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Relation between fragmented QRS complex to the right ventricular volumes and fraction of pulmonary regurgitation in patients with repaired tetralogy of Fallot

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ABSTRACT

Patients with repaired tetralogy of Fallot (TOF) have not uncommonly fragmented QRS complexes (fQRS) on surface electrocardiogram. We suggested that the right heart hemodynamics might be correlated with both the number of leads showing fQRS (fQRS extent) and the QRS duration. A retrospective analysis of the magnetic resonance imaging (MRI) derived data of 30 patients following total correction of TOF was performed. The number of leads showing fragmentation (fQRS extent) as well as the QRS duration were assessed and tested for correlation with the right ventricular volumes and severity of pulmonary regurgitation (PR) as detected by MRI. Twenty-one patients had fQRS in at least 2 consecutive leads. fQRS correlated with larger right ventricular volumes and lower ejection fraction. fQRS in 5 leads was an accurate parameter in identifying an indexed right ventricular end diastolic volume $> 150\ ml/m^2$ with a sensitivity of 87.5% and a specificity of 85.7%. Moreover, it was the most accurate parameter in detecting a PR fraction $>$ 45%. To conclude, assessment of fQRS extent and duration is a simple, available, and an accurate parameter in identifying patients with significant right ventricular hemodynamic changes in repaired TOF patients.

1. Introduction

Tetralogy of Fallot (TOF) is the most common congenital cyanotic heart disease [1–5]. Currently, more children born with TOF undergo surgical intervention early in childhood making them able to reach adulthood [6]. These patients are, however, prone to the development of many complications and need to be followed up in specialized centers [1,7]. Right ventricular (RV) dysfunction, progressive pulmonary valve regurgitation (PR), and RV dilation/fibrosis are common complications following TOF repair [8–10]. Moreover, PR accelerates the RV structural and functional derangements among these patients [11]. Myocardial fibrosis resulting in conduction abnormalities might express itself on the surface electrocardiogram in the form of fragmented QRS complexes (fQRS). fQRS was previously found to be closely associated with extensive RV fibrosis as assessed by late gadolinium enhancement among adult patients with repaired TOF [10]. A QRS duration ≥ 180 ms is considered to be a highly sensitive finding predicting malignant arrhythmias and sudden death in such group of patients [12]. We suggested that the RV hemodynamic changes might be better correlated with both the number of leads showing fQRS (fQRS extent) as well as the QRS duration. Accordingly, the extent of fQRS and QRS duration were assessed and correlated with the RV indices and PR fraction as assessed by cardiac magnetic resonance imaging (MRI).

2. Methods

A retrospective analysis of the clinical and imaging data of thirty patients who underwent cardiac MRI for assessment of the severity of cardiac lesions following total correction of TOF was performed. Both adolescents and adults were enrolled if they were > 12 years of age and have no contraindications for MRI study.

Standard 12-lead electrocardiogram was obtained using the Schiller electrocardiographic machine immediately prior to the MRI study. The speed was set at 25 mm/s. Both the number of leads showing fQRS (fQRS extent) and the duration of the QRS complexes were assessed by an expert cardiologist who was blinded to the clinical status and

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findings of the MRI. fQRS pattern in patients with narrow QRS complex (duration < 120 ms) was defined as the presence of an additional R wave (R') or notching in the nadir of the S wave or the presence of > 1 R′ in two contiguous anterior (V_1 to V_5), inferior (II, III, aVF), or lateral (I, aVL, V_6). In the case of wide QRS complex (duration ≥ 120 ms), the presence of > 2 R waves or > 2 notches in the R/S wave was used to judge fragmentation [13]. To calculate the QRS duration, the widest QRS in any lead was measured. The echocardiographic parameters of both the left and right heart were measured in accordance to the guidelines [14].

CMR studies were acquired with 1.5 T (Achieva, Philips systems) and processed in a commercially available workstation. Cardiac volumes were done using the retrospectively electrocardiographically gated steady-state free-precession cine CMR acquisitions in axial and short-axis planes from the entire ventricles (TR: 4.2 ms, TE: 2.1 ms, slice thickness: 8 mm averages). Cardiac volumes were measured by manually tracing the area of the endocardial surfaces. All volumes were indexed to the body surface area using the Monsteller equation. Indexed RV end diastolic volume (RVEDVi) > 150 ml/m^2 was considered the cutoff value for diagnosing significant RV dilation. Phase shift velocity encoding (PC-VENC) was used to assess the flow in the aorta and pulmonary arteries. Imaging was performed with a non-breath-hold technique (15 s per slice level). The main pulmonary artery was targeted at its midpoint between the pulmonary valve and its bifurcation, the right branch behind the ascending aorta, and the left pulmonary below the distal aortic arch and/or above the left main bronchus. Regurgitant fraction (RF%) was calculated automatically [15]. The MRI studies were analyzed by a single expert radiologist blinded to both the clinical and electrocardiographic findings.

2.1. Statistical Analysis

Data were coded and analyzed using the statistical package SPSS (Statistical Package for the Social Science, version 23). Data are presented as mean and standard deviation for quantitative variables and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi-square test was performed. Fisher's exact test was used instead when the expected frequency was < 5. Correlations between the quantitative variables were done using Spearman correlation coefficient. Receiver operating characteristic (ROC) curve was constructed with area under curve analysis performed to detect best cutoff values for detection of a RVEDVi > 150 ml/m^2, a RV ejection fraction < 45% and a PR > 45%. *p*-Values < 0.05 were considered statistically significant.

3. Results

Baseline demographic, echocardiographic and MRI characteristics of the studied patients are summarized in Table 1. Five patients (16.6%) had evidence of RV dysfunction according to the CMR criteria. CMR calculation of RV volumes showed that 16 patients (53%) had a RVEDVi > 150 ml/m^2. Twenty-nine patients (97%) had wide QRS complexes (right bundle branch block pattern) with 72% of them (21 patients) had fQRS in at least 2 consecutive leads. The mean number of leads showing fQRS was 4.97 ± 3. fQRS were detected predominantly in the inferior and lateral leads.

There was no statistically significant difference in the baseline clinical and echocardiographic data between patients with fQRS and those without with only a trend towards a lower S wave velocity as assessed by tissue Doppler imaging ($p = 0.091$) in the fragmented group. It was noted, however, that patients showing fQRS on surface electrocardiogram had larger RVEDVi (Fig. 1), indexed RV end systolic volume, higher RVEDVi/left ventricular end diastolic volume index ratio ($p < 0.01$) and PR fraction (p < 0.01). RV ejection fraction as well as the left ventricular parameters were comparable in both groups of patients (Table 2). Similarly, fQRS extent correlated positively with the RVEDVi (r = 0.8, $p < 0.001$), indexed RV end systolic volume (r = 0.7, $p < 0.001$), indexed RV stroke volume (r = 0.6, $p < 0.001$), PR fraction (r = 0.5, $p = 0.004$) and negatively with the RV ejection fraction (r = −0.4, $p = 0.018$). On the other hand, QRS duration correlated positively only with the RVEDVi (r = 0.5, $p < 0.01$) and indexed RV stroke volume (r = 0.5, $p < 0.01$). Table 3 summarizes the correlation between the detection of fQRS in the anterior chest leads (V1–V5) and right heart hemodynamics.

Table 1
Baseline demographic, echocardiographic and MRI characteristics of the studied patients.

	n = 30
Age, ys	15 ± 3.1
Male gender, %	70
Height, cm	151 ± 17
Weight, kg	45 ± 17
Body mass index, kg/m^2	19 ± 4
Age of repair, ys	4 ± 2
Time passed since repair, ys	12 ± 2
TAPSE, mm	15 ± 6
RV S′ wave velocity, cm/s	8 ± 1
Indexed RV end-diastolic volume, ml/m^2	155 ± 43
Index RV end-systolic volume, ml/m^2	76 ± 30
RV ejection fraction, %	52 ± 8
Indexed LV end-diastolic volume, ml/m^2	89 ± 17
Indexed LV end-systolic volume, ml/m^2	41 ± 12
Indexed LV stroke volume, ml/min/m^2	51 ± 8
LV ejection fraction, %	56 ± 5
Indexed RVEDV/LVEDV	1.7 ± 0.4
Pulmonary regurgitant fraction, %	41 ± 15

Data are presented as mean ± SD or percentage. Abbreviations: LV; left ventricle, RV; right ventricle, RVEDVi/LVEDVi; indexed right ventricular end diastolic volume/left ventricular end diastolic volume, TAPSE; tricuspid annular plane systolic excursion.

The presence of fQRS complexes in 5 electrocardiographic leads was the most accurate parameter identifying patients with RVEDVi > 150 ml/m^2 with a sensitivity of 87.5% and specificity of 85.7%. Using the ROC curve analysis, the optimum point for separation of patients with a PR fraction > 45% was the presence of fQRS in 5 electrocardiographic leads with a sensitivity of 83% and specificity of 67%.

4. Discussion

In this study, patients with repaired TOF and fQRS on resting electrocardiogram had larger RV volumes and a significantly higher PR fraction as assessed by cardiac MRI. Interestingly, the presence of fQRS complexes in 5 electrocardiographic leads was an accurate parameter in identifying a RVEDVi > 150 ml/m^2 and a PR fraction > 45%.

TOF is the most common congenital cyanotic heart disease. About 10% of adult patients with congenital heart disease in Egypt had TOF in a previous report [5]. The majority of these patients undergo corrective surgery either during infancy or childhood and are considered prone to the development of late complications especially fatal ventricular arrhythmias, RV dysfunction, and significant PR necessitating re-intervention [7,8]. The electrocardiogram plays an important role in risk stratification of these patients with prolongation of the QRS complexes being a sensitive marker in predicting the development of fatal ventricular arrhythmias [12]. Recently, studies testing the importance of fQRS in predicting ventricular arrhythmias and sudden cardiac death in a variety of cardiac diseases have been published. [16–20] Most of these studies enrolled patients with ischemic heart disease [21]. Fewer reports were published about the importance of QRS fragmentation in patients with congenital heart disease especially patients with repaired

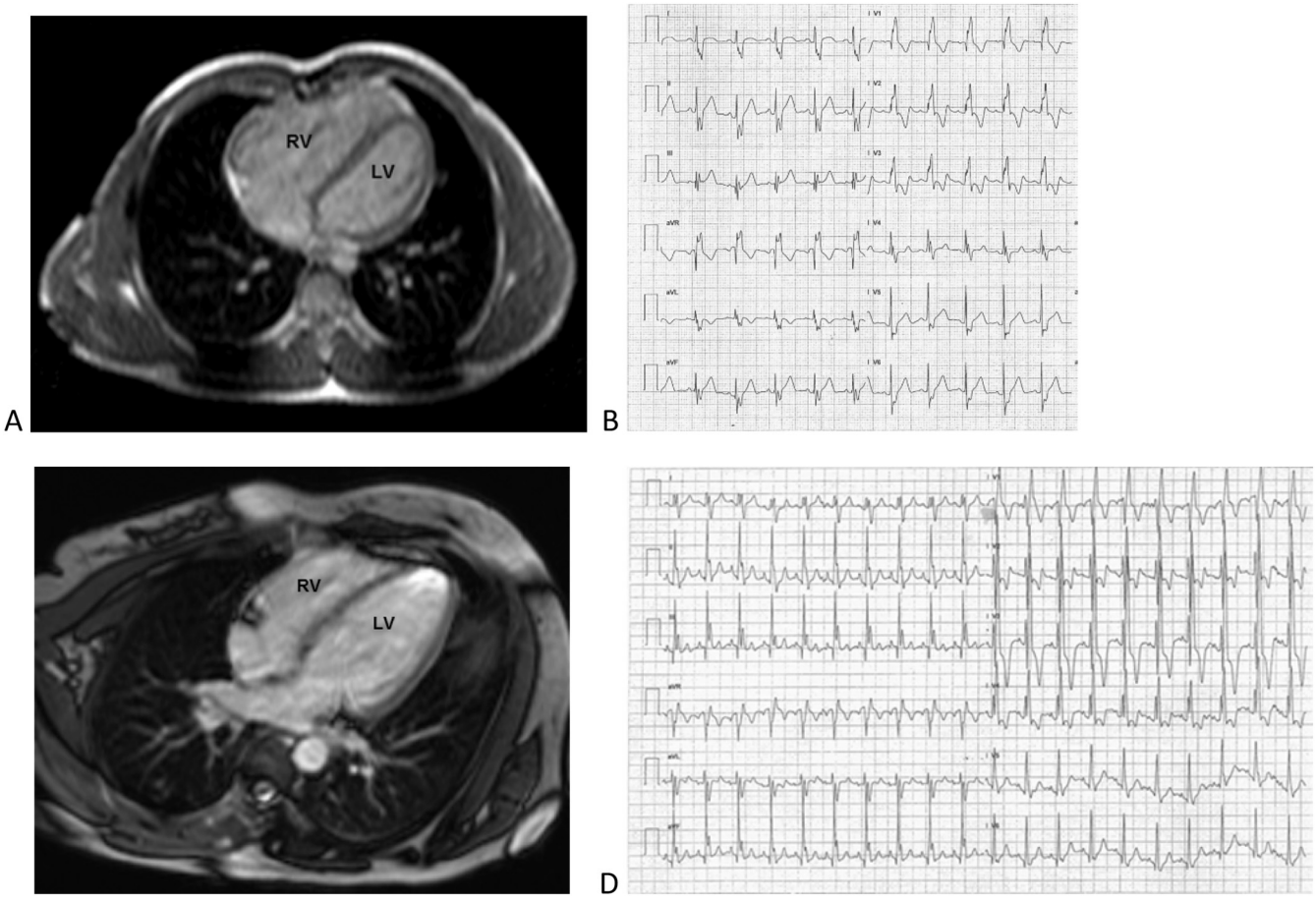

Fig. 1. Cardiac MRI and electrocardiogram of 2 patients who had underwent TOF repair showing a dilated right ventricle (A) in a patient with fQRS (B) and a non-dilated right ventricle (C) in another with narrow non-fragmented QRS (D).

Table 2
MRI findings of the study population.

	Patients with fQRS (n = 21)	Patients without fQRS (n = 9)	*p* value
QRS duration	138 ± 18	119 ± 16	0.01
Indexed RV end-diastolic volume, ml/m^2	174 ± 36	111 ± 15	0.01
Indexed RV end-systolic volume, ml/m^2	86 ± 29	50 ± 13	0.001
Indexed RV stroke volume, ml/min/m^2	87 ± 14	61 ± 12	0.001
RV ejection fraction, %	51 ± 8	55 ± 9	0.2
Indexed LV end-diastolic volume, ml/m^2	92 ± 17	82 ± 16	0.1
Indexed LV end-systolic volume, ml/m^2	41 ± 10	42 ± 16	0.9
Indexed LV stroke volume, ml/min/m^2	51 ± 8	50 ± 10	0.7
LV ejection fraction, %	55 ± 4	58 ± 5	0.1
Indexed RVEDVI/ LVEDVI	1.9 ± 0.3	1.4 ± 0.4	0.002
Pulmonary regurgitant fraction, %	46 ± 9	28 ± 19	0.02

Data are presented as mean ± SD. Abbreviations: LV; left ventricle, RV; right ventricle, RVEDVi/LVEDVi; indexed right ventricular end diastolic volume/left ventricular end diastolic volume.

TOF and to a lesser extent those with other congenital anomalies [22,23]. Park et al., studied the association of the fQRS with both the severity of Ebstein's anomaly as well as with the development of arrhythmias in 51 consecutive adult patients (> 18 years). About two thirds of their enrolled patients showed fQRS on surface electrocardiogram, had worse functional class, higher Ebstein severity scores, larger atrialized RV areas, and more arrhythmic events as compared to those showing no fragmentation of the QRS. The fQRS complexes were seen more commonly, unlike patients with repaired TOF, in the inferior leads [24]. Similar findings were also documented in a study conducted to assess the association between the QRS fragmentation and severity of hemodynamic abnormalities in patients (40% were < 18 years) with Ebstein's anomaly. The QRS duration in this study correlated positively with RV end diastolic volumes while inversely with the RV ejection fraction. fQRS-detected in 70% of the enrolled patients- predicted greater hemodynamic derangements among these patients [25].

Table 3
Correlation of the fQRS extent and anterior fQRS with the right heart hemodynamics.

	fQRS extent		fQRS in the anterior chest leads	
Variable	r	p	r	p
RVEDVi (ml/m^2)	0.8	< 0.001	0.4	0.02
RVESVi (ml/m^2)	0.7	< 0.001	0.3	0.03
RVSVi (ml/min/m^2)	0.6	< 0.001	0.1	0.3
RV ejection fraction (%)	−0.4	0.018	−0.2	0.2
Pulmonary regurgitant fraction, %	0.5	0.004	0.2	0.1

Abbreviations: RV; right ventricle, RVEDVi; indexed right ventricular end diastolic volume, RVESVi; indexed right ventricular end systolic volume, RVSVi; indexed right ventricular stroke volume.

In their study designed to test whether the presence of fQRS complexes correlates with the presence of RV fibrosis as assessed by late gadolinium enhancement in 37 adults with repaired TOF, Park et al., found that the presence of fQRS was associated with lower RV ejection fraction, more RV fibrosis, and larger RV volumes. They enrolled, however, only adults (defined in the study as those > 15 years) and fragmentation in their study was mainly detected in the right and mid precordial leads [10]. Schanmugam et al. found that 80% of operated TOF patients showed fQRS that correlated with the RV volumes and ejection fraction. Such association was more significant in patients with fragmentation seen in the anterior leads while fQRS in the inferior leads predicted the presence of RV outflow tract aneurysms [26]. A recent multi-center registry showed that fQRS is a predictor of sudden cardiac death in a large cohort of adult patients with congenital heart disease predominantly in patients with repaired TOF [23].

Cardiac MRI is considered nowadays to be a very useful and accurate method for the assessment of the RV volumes, function, as well as the PR fraction in patients with repaired TOF [27,28]. Some factors, however, may limit its use especially in developing countries where MRI studies are very expensive. In addition to claustrophobia (especially among children and adolescents), cardiac MRI is not available in every center managing patients with congenital heart disease along the country. [29] Since fragmentation of the QRS complexes is believed to reflect a delayed conduction secondary to impaired RV function and fibrosis in patients with repaired TOF, we think that the presence of fQRS, its extent, as well as the QRS duration might be a useful, available, non-expensive method reflecting significant hemodynamic abnormalities in patients with repaired TOF and might be used routinely as a bed side clinical marker for follow-up of patients attending regularly the outpatients clinics.

The present study had the following limitations: (1) due to the retrospective design of the study, some other important variables and parameters as the operative details were not included in the statistical analysis and (2) due to the limited number of the enrolled patients, we cannot conclude that our findings might be used as an indication for re-intervention but rather guiding the clinicians when the clinical and echocardiographic findings are discordant. Studies comprising a larger number of patients would be of value to validate the fQRS cutoff point.

5. Conclusion

fQRS is a common finding in repaired TOF patients. fQRS extent on surface electrocardiogram predicts both significant right ventricular dilation and pulmonary regurgitation.

Abbreviations

fQRS	fragmented QRS
TOF	tetralogy of Fallot
MRI	magnetic resonance imaging
ROC	Receiver operating characteristic
RV	right ventricular
RVEDVi	indexed right ventricular end diastolic volume
PR	pulmonary regurgitation

Author Contribution

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Data analysis and interpretation: Ahmed El-Damaty, Heba El-Deeb.
Statistics: Mohamed Eshra.
Drafted the manuscript: Heba Farouk, Ahmed El-Boraey.
Critically revised the manuscript: Khalid Sorour, Heba Farouk.
Approval of the manuscript: All authors.

Conflict of Interest

All authors have no conflict of interest to declare.

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