic strain of the left ventricle was significantly lower in both PVR (-17.5 ± 2.5) and rTOF (-17.1 ± 4.7) groups compared to the normal group (-20.2 ± 0.7) (P = 0.003, Table 3). The results of segmental analysis also showed a significant difference between the normal group and the rTOF and surgical PVR groups regarding most segments. Accordingly, all basal segments had a lower Longitudinal Strain (LS), except for the basal inferior and inferolateral segments. The apical level was the most spared area. In the mid-level, both anterior and anterolateral segments had a lower LS (Table 3). PVR did not change the segmental strain pattern and no improvement was found in the global or segmental LS compared to the rTOF group.

Table 2. 2D Echocardiographic Parameters in the PVR and rTOF Patients

Characteristics	**sPVR**	**rTOF**	**P-value**
LVEF (%)	64.5 ± 6.5	60 ± 10.2	0.127
RVOT PG	18.6 ± 12	12.7 ± 8	0.021*
RV FAC (%)	44 ± 7.2	35.3 ± 8.9	0.002
TAPSE (mm)	15.3 ± 2.7	12.2 ± 2.5	< 0.001
RV end-systolic dimension (A4C view) (mm)	14.4 ± 3.2	26 ± 4.6	< 0.001
RV end-diastolic dimension (A4C view) (mm)	26.2 ± 6	40.4 ± 4	< 0.001

Abbreviations: EDD, end-diastolic dimension; EF, ejection fraction; FAC, fractional area change (%); RV, right ventricular; RVOT PG, right ventricular outflow tract pressure gradient; TAPSE, tricuspid annular planar systolic excursion; TDI, tissue Doppler imaging. *Data have been expressed as mean ± SD.

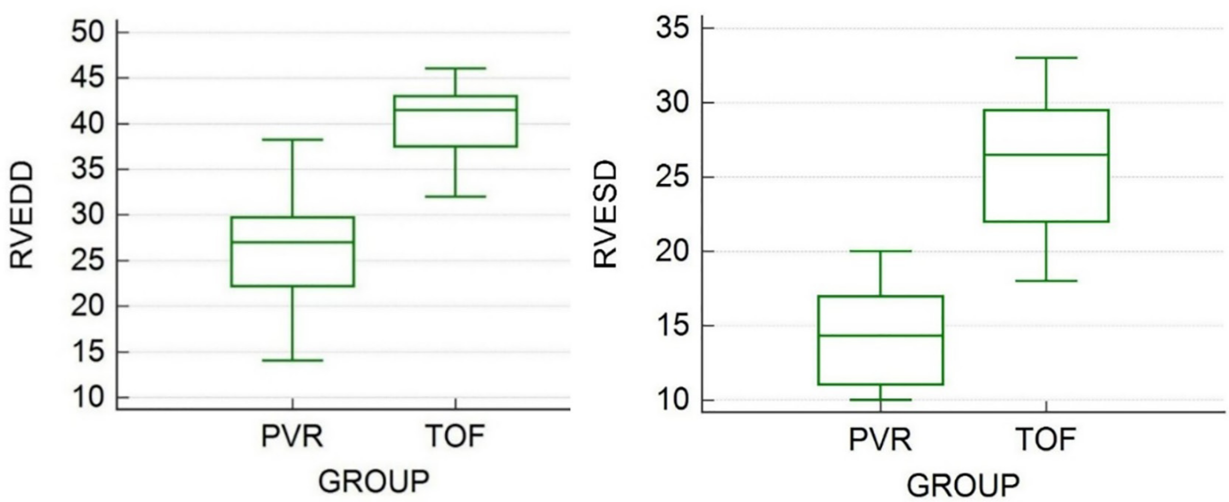

Figure 1. Box Plot Showing RV End-Diastolic (mm) and RV End-Systolic Dimensions (mm) in Pulmonary Valve Replacement and Repaired Tetralogy of Fallot Groups

Table 3. The Peak Systolic Longitudinal Strain of the Left Ventricular Walls in the Surgical PVR and rTOF Patients and the Healthy Controls (P < 0.05 Indicated Significant Differences between the Study Groups)

Segments		sPVR n = 22	rTOF n = 16	Normal n = 20	P-value between Groups (Significant Results Have Been Bolded) [a]	PVR vs. rTOF P-value
Global longitudinal LV strain (%)		-17.5 ± 2.5	-17.1 ± 4.7	-20.2 ± 0.7	0.003 [*]	0.988
Basal	**Anterior**	-14.04 ± 5.7	-14.88 ± 4	-19.7 ± 1.9	< 0.001 b	0.613
	Anteroseptal	-15.63 ± 3.8	-15.81 ± 5.4	-18.85 ± 2.8	0.021 [a]	0.892
	Inferoseptal	-17.13 ± 5.6	-18.56 ± 4.7	-20.9 ± 2.5	0.028 [a]	0.400
	Inferior	-18.46 ± 4.3	-18.19 ± 5.5	-21 ± 2.2	0.071	0.860
	Anterolateral	-14.92 ± 5.8	-15.06 ± 4.7	-19.5 ± 2.8	0.004 b	0.939
	Inferolateral	-18.04 ± 5.3	-15.94 ± 5.9	-19.15 ± 3.7	0.165	0.277
Middle	**Anterior**	-15.5 4.1	-15.25 ± 4.1	-20.2 ± 1.8	< 0.001 [b]	0.852
	Anteroseptal	-17.92 ± 4.6	-17.25 ± 5.8	-19.7 ± 2	0.211	0.680
	Inferoseptal	-19.42 ± 5.2	-19.63 ± 5.8	-22.2 ± 3.1	0.126	0.903
	Inferior	-19.25 ± 3.4	-18.69 ± 5.7	-21.1 ± 1.5	0.123	0.690
	Anterolateral	-16.33 ± 3.8	-16.38 ± 4.9	-19.3 ± 2.6	0.024 [a]	0.974
	Inferolateral	-17.58 ± 4.4	-17.69 ± 5.6	-20 ± 3.8	0.175	0.943
Apical	**Anterior**	-17.83 ± 4.6	-16.56 ± 6.1	-19.6 ± 2.2	0.128	0.450
	Anteroseptal	-16.4 ± 3.5	-16.4 ± 3.9	-20.4 ± 2.8	< 0.001 [b]	0.981
	Inferoseptal	-20.2 ± 3.8	-18.4 ± 4.5	-20.9 ± 3.9	0.170	0.200
	Inferior	-19.92 ± 4.3	-18.75 ± 6.1	-20.45 ± 2	0.497	0.45
	Anterolateral	-18.75 ± 3.3	-16.7 ± 3	-18.7 ± 2.4	0.7	0.053
	Inferolateral	-16.83 ± 3.5	-17.06 ± 4.3	-19.15 ± 2.9	0.78	0.85

[a] Post-hoc test (Tamhane test) revealed a significant difference between the PVR and normal cases (P < 0.05), [b] Post-hoc test (Tamhane test) revealed a significant difference between both PVR and rTOF patients and the normal cases (P < 0.05), [*] ANOVA showed P = 0.003 among the study groups, and post-hoc tests (Tamhane) showed P < 0.001 for the PVR group vs. the normal group and for the rTOF group vs. the normal group.

5. Discussion

To best of our knowledge, this was one of the few studies focused on LV function using 2D STE in rTOF after surgical PVR. As expected, after eliminating the RV volume overload via surgical PVR, the impaired RV function returned to normal or near normal levels. The results demonstrated a significant difference in RV FAC after the surgical PVR, which was in agreement with the results obtained by Hasan et al. (13). This parameter depends on the time of surgery, right ventricle condition before PVR, and surgical technique as well as its complications. RV improvement might affect LV parameters by interventricular interaction. While LVEF was within normal range with no significant changes after surgical PVR similar to other studies (2, 14-17), 2D speckle tracking showed the deterioration of global longitudinal peak systolic strains in both PVR and rTOF patients. This revealed the limitation of the routine 2D echocardiography in assessment and follow up of LV function in these patients. STE is more sensitive than 2D echocardiography for detection of LV abnormalities (2, 15, 18-23). Considering the present study findings, it may be useful to unmask LV dysfunction in the setting of rTOF follow-up. This change might be related to the side effects of the surgical RV approach, interventricular interaction, or some ischemic events during the operation. To evaluate this hypothesis, further studies and prospective analysis of STE have to be conducted among patients with rTOF.

The current study results revealed a non-significant change in the LV STE at both global and segmental LS in surgical PVR patients compared to those with rTOF. These results were consistent with those of the studies carried out by Moiduddin et al., Myrthe E. Menting et al., and Burkhardt B. et al. in different settings (interventional PVR and six-month follow-up) (14, 17, 19). However, contradictory results were found by Chowdhury et al., which indicated an improvement in the LV strain after transcutaneous PVR (15). With regard to these findings and controversies in the field, it seems that the current criteria for PVR may not have great benefits for LV function when assessed by STE. Now the question is 'when has LV dysfunction occurred in STE of rTOF' and 'whether permanent damages to the left ventricle have happened at the time of rTOF surgery or the damage has gradually developed after rTOF as a complication of pulmonary valve regurgitation and delayed PVR (related to the current PVR criteria)'. The conflict among different studies regarding the improvement of STE might indicate the non-permanent nature of theses damages and, consequently, the second hypothesis is more likely (LV dysfunction gradually develops during the time passed from surgical PVR). To clarify the role of STE in the decision for the time of surgical PVR, further prospective studies focusing on STE after rTOF are recommended. Meanwhile, in case any LV dysfunction is detected by STE after surgical PVR, secondary problems such as coronary abnormalities may need further evaluation by other modalities.

5.1. Limitation

One of the study limitations was the limited number of the study participants, so that matching was done with respect to PVR and TOF age and sex. Another study limitation was that preoperative STE data were not available in surgical PVR patients. Therefore, the data were compared to those of the rTOF patients as the control group.

5.2. Conclusion

STE was found to be more sensitive than 2D echocardiography in detection of LV abnormalities in rTOF and surgical PVR, particularly for segmental abnormalities. The results revealed no significant difference in the GLS of the surgical PVR and rTOF patients. The apical anteroseptal, middle anterior, and anterolateral segments and basal septal, anterior, and anterolateral segments were the most involved areas in surgical PVR with deteriorated LS. In conclusion, intermittent STE has been recommended during the follow-up of rTOF and surgical PVR patients to detect any deterioration of LV function, especially when 2D echocardiography is not consistent with the patients' signs and symptoms.

5.3. Ethics Approval and Consent to Participate

This study was submitted to and approved by the Research Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1395.S633, available on http://research.sums.ac.ir/fa/ethicrc/EthicsCodes.html).

5.4. Ethical Approval and Consent to Participate

The study was explained to the patients or their guardians and their written informed consent forms were obtained.

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Authors' Contribution

GhA: design, analysis, and manuscript preparation; FA: sample collection, data preparation, and manuscript preparation; HM: design, analysis, statistics, and manuscript preparation; M.R.E: data collection, drafting, and analysis; HAm: critical revision and manuscript preparation; AAA: patient referring, data collection, and drafting; NM: critical revision and manuscript preparation; HAr: drafting; MB: critical revision; KK: sample collection and data preparation; FP: critical revision and patient referring; AN: critical revision and patient referring; BGh: patient referring, data collection, and drafting; All authors have read and approved the final manuscript.

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The authors have no financial interests related to the material in the manuscript.

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