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Pulmonary regurgitation is a powerful factor influencing QRS duration in patients after surgical repair of tetralogy of Fallot

A Magnetic Resonance Imaging (MRI) study

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Summary *Aims* QRS prolongation is a negative prognostic factor for the development of ventricular arrhythmia after repair of tetralogy of Fallot (TOF). In this MRI study, we performed a multivariate analysis to determine the influence of volumetric and functional parameters as well as time factors on QRS duration. *Methods and results* Sixty-seven patients after surgical repair of TOF were studied using a 1.5T MRI. Measurement of the ventricles was performed with a multislice-multiphase sequence. Left and right ventricular volumes, ejection fractions (EF) and myocardial masses were determined. Pulmonary regurgitant fraction (PRF) was quantified by velocity encoded flow measurement in the main pulmonary artery. Maximum QRS duration was taken from a 12-channel ECG. Mean maximum QRS duration was 132 ms (±29 ms). Mean PRF was 29.2% (±13.4%). QRS duration correlated significantly with PRF ($r = 0.49$; $p < 0.01$; $n = 54$) and with right ventricular enddiastolic volume index (RVEDVI) ($r = 0.29$; $p < 0.05$; $n = 67$). Multivariate analysis revealed that the combination of PRF, postoperative period, age at surgical repair, and left ventricular (LV) enddiastolic volume are correlated with QRS prolongation. *Conclusion* – In patients after repair of TOF, pulmonary regurgitation is related to QRS prolongation. Furthermore, even LV size plays a role in the enlargement of the QRS complex.

Key words Cardiac MRI – QRS duration – tetralogy of Fallot – pulmonary regurgitation – arrhythmia

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease beyond infancy with a prevalence of 0.26–0.8 per 1000 live births [1]. "Corrective" intracardiac repair has been performed for over four decades with good results and most patients reach adulthood [2, 3]. Using current surgical techniques, pulmonary regurgitation and ECG changes secondary to right bundle branch block are quite common [4–6]. Previous studies have demonstrated that QRS prolongation is associated with an increased risk of malignant ventricular arrhythmia and sudden cardiac death [7, 8]. In univariate analyses, QRS duration correlates significantly with biventricular volumes and masses, hemodynamic parameters like pulmonary regurgitation and time factors [9, 10].

In our opinion genesis of arrhythmia is a multifactorial process. Hence, the aim of this study was to use the manifold abilities of magnetic resonance imaging in order to assess volumetric and hemodynamic data [11–13], include important time factors,

and to perform a multivariate analysis with a large number of patients to see which combination of parameters is correlated with QRS prolongation.

In addition, the role of interventricular interaction between the left and the right ventricle has not been systemically evaluated in these patients. Thus, another aim of this study was to evaluate the effect of right ventricular (RV) overload on the functional and volumetric change of the left ventricle and the relation to QRS duration.

Methods

Patient population

This study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients or parents had given their informed consent before the examination. We examined 67 selected patients, 45 male and 22 female, who all underwent corrective surgery of tetralogy of Fallot and came for routine follow-up examinations to regular outpatient visits. These patients were selected on the basis that they had no pacemaker or cardioverter/defibrillator implanted and were able to stay in the MR-scanner for at least half an hour. In 39 patients, surgery was performed by using a transannular patch for enlargement of right ventricular outflow tract (RVOT), whereas in 28 patients a different method was used to preserve the annular ring. Twenty-three patients underwent one and 8 patients underwent two re-operations. Median age at surgical repair was 2.1 years (range 0.2–51.5 years). A prior palliative shunt procedure had been performed in 11 patients.

Median age at MRI study was 14.1 years (range 3.8–54.2 years) and time between surgical repair and MRI study was 10 years (1.7–45 years).

Results of the MRI studies were compared to control groups taken from literature [14, 15]. These control groups consisted of infants, children and adolescents without any cardiovascular diseases.

Measurement of cardiac volumes and masses

All MR examinations were performed on a 1.5 Tesla Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands) with a 4-channel phased-array coil.

For assessment of endsystolic and enddiastolic volumes of both ventricles, a multislice-multiphase sequence in a short axis view was performed. This provides multiple slices that cover the entire volume of both ventricles. Each slice is recorded in multiple phases of the cardiac cycle. By manually tracing endocardial contours of the enddiastolic and endsystolic phases of each slice, it is possible to calculate endsystolic and enddiastolic volumes as well as myocardial masses of both ventricles [16].

Short axis views with ECG-triggering with breath-hold technique were performed in 28 patients who could hold their breath for 19 s maximum. A steady state free precession (SSFP) sequence was used with a minimal, heart rate depending echotime and repetition time (average TE was 1.5 ms; average TR was 3.0 ms). Flip angle was 50°, matrix size was 128×256. Slice thickness was chosen depending on heart size with a minimum of 12 and a maximum of 20 slices covering the entire volume from apex to the level of the mitral valve (range: 4–10 mm).

Short axis views with ECG triggering in free-breathing had to be performed in 39 patients. In these patients, the navigator technique was combined with a CINE gradient echo (GE) sequence with the following parameters: TE = 2.0 ms, TR = 5.6 ms, Flip angle = 25°, matrix size and number of slices were the same as in breath-hold measurements (range: 4–10 mm).

All obtained volumes and masses were related to the body surface.

MR-flow measurement

MR phase shift velocity mapping was performed with a flow-sensitive gradient echo sequence. This method can calculate flow velocity and flow volume by velocity depending phase-shift of the moving spins [17, 18]. A perpendicular orientation ("through plane") directly cranial to the pulmonary valve (Fig. 1) was used to quantify flow velocity and flow volumes. Encoded velocity (Venc) was 200 cm/s. In case of aliasing, we increased Venc in steps of 50 m/s. The acquisition was performed during free breathing using a sequence with retrospective gating to cover the whole heart cycle (TE = 5.2–5.5 ms, TR = 20 ms, flip angle 30°).

QRS duration

QRS duration was obtained by a conventional 12-channel surface ECG (Marquette-Hellige, Cardio Smart) that was performed within 1 month prior to or after MR examination. QRS analyses were made during the routine cardiac examination. In all patients undergoing ambulatory cardiac examination, ECG was obtained in 50 and 25 mm paper speed in the lead II. In addition, all time intervals were automatically measured by the ECG recorder and printed out simultaneously to the paper prints. QRS dura-

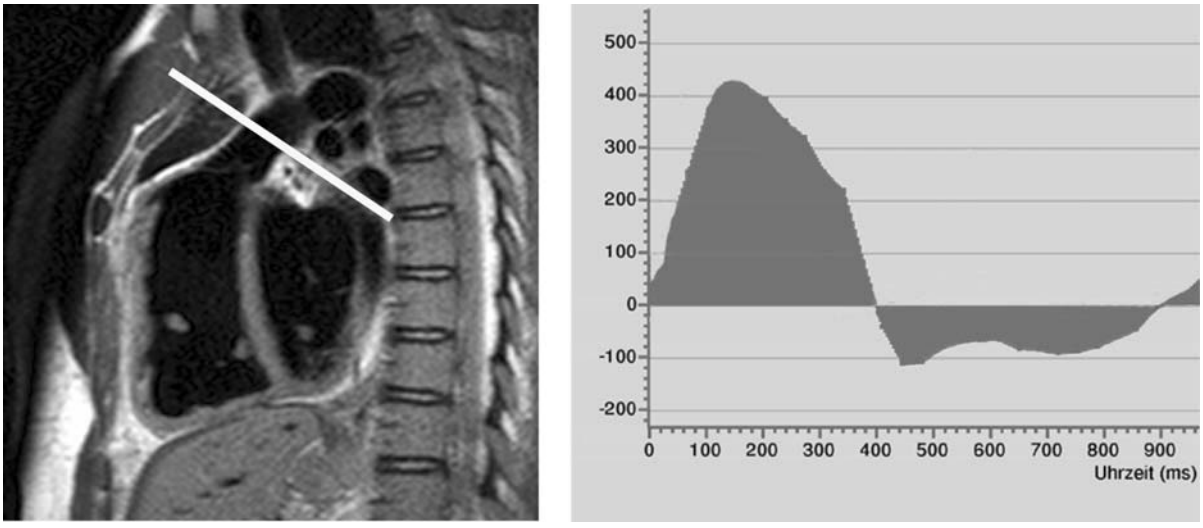

Fig. 1 Orientation of "through plane" flow measurement in the pulmonary artery (left) and the resulting flow diagram (right). Calculation of area under the curve (right) provides systolic flow volume and regurgitant volume of the main pulmonary

tion was evaluated without knowledge of the results of the MR analysis.

Statistical analysis

The statistical software was SPSS 10.0. Data were expressed as mean ± SD or median and range when not normally distributed. The nonparametric Mann-Whitney test was used to assess the difference between two unpaired groups. For analysis of correlations, the nonparametric Spearman rank correlation was performed. A probability value of $p < 0.05$ was considered to indicate significance. According to the results of the univariate analysis, multivariate regression analysis with stepwise backward selection was performed to assess the independent influence on the QRS duration [19].

The statistical analysis was performed by a biomedical statistician.

Results

MR-volumetry and MR flow measurement

We acquired volumetric data in all 67 patients. The nonparametric Mann-Whitney test showed no difference between breath-hold and navigator technique in any of the obtained parameters. Results of calculation of ventricular masses, ventricular volumes and ventricular ejection fractions are shown in Table 1. In the Fallot-group, the right ($p = < 0.01$) and left ($p = < 0.01$) ventricular ejection fractions were significantly lower when compared to the control group (Table 1). In the TOF group, right ventricular ejection fraction correlated significantly with left ventricular ejection fraction ($p < 0.001$, $r = 0.54$, Fig. 2). As expected, the right ventricular enddiastolic myocardial mass index (RV-MMI-ED) among the TOF group was significantly higher when compared

Table 1 Comparison of the results of MR multislice-multiphase volumetry with corresponding values of two control groups. Data are given as mean value ± standard deviation. RV-MMI-ED, RV-EF and LV-EF show significant differences compared to the control group

	Control group (n = 75) [a] (n = 12) [b]	Fallot-group n = 67	Significance
RV-MMI-ED g/m^2	26 ± 5 [a]	57.8 ± 32.2	$p < 0.01$
LV-MMI-ED g/m^2	87 ± 12 [a]	75.4 ± 26.1	n.s.
RV-EDVI ml/m^2	75 ± 13 [a]	91.3 ± 31.5	n.s.
LV-EDVI ml/m^2	66 ± 12 [a]	74.0 ± 20.1	n.s.
RV-SVI ml/m^2	46 ± 8 [a]	47.7 ± 13.1	n.s.
LV-SVI ml/m^2	45 ± 8 [a]	40.2 ± 11.2	n.s.
EF-RV %	66 ± 7 [b]	53.4 ± 10.4	$p < 0.01$
EF-LV %	68 ± 9 [b]	55.3 ± 10.6	$p < 0.01$

[a] Data from [15]; [b] data from [14]
All parameters have a normal distribution (David's test)

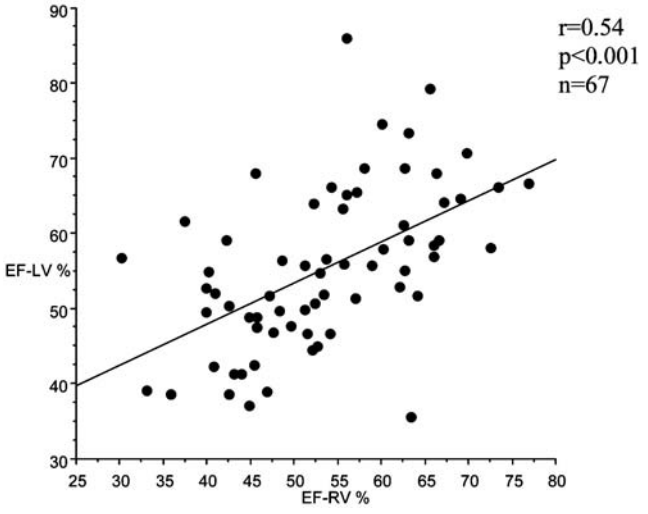

Fig. 2 Regression analysis of right ventricular ejection fraction to left ventricular ejection fraction. Impaired right ventricular function is significantly related to impaired left ventricular function. Correlation is r = 0.54

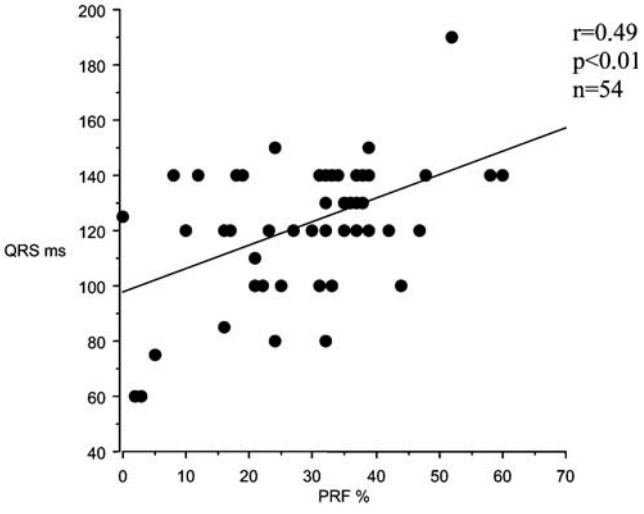

Fig. 3 Regression analysis of QRS duration to pulmonary regurgitation fraction (PRF). Of all acquired parameters PRF shows the highest relation to a prolonged QRS complex. Correlation coefficient is r = 0.49

to controls ($p = < 0.01$, Table 1). Right ventricular enddiastolic volume was slightly increased in the Fallot-group, but without statistical significance due to a high standard deviation (Table 1).

In 13 patients, flow measurement was not performed or could not be evaluated due to compliance problems at the end of the MRI-study (3 pts), insufficient angulation in the "through plane" measurement (6 pts), and flow turbulences (4 pts).

Mean (SD) pulmonary regurgitant fraction (PRF) of the remaining 54 patients was 29.2% (± 13.4%). PRF correlated significantly with right ventricular enddiastolic volume index ($p < 0.01$, $r = 0.45$). No relation was found between right ventricular ejection fraction and PRF (Fig. 5).

There were differences in pulmonary regurgitant fractions corresponding to the surgical method used. Patients with an annular patch had a significantly higher ($p < 0.05$) PRF (39.9 ± 11.6%) than patients in whom no annular patch was used (23.6 ± 11.4%).

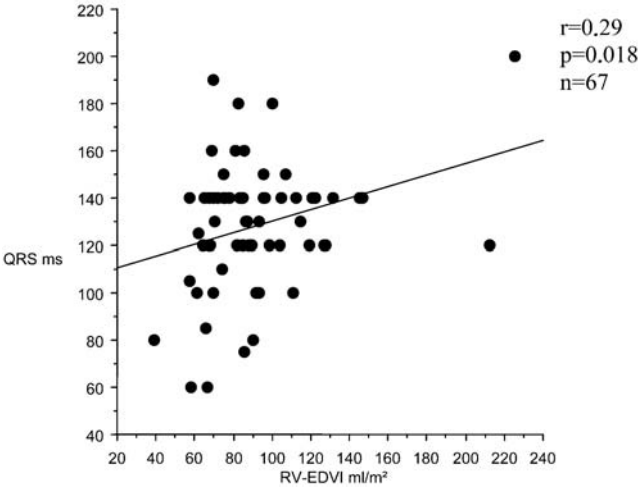

Fig. 4 Regression analysis of QRS duration to right ventricular enddiastolic volume index. Correlation is statistically significant but weak with a correlation coefficient of r = 0.29

QRS duration and its relation to pulmonary regurgitation and right ventricular volume load

Fifty-three of 67 patients (78%) showed a complete right bundle branch block and 8 patients (12%) an incomplete right bundle branch block. Mean (SD) QRS duration was 128.5 ms (± 26.5 ms). The QRS duration correlated significantly with pulmonary regurgitation fraction ($p < 0.01$, $r = 0.49$, Fig. 3) and with right ventricular enddiastolic volume index ($p = 0.018$, $r = 0.29$, Fig. 4). We did not identify an association between right ventricular enddiastolic myocardial mass index and QRS duration. Furthermore, there was no correlation between QRS duration and right ventricular ejection fraction (Fig 5).

Multivariate regression analysis

We performed a multivariate regression analysis with backward selection to determine the main parameters associated with QRS duration. This analysis included all 54 patients with a complete evaluation. As co-variables, ventricular volumes, ventricular

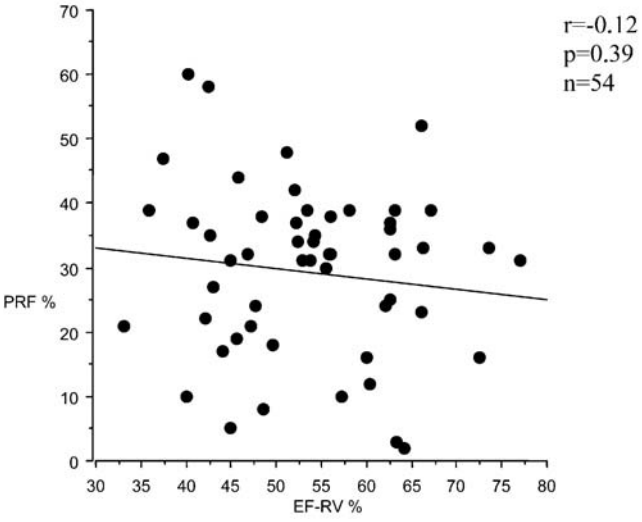

Fig. 5 Regression analysis of pulmonary regurgitation fraction to right ventricular ejection fraction. There is no significant relation betweeb these two parameters

Table 2 Results of the multiple regression analysis with backward selection. The combination of these four parameters has the greatest effect on QRS duration

n = 54	r	p
Pulmonary regurgitation fraction (RF-F)	0.677	0.03
Left ventricular enddiastolic volume index (LV-EDVI)	0.421	0.027
Time since surgical correction (post 1. OP)	0.486	0.077
Age at surgical correction (age 1. OP)	–0.915	0.033

masses, ejection fractions, age at surgery, and postoperative follow-up period were included. Multivariate analysis revealed that pulmonary regurgitation has the most important impact on QRS duration besides age at surgical repair (Table 2). The combination of pulmonary regurgitant fraction (PRF), left ventricular enddiastolic volume index, age at surgical repair and time since surgical correction has the greatest influence on QRS duration.

Discussion

Relation between pulmonary regurgitation and QRS duration

This MRI study demonstrates the impact of pulmonary regurgitation on QRS prolongation in a large number of patients with surgically repaired tetralogy of Fallot. Of all measured volumetric and functional parameters, PRF showed the strongest correlation to QRS duration in the multivariate as well as in the univariate regression analysis.

Although technologic innovations have led to improvements in diagnosis and therapy of cardiac arrhythmia [20, 21], ventricular tachycardia is still one of the most important complications in adults with repaired TOF. QRS prolongation is a major risk factor for ventricular tachycardia. The precise mechanism for QRS prolongation is still unclear. Our study showed that main factors associated with QRS prolongation were the degree of pulmonary regurgitation, postoperative follow-up period, age at surgical repair and enddiastolic left ventricular volume index.

Gatzoulis et al. demonstrated that QRS duration is related to the cardio-thoracic ratio [8]. Abd El Rahman et al., using three-dimensional echocardiography, illustrated a relation between the QRS duration and the right ventricular enddiastolic volume [22], and Helbing et al. showed the correlation between QRS duration and PRF [10]. In the present study, we were able to confirm their findings even though correlations were weaker than in the previous studies. This might be caused by the relative inhomogeneity in this large group of patients. Van Huysduynen et al. showed that pulmonary valve replacement reduces QRS duration and is also related to a reduction of RV end-diastolic volume [9]. Further studies are needed to assess whether replacing the pulmonary valve will also hamper the prolongation of the QRS complex in patients with normal right ventricular size.

The fact that alteration of LV volume has a significant influence on the QRS duration is in accordance of our clinical follow-up observations, indicating not only the occurrence of right ventricular but also left ventricular morbidities such as altered LV function and evidence of left ventricular asynchrony in these patients.

Surprisingly, the time factor age at surgical repair showed an inverse correlation to QRS duration: the younger patients were when surgical correction was performed, the longer QRS duration was. One possible explanation for this finding might be that in most cases there are certain reasons for a very early repair. Severe forms of right ventricular outflow tract obstruction, cyanotic spells, arrhythmia and RV-hypertrophy should influence QRS duration before correction and complications might occur not because of but despite early surgical intervention.

Relation between pulmonary regurgitation and right ventricular size and function

Pulmonary regurgitation is considered to enlarge right ventricular size due to volume overload [23]. In this study, a statistically significant correlation was found between pulmonary regurgitant fraction obtained by MR phase contrast flow measurement (PRF) and right ventricular enddiastolic volume. In contrast, right ventricular ejection fraction did not correlate with pulmonary regurgitation. An MRI study by Rebergen et al. (1993) in patients after TOF repair showed similar results [24]. Obviously, also in Fallot patients, right ventricular enlargement can be compensated in some cases and does not inevitably lead to impairment of right ventricular function. Other studies, however, show a direct relation between pulmonary regurgitation and right ventricular function [14, 22]. A longitudinal study is necessary to clear the influence of time factors.

Interaction between the right and the left ventricle

An important result of this study was the close correlation between the right and left ventricular systolic function. Long-lasting volume overload of the RV due to the PRF seems to impair left ventricular function. This finding can be explained by a displacement of the interventricular septum towards the left ventricle when right ventricular volumes enlarge, and could be seen in seven patients with high-degree pulmonary insufficiency in this study in the multislice-multiphase sequence. Also, other authors point out that impairment of the right ventricular function has an effect on left ventricular and left atrial function [25–27]. Left ventricular dysfunction has been found in older patients who were operated in the initial era of surgical correction of TOF. Other factors such as duration of preoperative pressure overload and degree of preoperative hypoxemia, the magnitude of tissue excision in the right ventricular outflow tract and perfusion methods may also contribute to altered LV function late after TOF-repair. Hence, follow-up examination after correction of TOF has also to be focused on quantitative assessment of left ventricular function and dimensions.

Patients with an annular patch had a significantly higher pulmonary regurgitation fraction than patients in whom a different method, e.g., subvalvular patch or extracardial conduit, was used. Destruction of the annular ring has always a deleterious effect on pulmonary valve function. Our results correspond to those of de Ruijter and co-workers, who found both an increased pulmonary regurgitation and right ventricular impairment in patients in whom an annular patch was used compared to a non-transannular approach [5].

Limitations of the study

This is a cross-sectional study. Further longitudinal assessment of right and left ventricular parameters is needed to seize development of ventricular volumes and function and corresponding influencing factors over years.

Patients with manifest ventricular tachycardia in whom a cardioverter/defibrillator was implanted were excluded from the study due to contraindication for MRI. Thus, it was not possible to correlate the obtained parameters with the most interesting subgroup of patients within the meanings of this study.

We did not perform "late enhancement" sequences to detect myocardial scarring. This might have been a further interesting parameter for the multivariate analysis, since it is known that scarring leads to ECG changes as well as to severe arrhythmias [28].

Due to patient limitations, we performed volumetric measurements with breath-hold and navigator technique. Statistical analysis, however, showed no difference in the obtained data between these two methods.

Conclusions

Pulmonary regurgitation is an important factor influencing QRS prolongation in patients after surgical repair of TOF even without enlargement of the right ventricle. This may increase the risk of malignant ventricular arrhythmia and sudden cardiac death. Whether early pulmonary valve replacement even with preserved right ventricular function should be performed needs further elucidation.

Furthermore, there is an association between pulmonary regurgitation and left ventricular dysfunction. The precise mechanism remains unclear.

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