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Correlation of Fragmented QRS with Right Ventricular Indexes and Fibrosis in Patients with Repaired Tetralogy of Fallot, by Cardiac Magnetic Resonance Imaging

Zahra Alizadeh Sani [1], Ali Vasheghani farahani [1], Zahra Khajali [1], Majid Jamshidi [1], Mahshid Hesami [1], Hamidreza Fallahabadi [1], Mousa Alimohammadi [1], Azin Seifi [2], Majid Nejati [3], Mohaddeseh Behjati [1, 4, *]

[1] Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[2] Electrophysiology Department, Tehran University of Medical Sciences, Tehran, IR Iran
[3] Anatomical Sciences Research Center, Kashan University of Medical Sciences, Kashan, IR Iran
[4] Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, IR Iran

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ABSTRACT

Background: Repair of tetralogy of fallot (TOF) is associated with diffuse myocardial fibrosis. Cardiac magnetic resonance imaging (CMR) can visualize the areas with myocardial fibrosis. Presence of fragmented QRS (fQRS) implies the presence of the underlying myocardial scar. Despite the strong association between fQRS and myocardial pathologies, the impact of fQRS with myocardial fibrosis in post-TOF correction is unknown.

Objectives: Here, we evaluated the possible predictive role of fQRS in repaired TOF cases and its relationship with cardiac function.

Patients and Methods: Thirty two patients with previous history of repaired TOF were enrolled. The extent of fQRS was evaluated according to the number of leads with fQRS. After electrocardiographic evaluation, the participants underwent CMR.

Results: Results showed a significant relationship between the right ventricular (RV) systolic diameter and fQRS (P = 0.014). Also, an inverse linear relationship was found between the number of fQRS edges and RVEF (r = 0.77, P = 0.0001). The mean QRS duration in those with positive and negative fQRS was 132 mm and 115.8 mm (P = 0.0001). Furthermore, a linear correlation was observed between the number of edges and the percentage of scar tissue (r = 0.88, P = 0.001). However, no relevance between gender and fQRS was detected (P = 0.26), and the relationship between RV diastolic diameter and fQRS was not significant (P = 0.1). Thus, fQRS could be used as a marker of RV systolic dysfunction in patients with tetralogy of fallot.

Conclusions: We suggested the fQRS as a surrogate indicator of RV dysfunction in repaired TOF patients and showed that diagnostic and prognostic information of the patients were available by fQRS.

1. Background

Prevalence of TOF is about 3 in every 10 thousand live birth (1). Repair of this congenital cyanotic heart disease is associated with diffuse myocardial fibrosis (2). Determination of myocardial fibrosis could be made through various image modalities like echocardiography. Since echocardiography is unsuccessful for visualizing of all the heart segments, cardiac magnetic resonance imaging (CMR) can visualize the unseen cardiac areas fully such as all segments of the left ventricle. Also, CMR can show the area of myocardial fibrosis (3). However, this technique is not always an appropriate choice because of its cost and availability. Electrocardiography as a fast and easy method for determination of cardiac pathologies is another possible choice. Presence of QRS complex abnormalities implies the presence of underlying myocardial scar and can represent conduction disturbances (4). Fragmented QRS

*Corresponding author: Mohaddeseh Behjati, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.
Tel: +98-9132307657,
E-mail: behjati@med.mui.ac.ir

(fQRS) is one of these abnormalities, which is related to various cardiac conditions and prognoses (4). The fQRS may be a manifestation of myocardial scar which is not responsive to cardiac resynchronization therapy. fQRS could be used for proper selection of cardiac re-synchronization therapy candidates (5). Higher amounts of intensive treatment and follow up are needed in cases with fQRS and prolonged QRS after coronary artery bypass surgery (6). Indeed, the lower disease-free survival in cases with hypertrophic cardiomyopathy or heart failure and abnormal QRS fragmentation indicates the prognostic implication of fQRS (7).

2. Objectives

This study aimed to evaluate the impact of fQRS in prediction of repaired TOF cases and its relationship to cardiac function.

3. Patients and Methods

Thirty two patients aged 12 - 23 years with previous history of repaired TOF were selected randomly for this study. None of these participants had left ventricular dysfunction or any of co-morbid renal or pulmonary illnesses. Every patient was evaluated by the same cardiologist with GE Marquette, Milwaukee, Wisconsin. FQRS was evaluated by standard 12 lead electrocardiography, with optimal low-pass filter (filter range 0, 15 - 100HZ) (alternating current filter 60HZ) (10 mm/mv, 25 mm/s) before CMR. The prominent morphological pattern was complete right bundle branch block. Presence of two or more notching in the R-S wave in two adjacent leads was considered as FQRS (adjacent leads were as: Anterior leads = V1 - V5; Inferior leads = II, III, aVF; Lateral leads = I, aVL, V6). The extent of FQRS was evaluated according to the number of leads with FQRS. The electrocardiograms of these 32 patients were evaluated by two cardiologists who were unaware of CMR of the patients. There were 96 to 98 percent agreements between the cardiologists about the presence of FQRS. After electrocardiographic evaluation, the participants underwent CMR.

This cross-sectional study was approved by Iran University of Medical Science human research committee and conducted in CMR department, Rajaei Cardiovascular, Medical and Research Center, Iran, during 2012 to 2014. Thirty-two participants who met the following inclusion criteria were enrolled in this study: 1- participants ≥ 15 years of age; 2- those who underwent corrective surgery for TOF ≥ 10 years ago; 3- participants who referred to our center for further evaluation of their dyspnea and palpitation. Participants who had left ventricular dysfunction or any co-morbid renal or pulmonary diseases were excluded. The study protocol was approved by the institutional review board of Rajaei Cardiovascular, Medical and Research Center, and the requirement for written informed consent was waived. In order to assess the fQRS, an electrocardiogram was recorded before CMR analysis. Standard 12-lead electrocardiograms were obtained with an optimal low-pass filter setting (filter range 0.15 to 100 Hz, alternating current filter 60 Hz, 25mm/s, 10 mm/mV; GE Marquette, Milwaukee, Wisconsin). Most often, the QRS morphology after TOF repair demonstrates complete right bundle branch block pattern. QRS complexes were defined as fragmented when ≥ 2 notches in the R/S wave were present in 2 contiguous anterior (V1 to V5), inferior (II, aVF, and III), or lateral (I, aVL, and V6) leads. The extent of fQRS in each patient was estimated by counting the number of electrocardiographic leads with fQRS. Electrocardiograms of all these 32 patients were reviewed by two independent cardiologists who were blinded to CMR reporting cardiologist and clinical data. There were 98% and 96% intra- and inter-observer agreements for the presence of fQRS, respectively. Electrocardiographic parameters such as QRS duration and views were also measured. One month after evaluation of electrocardiograms, the patients underwent CMR examinations. All scans were obtained using a 1.5-T scanner (Magnetom Avanto Simense). Cine images were obtained using steady-state free precession (SSFP) sequence along the long and the short axis from the atrio-ventricular ring to the apex of the right ventricles. Delayed images using LGE CMR were obtained after 10 - 15 minutes following intravenous injection of 0.2 mmol/kg gadodiamide. Similar sequences for the measurement of the scar and normal tissue of the right ventricle was obtained. Volumetric variables were calculated using Simpson's algorithm from the short-axis view obtained at end-diastole and end-systole during a period of breath holding. These parameters were indexed according to the body surface area (BSA = Weight (kg) $^{0.425}$ × Height (cm) $^{0.725}$ × 0.007184) and Du Bois Method. Volumes were determined before and after the gadolinium injection by manual planimetry and summation of discs methodology. In this study, RVOT region was considered for calculation of RV volumes or mass index. Delayed enhancement images were obtained 10 to 15 minutes after intravenous injection of gadolinium. RV long-axis planes including a sagittal RVOT, RV oblique and 4-chamber views were also obtained. RV fibrosis assessment was done through measurement of both RV fibrosis and residual volumes derived from 8 to 12 slices in short axis view of LGE sequences in RVOT, RV anterior wall, RV inferior wall and basal septal and in the ventricular septal defect patch area. Then, the normal RV mass was assessed in these views. The proportion of fibrotic RV myocardium mass to the normal RV myocardium was calculated, and this percentage was evaluated with both RV functional indexes and fQRS.

The patient's demographic data, RV-related indexes and electrocardiogram data like fQRS were gathered. All statistical analyses were performed using SPSS version 16 (SPSS, Inc., Chicago, Illinois). Sample T test and Pearson Correlation coefficient were used for data comparison. After analyzing these data, the relationship between fQRS and RV indexes and RV fibrosis was determined. P values less than 0.05 were considered statistically significant.

4. Results

Thirty two patients participated in this study (19 males and 13 females). The age range of the patients was 12 - 23 years and their mean body mass index was 19.9 ± 0.7 kg/m2 (mean ± SD). Demographic data according to CMR indexes are shown in Table 1. The mean percentage of scar tissue was

Table 1. Primary Demographic Parameters and CMR

Parameters	CMR (mean ± SD)	Range
RV diastolic diameter (mm)	4.31 ± 0.34	3.7 - 4.8
RV systolic diameter (mm)	3.72 ± 0.4	3.1 - 4.3
RV stroke volume (mL)	82.5 ± 13.21	60 - 100
RV ejection fraction (%)	45.97 ± 9.6	30 - 60
RV end diastolic index (mL/m2)	137.97 ± 21.9	83 - 180
RV end systolic index (mL/m2)	81.22 ± 20.05	35 - 115
BMI (Kg/m2)	19.91 ± 0.73	18.8 - 22
RV scar tissue (%)	16.25 ± 9.62	3 - 38
Age (year)	15.7 ± 3.25	12 - 23

24% and 5.8% in those who had RVEF < 45% and RVEF ≥ 45%, respectively which was statistically significant (P = 0.0001). With 12% of scar tissue, the patients with LVEF < 45% could be identified through sensitivity and specificity of 100% and 88%, respectively. The overall accuracy of the test in order to identify the patients with RVEF < 45% was 98%; this was statistically significant and could be generalized to the target population (P = 0.0001). There was also a meaningful relationship between fQRS and RV end diastolic volume index (P = 0.003). The sensitivity and specificity of fQRS in identification of patients with RVEDVI > 150 cc/m2 were 87% and 62%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were 70% and 83%, respectively. The relationship between fQRS and RV end systolic volume index was statistically significant (P = 0.02). The sensitivity and specificity of fQRS in identification of patients with RVESVI > 82 cc/m2 were 80% and 66%, respectively. PPV and NPV were 70% and 83%, respectively. The mean right ventriculardiastolic diameters in patients with RVEF < 45% and RVEF ≥ 45% were about 4.54 cm and 4.09cm, respectively; this was statistically considerable (P = 0.0001). But there was not any meaningful relationship between RV diastolic diameter and fQRS (P = 0.1). The mean right ventricular systolic diameters in patients with RVEF < 45% and RVEF ≥ 45% were about 4.03 cm 3.4 cm, respectively, which was statistically significant (P = 0.0001). Indeed, there was a significant relationship between RV diastolic diameters and fQRS (P = 0.014). There was a strong inverse linear relationship between the number of fQRS edges and RVEF according to Pearson Correlation coefficient (r = 0.77) which was significant (P = 0.0001). The mean QRS duration in those with positive and negative fQRS was 132 mm and 115.8 mm, respectively (P = 0.0001). The median age of the patients with positive and negative fQRS was 15.3 and 16.5 years, respectively which was not meaningful (P = 0.32). There was not any relationship between gender and fQRS (P = 0.26). The mean BMI in the positive and negative fQRS group was 20.09 and 19.6, respectively (P = 0.07). There was a strong positive linear correlation between the number of edges and the percentage of scar tissue (r = 0.88) which was statistically meaningful (P = 0.001).

5. Discussion

Pulmonary valve replacement is increasingly used for treatment of RV dysfunction due to pulmonary regurgitation in patients with repaired tetralogy of fallot. Patients usually require repeated valve replacement every ten years (8). Repair of tetralogy of fallot is not a totally safe procedure or without complications. Mortality rate was approximately 2% for all patients has been reported (9). CMR is a standard diagnostic method for evaluation of RV function, RVEVSI and RVEDVI (10, 11). Since CMR is an expensive and hardly available technique, using other methods such as fQRS seems reasonable for screening of TOF patients. Based on pre-operative CMR findings, Lee et al.'s study supports PVR in terms of RVEDVI higher than 163 mL/m^2 or RVESVI higher than 80 mL/m^2 (12). Also, Oosterhof et al. reported RVEDVI higher than 150 mL/m^2 to be an optional cut off volume (13). We demonstrated that fQRS was 87% sensitive and 62% specific in determining RVEDVI higher than 150 mL/m^2 with P2PV but sensitivity and spicifity with NPV are 70% and 83%, respectively. RVEF less than 47% is another indication for PVR (8, 14). We found that the overall accuracy of fQRS in identification of patients with RVEF less than 45% is 98%. In this study, there was a significant relationship between the amount of scar tissue with RV function and RV function with fQRS. Therefore, fQRS can be used to identify and screen the patients with repaired TOF who suffer from RV dysfunction (15). In previous clinical studies, late after repair of TOF, considerable RV fibrosis was associated with higher occurrence of ventricular arrhythmias (16). Hence, there was a strong correlation between fQRS and RV scar tissue; patients with fQRS might have greater risk of ventricular tachyarrhythmia in comparison to non-fragmented QRS widening. Evaluation of fQRS is inexpensive and easily accessible in patients of repaired TOF. It could also provide complementary information to CMR findings. The presence of fQRS or an increased extent (the number of involved leads) accompanied by RV scar tissue could be a warning for further evaluation for these patients (17). However, some studies like Wang et al. found that fQRS could not be used routinely (18). But it might be due to the different study population. Thus, we suggest fQRS as a surrogate indicator of RV dysfunction in repaired TOF cases. Based on our data, fQRS brings diagnostic and prognostic information for these patients. However fQRS is consistently related to RV systolic function and its prognostic role is highest in the cases with systolic dysfunction who have increased end diastolic volumes. The sensitivity and specificity of this test are high although its sensitivity is slightly higher than specificity. Indeed, fQRS is a safe test without the essential need to other expensive equipment and can be easily measured just using a bed side or outpatient electrocardiogram.

5.1. Conclusions

We suggest fQRS as a surrogate indicator of RV dysfunction in repaired TOF cases. Based on our data, fQRS brings diagnostic and prognostic information for these patients.

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Authors' Contribution

All authors contributed to data collection, analysis of data and writing articles. Corresponding author supervised this study.

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