Iranian Heart Journal; 2020; 21 (3)

Original Article

Assessment of Right Ventricular Myocardial Fibrosis and Restrictive Physiology in Patients With Repaired Tetralogy of Fallot: A Comparison Between Cardiac Magnetic Resonance and Transthoracic Echocardiography

Zahra Alizadeh Sani[1], MD; Niloufar Samiei[2], MD; Zahra Khajali[1], MD; Fatemeh Mirrazeghi[1], MD; Delara Gholamipoor[3],MD; Mostafa Rouzitalab[1], MD; Maryam Bayat[2], MD; Mohaddeseh Behjati[1], MD; Behshid Ghadrdoost[1], PhD; Shahin Rahimi[1*], MD

ABSTRACT

Background: Right ventricular (RV) restrictive physiology is a condition caused by the chronic elevation of systolic pressure in the RV, which is typically found in patients with tetralogy of Fallot (ToF) who had undergone total surgical correction and can be diagnosed either via cardiac magnetic resonance imaging (CMR) or finding the RV end-diastolic forward flow (EDFF) via echocardiography. We aimed to assess the relationship between RV restrictive physiology with myocardial fibrosis and functional indices on CMR, along with exercise capacity and diastolic dysfunction indicators measured by transthoracic echocardiography (TTE).

Methods: All patients with a history of the total correction of ToF at childhood who referred to our center for the evaluation of postoperative severe pulmonary regurgitation were included. All the patients were examined using electrocardiography, the exercise test, TTE, and late gadolinium enhancement (LGE) CMR.

Results: Among the study population, 17 (56.7%) patients were found to have RV EDFF on their echocardiograms, while 18 (60.0%) had RV restrictive physiology on their CMR. The 2 diagnostic modalities had a moderate significant agreement for the diagnosis of RV restrictive physiology (Kappa = 0.521, *P*= 0.004). There was a significant difference between the patients with or without RV restrictive physiology based on CMR findings regarding the QRS duration (*P* = 0.015), Sm (*P* = 0.045), and the RV end-diastolic volume index (*P* = 0.036).

Conclusions: TTE may be a good alternative for the evaluation of RV restrictive physiology after the total correction of ToF. However, RV restrictive physiology measured by CMR and RV EDFF measured by echocardiography could not correlate with quantitative RV myocardial fibrosis measured by LGE CMR. ***(Iranian Heart Journal 2020; 21(3): 78-88)***

KEYWORDS: Right ventricular restrictive physiology, Tetralogy of Fallot, Echocardiography, Cardiac magnetic resonance imaging

[1] Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
[2] Heart Valve Disease Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
[3] Imam Khomeini Hospital Complex, Tehran University of Medical Science, Tehran, IR Iran.

***Corresponding Author:** Shahin Rahimi, MD; Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
Email: shahinrahimi566@gmail.com

Received: July 22, 2019 **Accepted:** September 19, 2019

Tetralogy of Fallot (ToF) is the most common cause of cyanotic congenital heart disease (CHD), accounting for approximately 10% of all cases. [1] It occurs in 3 to 6 infants for every 10 000 births and is typically sporadic and nonfamilial. [2] A male preponderance has also been observed in patients diagnosed with ToF. [3]

The ideal treatment for infants born with ToF is the complete surgical correction, which was first introduced in 1955. [4] Due to significant improvements in the surgical techniques applied for this condition, the surgery is now performed at earlier ages without any significant change in the rates of mortality and re-intervention. [5,6] Additionally, the mid- and long-term outcomes after the total correction of tetralogy of Fallot (TFTC) remain excellent. [7,8] The number of patients with repaired ToF is growing as they now survive into adulthood [9,10]; therefore more cases with late complications associated with pulmonary regurgitation (PR) are identified, [11,12] presenting as exercise intolerance, predisposition for arrhythmias, and increased risk of sudden cardiac death due to right ventricular (RV) enlargement and dysfunction. [13,14]

In some patients with repaired ToF, the RV is also affected by the chronic elevation of systolic pressure and loses its compliance with diastolic filling. RV diastolic dysfunction in such cases is known as RV restrictive physiology, which can be diagnosed either via cardiac magnetic resonance imaging (CMR) [15,16] or via Doppler echocardiography illustrating an end-diastolic forward flow (EDFF). [17] The RV can be visualized in 3 dimensions throughout the cardiac cycle via CMR, yielding a high accuracy rate in functional assessment. This modality also provides operator-independent phase velocity-encoded data, which can be used for the quantification of the blood flow in cases affected with PR. [15,16] Moreover, late gadolinium contrast enhancement (LGE) CMR can also be used for the visualization of myocardial fibrosis in the heart. [18-20]

Therefore, CMR is currently considered the reference standard for the evaluation of RV performance and PR. Nonetheless, it has lower widespread availability than does transthoracic echocardiography (TTE), and there are some conditions in which CMR cannot be performed. Hence, it may be important to determine the agreement between these 2 modalities in the diagnosis of RV restrictive physiology in patients with repaired ToF. Moreover, although a few studies have assessed the relationship between the presence of myocardial fibrosis and RV restrictive physiology in patients with ToF, further investigations into this correlation could be beneficial, particularly since fibrosis has never been assessed quantitatively.

In this regard, we sought to assess the agreement between the findings of TTE with those of LGE CMR in the diagnosis of RV restrictive physiology, the relationship between RV restrictive physiology and myocardial fibrosis and functional indices on CMR, along with exercise capacity and diastolic dysfunction indicators on TTE.

METHODS

Study Population and Protocol

In this cross-sectional study, all patients with a history of TFTC at childhood who referred to our center, Rajaie Cardiovascular Medical and

Research Center, Tehran, Iran, for the evaluation of postoperative severe PR between January 2015 and December 2016 were included. Surgery of TFTC includes the shaving of the right ventricular outflow tract (RVOT) and closure of ventricular septal defects; still, some patients need trans-annular patching of the pulmonary valve, which predisposes them to the development of PR. Informed signed consent forms were obtained from all the patients. The institutional review board of our center and local ethics committee in Iran University of Medical Sciences approved the study protocol. The inclusion criteria were comprised of age above 10 years, a history of TFTC, and severe PR based on TTE findings. TTE was performed using a 4V1c transducer. Cases with other valvular heart diseases and the presence of other palliative shunts were excluded from the study. The echocardiographic criteria for severe PR were as follows: a jet width to pulmonary annulus width ratio of more than 0.5, a short diastolic time, a short pressure half time, and a long no-flow time. [21] The exclusion criteria consisted of age below 10 years, moderate-to-severe stenosis or regurgitation of the mitral or aortic valves, residual pulmonary stenosis with a pressure gradient of greater than 25 mm Hg on Doppler echocardiography, concomitant atrioventricular septal defects, a double-outlet RV of the Fallot type, pulmonary atresia with a ventricular septal defect, ToF with absent pulmonary valves, and a history of pulmonary valve replacement. A total of 30 patients were consecutively recruited; they underwent proper examinations using 12-lead electrocardiography (ECG), the exercise test via the Bruce protocol, TTE, and LGE CMR. The mean heart rate during TTE and CMR was 78 and 75 bpm, respectively. The QRS duration was measured from surface ECG by a blinded cardiologist. A fragmented QRS was defined as notching of the R or S wave or the R' wave in the presence of a narrow QRS.

Echocardiographic Examination

TTE was performed using the ACUSCON Siemens SC2000 Ultrasound Device (Siemens Healthcare, Erlangen, Germany). Restrictive RV physiology was defined as a forward pulmonary flow in late diastole present throughout the respiratory cycle. The parameters recorded during the echocardiographic examination comprised tricuspid annular plane systolic excursion (TAPSE) at the lateral tricuspid annulus; peak systolic velocity at myocardial segments (RV-Sm) at the lateral tricuspid annulus; EDFF, defined as the gradient between the early peak and the early end Doppler curve of PR; the Tei index, calculated by the ratio of the isovolumic relaxation time + the isovolumic contraction time/the ejection time; the E/A of the tricuspid valve (the ratio of the early-to-late diastolic flow within the lateral tricuspid annulus); and the E/e′ ratio of the tricuspid valve (the ratio of the maximum flow velocity at the beginning of ventricular filling to the flow velocity at the beginning of diastole within the lateral tricuspid annulus). The normal reference limits of E/A, E/e', and Tei index using tissue Doppler were less than 0.8 or greater than 2.1, less than 6, and 0.55, respectively. [22] Additionally measured were dp/dt, calculated as 12/time required for the TR jet to increase from 1 to 2 m/s; the systolic (S) fraction of the flow across the pulmonary valve (the ratio of the velocity-time integral of the pulmonary vein systolic fraction to the sum of both systolic and diastolic vein waves); and pulmonary artery systolic pressure. The normal limit of dp/dt was considered to be greater than 400 mm Hg/s. [22]

Cardiac Magnetic Resonance Imaging

The Avanto SIEMENS 1.5T (Siemens Healthcare, Erlangen, Germany) was used to

obtain cine, pulmonary flow velocity mapping, and LGE CMR images. The time interval between the performance of the echocardiographic examination and CMR was less than 2 days in all the patients. The right ventricular end-diastolic volume (RVEDV), the right ventricular end-systolic volume (RVESV), and the right ventricular ejection fraction (RVEF) were determined according to the cine images acquired in the right RVOT plane, the oblique transverse plane, and the left ventricular short-axis plane. The forward flow across the pulmonary valve during atrial contraction was considered to be the presence of restrictive physiology. Nevertheless, even in normal subjects, the movement of the pulmonary valve during atrioventricular displacement causes a slight forward flow in late diastole. Therefore, the mean percentage of the forward flow during atrial contraction in healthy subjects plus 2 standard deviations (SDs) was set as the threshold (2.5%) for normal RV physiology and values above this figure were considered to be restrictive physiology.

LGE CMR images were also acquired in the same plane as cine CMR for the visualization of myocardial fibrosis. The images were obtained 10 to 20 minutes after intravenous administration of a gadolinium-based contrast agent, either gadolinium-DOTA or gadolinium-DTPA, at a dosage of 0.2 mmol/kg.

The parameters measured by CMR comprised the right atrial area, the RVEF, the right ventricular end-diastolic volume index (RVEDVi), the right ventricular end-systolic volume index (RVESVi), RV restrictive physiology, the pulmonary artery size (proximal and distal), the left pulmonary artery size (origin and hilum), the right pulmonary artery size (origin and hilum), fibrosis mass, myocardial mass, fibrosis/myocardial mass and fibrosis in the RVOT, basal anterior, mid-anterior, apical anterior, basal inferior, mid-inferior, apical inferior, septum, trabecular band, and the insertion point.

Exercise Test

Functional capacity was reported in terms of the estimated metabolic equivalents of task (METs). The MET unit reflects the resting volume oxygen consumption per minute (VO_2) for a 70-kg, 40-year-old man, with 1 MET equivalent to 3.5 mL/min/kg of the body weight. Exercise testing was performed for all the patients using the standard Bruce protocol. [23] The indications for the termination of the exercise test were the same as those applied in routine practice.

Statistical Analysis

The SPSS software for windows, version 22, (IBM Corp, Armonk, NY, USA) was used for data analysis. The qualitative and quantitative variables were presented as frequencies (percentages) and the mean (SD), respectively. The χ^2 test and the Fisher exact test were employed to assess the correlation between the qualitative variables. The Student *t*-test was also utilized for the quantitative parameters. A *P* value of less than 0.05 was considered statistically significant in all the analyses.

RESULTS

The study population was comprised of 30 patients at a mean age of 26.5 ± 9.3 years (14 to 45 y). Men accounted for 56.7% (n =17) of the study patients. A mean time of 20.2 ± 8.3 years had passed from TFTC (8–39 y). Table 1 presents all the variables evaluated in the study population. Echocardiography demonstrated that 17 (56.7%) patients had EDFF, while CMR showed that 18 (60.0%) patients had RV restrictive physiology. LGE CMR showed RVOT fibrosis in all the patients: 16 (53.3%) in the basal anterior area, 16 (53.3%) in the mid-anterior fibrosis, and 9 (30.0%) in the apical anterior region. One (3.3%) patient had fibrosis in the basal inferior area.

Table 1: Results regarding all the evaluated variables in the whole sample population

Variable	Value
Age (y)	26.5 ± 9.3
Sex (male/female)	17/13
Body surface area (m^2)	1.7 ± 0.2
Postoperative duration (y)	20.2 ± 8.3
Exercise Test and Electrocardiogram	
METs (kcal/kg.h)	11.5 ± 2.6
QRS duration (ms)	151.0 ± 15.6
QRS fragmentation	20 (66.7%)
Echocardiographic Parameters	
EDFF	17 (56.7%)
TAPSE (mm)	16.4 (2.6)
Sm (cm/s)	10.0 (1.9)
Tei index	0.5 (0.2)
E/A TV	1.2 (0.5)
E/E' TV	4.7 (2.0)
dp/dt	414.1 (282.4)
S fraction	0.5 (0.1)
PASP (mm Hg)	35.3 (8.2)
Cardiac Magnetic Resonance Imaging	
RV restrictive physiology	18 (60.0%)
RA area (cm^3)	19.4 (3.8)
RVEF	35.6 (6.3)
RVEDVi	176.7 (55.5)
RVESVi	112.1 (44.3)
PA proximal size (mm)	29.5 (8.8)
PA distal size (mm)	25.0 (6.6)
Left PA origin size (mm)	15.3 (6.0)
Left PA hilum size (mm)	19.9 (5.6)
Right PA origin size (mm)	16.7 (4.9)
Right PA hilum size (mm)	17.7 (4.5)
Fibrosis mass (g)	8.0 (5.6)
Myocardial mass (g)	91.0 (26.1)
Fibrosis/Myocardial mass (%)	8.5 (5.5)
RVOT fibrosis	30 (100.0%)
Basal anterior fibrosis	16 (53.3%)
Mid-anterior fibrosis	16 (53.3%)
Apical anterior fibrosis	9 (30.0%)
Basal inferior fibrosis	1 (3.3%)
Mid-inferior fibrosis	0 (0.0%)
Apical inferior fibrosis	0 (0.0%)
Septum fibrosis	0 (0.0%)
Trabecular band fibrosis	0 (0.0%)
Insertion point fibrosis	0 (0.0%)

Data are presented as the mean ± the standard deviation (SD) or numbers (percentages).
METs, Estimated metabolic equivalents of task; PASP, Pulmonary artery systolic pressure; RV, Right ventricle; EF, Ejection fraction: RVEDVi, Right ventricular end-diastolic volume index; RVESVi, Right ventricular end-systolic volume index; PA, Pulmonary artery; RVOT, Right ventricular outflow tract

Table 2 presents the qualitative classifications for the parameters measured in the exercise test or echocardiography. The majority of the subjects (90.0%) had excellent functional capacity (METs ≥ 10); in the rest of the patient (10%), functional capacity was found to be good (7 ≥ METs > 10). All the patients had QRS durations longer than 120 ms, which is considered prolonged. Considering a TAPSE value of more than 16 mm as the normal reference, moderate RV dysfunction was found in 11 (36.7%) patients. Peak systolic velocity at myocardial segments was also normal (Sm ≥10 cm/s) in 12 (40.0%) patients, whereas it was abnormal (Sm <10 cm/s) in 18 (60.0%). The myocardial performance index was found to be normal (Tei index ≤ 0.54) in 21 (70.0%) patients, while it was abnormal (Tei index >0 .54) in 9 (30.0%). The RV function was determined based on the E/A and E/e′ indices. In this regard, normal RV function (E/e′ < 6 and 0.8 ≤ E/A < 2.1), impaired RV relaxation (E/e′ < 6 and E/A < 0.8), pseudo-normal function (6 ≤ E/e′ and 0.8 ≤ E/A < 2.1), and restrictive RV function (6 ≤ E/e′ and 2.1 ≤ E/A) were found in 43.3%, 26.7%, 23.3%, and 6.7% of the cases. Normal dp/dp (≥ 400 mm Hg/ms) and abnormal dp/dt (< 400 mm Hg/ms) were found in 36.7% and 63.3% of the study population, respectively. The S fraction was normal (S ≥ 0.55) in 80.0% of the cases. The other parameters are summarized in Table 2.

Table 2: Qualitative classifications of the parameters measured in the exercise test or echocardiography

Variables	Value
METs	
excellent	27 (90%)
good	0 (0%)
intermediate	3 (10%)
TAPSE	
normal	3 (10%)
mild	16 (53.3%)
moderate	11 (36.7%)
severe	0 (0%)
Sm	
normal	12 (40%)

abnormal	18 (60%)
Tei Index	
normal	21 (70%)
abnormal	9 (30%)
RV Function	
normal	13 (43.3%)
impaired relaxation	8 (26.7%)
pseudo-normal	7 (23.3%)
restrictive	2 (6.7%)
dp/dt	
normal	11 (36.7%)
abnormal	19 (63.3%)
S Fraction	
abnormal	24 (80%)
normal	6 (20%)
RVEF	
mild	13 (43.3%)
moderate	14 (46.7%)
severe	3 (10%)
RVEDVi	
normal	2 (6.7%)
mild	2 (6.7%)
moderate	2 (6.7%)
severe	4 (13.3%)
very severe	20 (66.7%)
RVESVi	
normal	0 (0%)
mild	1 (3.3%)
moderate	1 (3.3%)
severe	5 (16.7%)
very severe	23 (76.7%)
PA Size	
normal	14 (46.7%)
abnormal	16 (53.3%)
Left PA Size	
normal	17 (56.7%)
abnormal	13 (43.3%)
Right PA Size	
normal	18 (60%)
abnormal	12 (40%)

METs, Estimated metabolic equivalents of task; PASP, Pulmonary artery systolic pressure; RV, Right ventricle; EF, Ejection fraction; RVEDVi, Right ventricular end-diastolic volume index; RVESVi, Right ventricular end-systolic volume index; PA, Pulmonary artery; RVOT, Right ventricular outflow tract; TAPSE, Tricuspid annular plane systolic excursion

The agreement between echocardiography and CMR in the diagnosis of RV restrictive physiology was also assessed. The data are depicted in in Table 3. A moderately statistically significant agreement was observed between the 2 diagnostic methods (Cohen's Kappa = 0.521, P = 0.004). If considering CMR as the gold standard, echocardiography had a sensitivity of 77.8%, a specificity of 75%, a positive predictive value of 82.3%, a negative predictive value of 69.2%, and a total accuracy of 76.7% for the diagnosis of RV restrictive physiology in our patients with repaired ToF. The patients were also compared in 2 groups according to the presence of RV restrictive physiology measured on CMR imaging. As is presented in Table 4, the QRS duration (P = 0.015), the QRS fragmentation (P = 0.018), and RVEDVi (P = 0.050) were found to be significantly higher among the patients with RV restrictive physiology, while Sm (P = 0.045) was significantly lower in these patients. The ECG data had no impact in our study, and the ECG measures were reported merely as co-findings.

Table 3: Agreement between echocardiography and CMR findings in the diagnosis of RV restrictive physiology

Agreement		RV Restrictive Physiology		Total
		Negative	Positive	
EDFF	Negative	9	4	13
	Positive	3	14	17
Total		12	18	30

CMR, Cardiac magnetic resonance imaging; RV, Right ventricle; EDFF, End-diastolic forward flow

Table 4: Comparisons between the 2 groups of positive and negative RV restrictive physiology

Demographic characteristic	RV restrictive physiology		*P* value
	Negative (n=12)	Positive (n=18)	
Gender (male/female)	6/6	11/7	0.547
Age (y)	28.2 (9.8)	25.4 (9.1%)	0.427
Body surface area (m^2)	1.8 (0.2)	1.7 (0.1)	0.185
Postoperative duration (y)	21.5 (9.1)	19.3 (8.0)	0.498
Exercise Test and Electrocardiogram			
METs (kcal/kg.h)	11.4 (3.2)	11.6 (2.3)	0.853
QRS duration (ms)	142.5 (14.8)	156.7 (13.7)	0.015
QRS fragmentation	5 (41.7%)	15 (83.3%)	0.018
Echocardiographic Parameters			
TAPSE (mm)	16.2 (3.4)	16.6 (2.0)	0.752
Sm (cm/s)	10.9 (2.0)	9.4 (1.5)	0.045
Tei index	0.4 (0.2)	0.5 (0.2)	0.118
E/A TV	1.2 (0.5)	1.2 (0.5)	0.967
E/E' TV	3.9 (2.0)	5.2 (1.9)	0.093
dp/dt	533.9 (335.2)	334.3 (215.5)	0.085
S fraction	0.5 (0.2)	0.4 (0.1)	0.253
PASP (mm Hg)	34.6 (7.8)	35.8 (8.6)	0.696
CMR			
RA area (cm3)	18.9 (3.6)	19.7 (3.9)	0.597
RVEF	36.2 (7.6)	35.2 (5.5)	0.700
RVEDVI	154.4 (37.6)	191.5 (61.3)	0.050
RVESVI	99.2 (31.9)	120.8 (50.0)	0.159
PA proximal size (mm)	26.2 (7.7)	31.7 (9.0)	0.084
PA distal size (mm)	25.1 (6.9)	24.9 (6.6)	0.956
Left PA origin size (mm)	14.8 (4.4)	15.6 (6.9)	0.730
Left PA hilum size (mm)	20.7 (4.6)	19.4 (6.2)	0.523
Right PA origin size (mm)	16.9 (4.4)	16.6 (5.2)	0.840
Right PA hilum size (mm)	18.4 (3.1)	17.2 (5.3)	0.424
Fibrosis mass (g)	6.7 (5.1)	8.9 (5.9)	0.279
Myocardial mass (g)	82.2 (17.0)	96.9 (29.7)	0.096
Fibrosis/Myocardial mass (%)	7.9 (5.9)	8.9 (5.3)	0.630
RVOT fibrosis	12 (100.0%)	18 (100.0%)	1
Basal anterior fibrosis	6 (50.0%)	10 (55.6%)	0.765
Mid-anterior fibrosis	7 (58.3%)	9 (50.0%)	0.654
Apical anterior fibrosis	4 (33.3%)	5 (27.8%)	0.745
Basal inferior fibrosis	1 (8.3%)	0 (0.0%)	0.213

METs, Estimated metabolic equivalents of task; PASP, Pulmonary artery systolic pressure; RV, Right ventricle; EF, Ejection fraction; RVEDVi, Right ventricular end-diastolic volume index; RVESVi, Right ventricular end-systolic volume index; PA, Pulmonary artery; RVOT, Right ventricular outflow tract; TAPSE, Tricuspid annular plane systolic excursion

DISCUSSION

This study showed a significant but moderate agreement between the presence of EDFF on echocardiography and the visualization of the forward flow during atrial contraction in CMR as diagnostic clues for RV restrictive physiology in adolescents and adults with a history of TFTC. Based on our LGE-CMR data, RVOT fibrosis was present in all the patients, while 16 (53.3%) had fibrosis in the basal anterior area, 16 (53.3%) in the mid-anterior fibrosis, and 9 (30.0%) in the apical

anterior region. Additionally, 1 (3.3%) patient had fibrosis in the basal inferior area. On the other hand, none of the patients had fibrosis in the mid-inferior or apical inferior regions, the septum, the trabecular band, and the insertion point. Accordingly, the relationship between RVOT fibrosis and RV restrictive physiology could not be assessed in these patients, and fibrosis in the other evaluated areas did not have any correlation with RV restrictive physiology. There were no significant differences regarding fibrosis mass and the ratio of fibrosis to myocardial mass between the subjects with or without RV restrictive physiology. Eventually, the QRS duration, the QRS fragmentation, and RVEDVi were found to be significantly higher among the patients with RV restrictive physiology, while Sm was significantly lower in these patients.

Our data chime in with other reported findings in this regard. Rathore et al [24] assessed the effects of RV restrictive physiology on exercise capacity and arrhythmogenesis in 80 patients with ToF after surgical repair and reported a lower but not statistically significant maximum heart rate, maximum predicted heart rate, and functional capacity based on METs in their patients with RV restrictive physiology. They also found no significant correlation between the presence of RV restrictive physiology and exercise intolerance, which is compatible with our findings. Moreover, Rathore and colleagues reported no correlation between RV restrictive physiology and the development of arrhythmias, which is different from our findings. This discrepancy might be attributed to the lower age range of the participants in their study.

Babu-Nyaran et al [25] scored LGE in the RV of 92 adult cases with a history of repaired ToF. The distribution of fibrosis in our study is compatible with that in the study by Babu-Nyaran and colleagues; however, they found a correlation between the QRS duration as a risk factor for the development of arrhythmias and myocardial fibrosis, which is incompatible with our findings. This discrepancy could be attributed to different methods applied for the calculation of fibrosis. Babu-Nayaran et al used a scale of 0 to 4 to score the percentage of fibrosis in each region, while we recorded LGE once as a dichotomous variable of the presence or absence and once again as a quantitative variable of the estimated fibrosis mass in grams.

Whal et al [26] evaluated 93 patients with repaired ToF with or without EDFF and compared them with 12 normal subjects using CMR regarding the timing of the flow patterns of the pulmonary artery, the ascending aorta, and the tricuspid and mitral flow. They showed a significant delay in the onset of the tricuspid inflow and a lower tricuspid inflow E/A ratio in subjects with EDFF by comparison with normal subjects. Their findings are mostly incongruent with our results as we did not find any significant correlation between EDFF and neither METs nor the E/A ratio. The difference in age of the sample populations (average of 26.5 vs 13 y) and the limited number of patients in our study might have contributed to the observed discrepancy between the 2 surveys.

Koestenberger et al [27] evaluated 131 patients with ToF after surgical repair and compared them with 252 age-matched healthy subjects using TAPSE, RVEF, and RVEDVi. They demonstrated a positive correlation between TAPSE values and age in normal subjects, but it was not low in infants and young children with ToF compared with normal subjects. They also found a significant reduction in TAPSE values with increasing time after surgical repair. The QRS duration was found to have a significant positive correlation with RVEDVi and a negative correlation with RVEF. None of the associations between TAPSE and the mentioned variables was observed in our study. However, the relationships between the QRS duration and

RVEF and RVEDVi were found in our study as well. These correlations appear to be logical since an increase in RVEDVi could lead to an increase in the QRS duration, which in turn can be associated with a decrease in RVEF due to the dysfunction of the dilated RV in pumping blood.

Munkhammar et al [28] evaluated 31 patients with ToF and compared them with 12 healthy children regarding RVOT fibrosis, RV restrictive physiology, RV volume, and PR using CMR and Doppler echocardiography. They showed a correlation between RVOT fibrosis measured by CMR and RV restrictive physiology. We could not demonstrate such a correlation, which may be due to our smaller sample volume.

CONCLUSIONS

Our data demonstrated that TTE could be used as an alternative method for the evaluation of RV restrictive physiology in patients with severe PR following TFTC. However, RV restrictive physiology measured by CMR and RV EDFF measured by echocardiography could not correlate with quantitative RV myocardial fibrosis measured by LGE CMR.

Study Limitations

Our study had some limitations. First, its sample size was small; consequently, to reach a consensus on the relationship between myocardial fibrosis detected by LGE CMR and RV restrictive physiology and to determine the accuracy of TTE in the diagnosis of this condition, we need further large-scale investigations with a wider range of age groups to compare the effects of time on myocardial fibrosis and RV restrictive physiology in such cases. Second, all the patients in our study had fibrosis in the RVOT, which precluded us from evaluating RV myocardial fibrosis in relation to RV restrictive physiology. We think that the interval between TFTC and the occurrence of severe PR was remarkably wide in our study (8–39 y), which may explain the absence of a correlation between fibrosis and other CMR and echocardiography features. We believe that serial evaluations of patients at similar intervals could provide valuable data in this setting.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgments

We would like to thank all the staff of Rajaie Cardiovascular Medical and Research Center for assisting us in implementing this study. We are also grateful to all the patients who kindly participated in the study.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW: Birth prevalence of congenital heart disease worldwide. *Journal of the American College of Cardiology* 2011, 58:2241-2247.

2. Bailliard F, Anderson RH: Tetralogy of fallot. *Orphanet Journal of Rare Diseases* 2009, 4:2.

3. Apitz C, Webb GD, Redington AN: Tetralogy of fallot. *The Lancet* 2009, 374:1462-1471.

4. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, DeWall RA, Varco RL: Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects: report of first ten cases. *Annals of surgery* 1955, 142:418.

5. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G: Early primary repair of tetralogy of Fallot in neonates and infants less than four months of age. *The Annals of Thoracic Surgery* 2008, 86:1928-1935.

6. Vohra HA, Adamson L, Haw MP: Is early primary repair for correction of tetralogy of

Fallot comparable to surgery after 6 months of age? *Interactive cardiovascular and thoracic surgery* 2008, 7:698-701.

7. Hamada H, Terai M, Jibiki T, Nakamura T, Gatzoulis MA, Niwa K: Influence of early repair of tetralogy of Fallot without an outflow patch on late arrhythmias and sudden death: a 27-year follow-up study following a uniform surgical approach. *Cardiology in the young* 2002, 12:345-351.

8. Pokorski RJ: Long-term survival after repair of tetralogy of Fallot. *JOURNAL OF INSURANCE MEDICINE-NEW YORK-* 2000, 32:89-92.

9. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, McGoon DC, Kirklin JW, Danielson GK: Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *New England Journal of Medicine* 1993, 329:593-599.

10. Bacha EA, Scheule AM, Zurakowski D, Erickson LC, Hung J, Lang P, Mayer JE, Pedro J, Jonas RA: Long-term results after early primary repair of tetralogy of Fallot. *The Journal of Thoracic and Cardiovascular Surgery* 2001, 122:154-161.

11. Discigil B, Dearani JA, Puga FJ, Schaff HV, Hagler DJ, Warnes CA, Danielson GK: Late pulmonary valve replacement after repair of tetralogy of Fallot. *The Journal of thoracic and cardiovascular surgery* 2001, 121:344-351.

12. Nørgaard MA, Lauridsen P, Helvind M, Pettersson G: Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. *European journal of cardio-thoracic surgery* 1999, 16:125-130.

13. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, Webb GD, McCrindle BW: Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *European Journal of cardio-thoracic Surgery* 2009, 35:156-164.

14. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC: Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *The Lancet* 2000, 356:975-981.

15. Lee W, Yoo S-J, Roche SL, Kantor P, van Arsdell G, Park E-A, Redington A, Grosse-Wortmann L: Determinants and functional impact of restrictive physiology after repair of tetralogy of Fallot: new insights from magnetic resonance imaging. *International journal of cardiology* 2013, 167:1347-1353.

16. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, Helbing WA: Diastolic Function in Repaired Tetralogy of Fallot at Rest and during Stress: Assessment with MR Imaging 1. *Radiology* 2007, 243:212-219.

17. Norgård G, Gatzoulis M, Josen M, Cullen S, Redington A: Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? *Heart* 1998, 79:481-484.

18. Prakash A, Powell AJ, Krishnamurthy R, Geva T: Magnetic resonance imaging evaluation of myocardial perfusion and viability in congenital and acquired pediatric heart disease. *The American journal of cardiology* 2004, 93:657-661.

19. Harris MA, Johnson TR, Weinberg PM, Fogel MA: Delayed-enhancement cardiovascular magnetic resonance identifies fibrous tissue in children after surgery for congenital heart disease. *The Journal of Thoracic and Cardiovascular Surgery* 2007, 133:676-681. e672.

20. Muzzarelli S, Ordovas KG, Cannavale G, Meadows AK, Higgins CB: Tetralogy of Fallot: impact of the excursion of the interventricular septum on left ventricular systolic function and fibrosis after surgical repair. *Radiology* 2011, 259:375-383.

21. Yang H, Pu M, Chambers CE, Weber HS, Myers JL, Davidson WR Jr. Quantitative assessment of pulmonary insufficiency by

Doppler echocardiography in patients with adult congenital heart disease. J Am Soc Echocardiogr. 2008 Feb;21(2):157-64.

22. Rudski LG1, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010 Jul;23(7):685-713; quiz 786-8.

23. Bires AM Lawson D, Wasser TE, Raber-Baer D. Comparison of Bruce treadmill exercise test protocols: is ramped Bruce equal or superior to standard bruce in producing clinically valid studies for patients presenting for evaluation of cardiac ischemia or arrhythmia with body mass index equal to or greater than 30? J Nucl Med Technol. 2013 Dec;41(4):274-8. doi: 10.2967/jnmt.113.124727.

24. Rathore KS, Agrawal SK, Kapoor A: Restrictive physiology in tetralogy of Fallot: exercise and arrhythmogenesis. *Asian Cardiovascular and Thoracic Annals* 2006, 14:279-283.

25. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA: Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation* 2006, 113:405-413.

26. Whal L, Roche SL, Yoo S-J, Grosse-Wortmann L: Restrictive physiology in repaired Tetralogy of Fallot: Prevalence, significance and pathophysiology. *Journal of Cardiovascular Magnetic Resonance* 2010, 12:P15.

27. Koestenberger M, Nagel B, Ravekes W, Everett AD, Stueger HP, Heinzl B, Sorantin E, Cvirn G, Fritsch P, Gamillscheg A: Systolic right ventricular function in pediatric and adolescent patients with tetralogy of Fallot: echocardiography versus magnetic resonance imaging. *Journal of the American Society of Echocardiography* 2011, 24:45-52.

28. Munkhammar P, Carlsson M, Arheden H, Pesonen E: Restrictive right ventricular physiology after tetralogy of Fallot repair is associated with fibrosis of the right ventricular outflow tract visualized on cardiac magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2013, 14:978-985.