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Pulmonary valve replacement in tetralogy of Fallot improves the repolarization

Bart Hooft van Huysduynen [a], Ivo R. Henkens [a], Cees A. Swenne [a,*], Thomas Oosterhof [b], Harmen H.M. Draisma [b], Arie C. Maan [b], Mark G. Hazekamp [c], Albert de Roos [d], Martin J. Schalij [d], Ernst E. van der Wall [d], Hubert W. Vliegen [d]

[a] *Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands*
[b] *Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands*
[c] *Department of Paediatric Surgery, Leiden University Medical Center, The Netherlands*
[d] *Department of Radiology, Leiden University Medical Center, The Netherlands*

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Abstract

Objective: To assess the effect of pulmonary valve replacement (PVR) on the repolarization of patients with tetralogy of Fallot.
Background: Pulmonary valve regurgitation may cause right ventricular failure in adult patients with Fallot's tetralogy. In these patients, prolonged depolarization and disturbed repolarization are associated with ventricular arrhythmias and sudden cardiac death.
Methods: Thirty Fallot patients (age 32±9 years, 19 male) eligible for PVR were studied with cardiac magnetic resonance imaging (CMR) before and 6 months after PVR. Electrocardiograms obtained during initial and follow-up CMR were analyzed and occurrence of ventricular arrhythmias was studied.
Results: Right ventricular end-diastolic volume (RV EDV) decreased from 322±87 to 215±57 ml after PVR ($P<0.0001$). The spatial QRS-T angle normalized from 117±34 to 100±35°, $P=0.0004$ (normal angle <105°). QT dispersion and T-wave complexity did not change significantly. T-wave amplitude decreased from 376±121 to 329±100 μV ($P=0.01$). T-wave area decreased from 43±15 to 38±13 μV s ($P=0.02$). Decreases in T-wave amplitude and area were most prominent in the right precordial leads overlying the RV. Three patients had sustained ventricular arrhythmias and one patient died suddenly. These patients had a QRS duration >160 ms. No severe ventricular arrhythmias were found in patients with a RV EDV <220 ml, QRS-T angle <100°, QT dispersion <60 ms or T-wave complexity <0.30.
Conclusion: Normal repolarization indices may be associated with the absence of severe ventricular arrhythmias. PVR in Fallot patients with dilated right ventricles has a beneficial effect on electrocardiographic indices of repolarization heterogeneity.

Keywords: Tetralogy of Fallot; Pulmonary valve replacement; Repolarization; Ventricular arrhythmias

1. Introduction

The prognosis of patients with a tetralogy of Fallot has improved dramatically after the introduction of complete surgical repair at young age. However, in adult Fallot patients, residual pulmonary regurgitation may cause right ventricular failure [1,2]. These patients are prone to develop ventricular arrhythmias and/or sudden cardiac death. This risk increases significantly when QRS duration is larger than 180 ms [3].

In addition to prolonged depolarization, disturbed repolarization may play a role in arrhythmogenesis. Repolarization disturbances are widely recognized as contributors to arrhythmias [4,5]. QT dispersion has been shown to refine

Abbreviations: PVR, pulmonary valve replacement; CMR, cardiac magnetic resonance imaging; RV, right ventricle; EDV, end-diastolic volume; ECG, electrocardiogram.

* Corresponding author. Tel.: +31 71 526 1972; fax: +31 84 221 8904.
E-mail address: c.a.swenne@lumc.nl (C.A. Swenne).

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risk stratification for arrhythmias in Fallot patients [6] and several other electrocardiographic indices have been suggested to assess various characteristics of the repolarization. The spatial angle between the QRS and T axes is an electrocardiographic index that comprises both depolarization and repolarization and has prognostic value in normal subjects and selected patient groups [7–9]. T-wave complexity is related to repolarization heterogeneity, which is a pro-arrhythmogenic factor [10]. T-wave amplitude and T-wave area are also measures of repolarization heterogeneity [11,12]. We have previously demonstrated that pulmonary valve replacement (PVR) reduces QRS duration and right ventricular end-diastolic volume [13]. In the present study we tested whether PVR has beneficial effects on the repolarization and whether electrocardiographic indices of the repolarization are related to ventricular arrhythmias.

2. Methods

Thirty Fallot patients (19 male/11 female) were evaluated. The age of the patients at the initial surgical procedure was 5.7±3.1 years. In 15 patients a transannular patch had been applied during the initial procedure. Age at PVR was 31.8± 9.1 years. Indications for PVR were moderate to severe pulmonary regurgitation in combination with right ventricular dilatation. In addition to PVR, tricuspid regurgitation was corrected in 6 patients and residual ventricular septal defects were closed in 4 patients.

2.1. CMR

CMR was performed on a 1.5 Tesla scanner (NT15 Gyroscan, Philips, Best). Briefly, short axis images of the heart were acquired with a multiphase, ECG-triggered, multishot echoplanar gradient echo technique. Images were acquired during breath holds with a slice thickness of 10 mm and a 0.8 to 1.0 section gap. The flip angle was 30° and echo time was 5 to 10 ms. Eighteen to 25 frames/cycle resulted in a temporal resolution of 22 to 35 ms [14].

2.2. ECG analysis

ECG were obtained before the initial CMR and during the follow-up procedure 6 months after surgery. The routinely-made 10-s ECGs, digitally stored (sampling rate 500 Hz, resolution 5 μV/bit) in our hospital ECG database, were imported into LEADS, a MATLAB (The MathWorks, Natick, USA) computer program that was developed for research-oriented ECG analysis [15]. The ECGs were randomly renamed to assure blinded analysis. After QRS detection and fiducial point determination, the QRS-T complexes in the 10-s ECG were averaged in order to minimize noise. Besides the standard 12-lead ECG representation of the averaged beat, a vectorcardiographic X–Y–Z representation and the magnitude of the heart vector were computed using the inverse Dower matrix [16]. Onset and end of QRS were computed in the vector magnitude signal by a threshold procedure and by determining the minimal vector size in between the QRS complex and the T wave, respectively. The default end-of-QRS instant was then manually adjusted to meet the Minnesota criteria [17] for end-of-QRS determination (being the last J point in any of the ECG leads, while in leads with two candidate J points the earliest J point is taken). End-of-T instant was set automatically in every lead at the intercept of the steepest tangent to the terminal limb of the T wave with the baseline. QT dispersion was calculated as the longest minus the shortest QT interval in any lead. The spatial angle between the mean electrical axes of the QRS complex and the T wave was computed from the vectorcardiogram [18]. T-wave complexity was derived by means of singular value decomposition of the 8 independent ECG leads I, II and V1–V6 [10,19]. T-wave complexity was calculated by dividing the square root of the summed squared singular values 2–8 by the first singular value. Finally, the absolute T-wave amplitude and T-wave area were computed and averaged from the ECG leads.

2.3. Ventricular arrhythmias

The occurrence of ventricular arrhythmias and the relation to ECG and CMR measurements were studied. Sustained ventricular tachycardias (lasting >30 s or causing symptoms) and sudden cardiac death were categorized as severe ventricular arrhythmias. Postoperative data were used for this analysis, except in one patient that suffered from arrhythmias before PVR only, from whom the preoperative measurements were used.

2.4. Statistical analysis

All data are reported as mean±standard deviation. Two-sided paired and unpaired Student's *t*-tests were used wherever appropriate. To correct for multiple testing, the significance level of the *P*-values was determined according to the false discovery rate method [20].

3. Results

3.1. Changes in right ventricular volume and QRS duration

Surgery had a positive effect on the right ventricular end-diastolic volume (RV EDV) which decreased from 322± 87 ml before surgery to 215±57 ml after surgery ($P<0.0001$). QRS duration decreased from 158±34 ms to 153± 32 ms ($P=0.002$).

3.2. Changes in repolarization

The spatial angle between QRS and T axes decreased significantly from a preoperative value of 117±34° to 100± 35° postoperatively ($P=0.0004$). QT dispersion did not change significantly, with a preoperative value of 78±27 ms and a postoperative value of 85±30 ms ($P=0.19$). Pre- and

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postoperative values of T-wave complexity were 0.49±0.22 and 0.44±0.21, respectively (P=0.16). T-wave amplitude decreased significantly from 376±121 μV to 329±100 μV (P=0.01). T-wave area decreased significantly from 43±15 μV s to 38±13 μV s (P=0.02).

These results and the cut-off values for significance according to the false discovery rate method [20] are summarized in Table 1. Changes in T-wave amplitude and area for all 12 leads are shown in Fig. 1a and b. Note that changes are most pronounced in the leads overlying the right ventricle.

3.3. Relations between right ventricular volume and QRS duration

The average of the pre- and postoperative QRS duration related linearly to the average RV EDV (R=0.58, P=0.003). Changes in QRS duration correlated with changes in RV EDV (R=0.45, P=0.03).

3.4. Relations between QRS duration and repolarization indices

Average QRS durations correlated with the spatial angle (R=0.70, P<0.0001), QT dispersion (R=0.62, P=0.0003), T-wave complexity (R=0.52, P=0.003) and T-wave area (R=0.43, P=0.02).

3.5. Ventricular arrhythmias

Follow-up was available up to 5.5±1.9 years after PVR. Three patients had sustained ventricular tachycardias and one patient died suddenly. This patient died 18 months post-PVR. The cause of death was uncertain, but the patient was hemodynamically stable and had no co-morbidity, making arrhythmia the most probable cause of death. Two of the patients had pre- as well as postoperative ventricular tachycardias and (pre)syncope, for which automatic internal cardiac defibrillators were implanted postoperatively. The last patient had preoperative repetitive sustained ventricular tachycardias, requiring cardioversion and hospitalization. After PVR this patient remained free of serious arrhythmias.

All patients with severe ventricular arrhythmias had a QRS duration >160 ms. Among the 26 patients without severe ventricular tachycardias, 10 patients also had a postoperative QRS duration >160 ms. The group size was too small to analyze whether the combination of QRS duration and a repolarization measure or RV EDV could improve the specificity. However, no severe arrhythmias were found in patients with QRS-T angle <100°, QT dispersion <60 ms, T-wave complexity <0.30 or a RV EDV <220 ml.

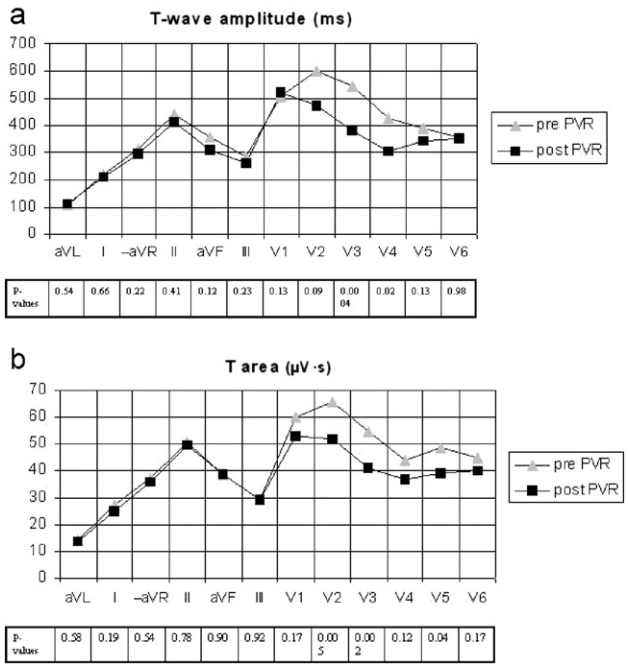

Fig. 1. a. T-wave amplitude pre- and post-PVR for all leads. Right precordial leads show the largest changes in T-wave amplitude. b. T-wave area pre- and post-PVR for all leads. The changes in T-wave area were most significant in leads V2 and V3, leads overlying the right ventricle.

Table 1
Values of end-diastolic volumes of the right ventricle, QRS duration and electrocardiographic repolarization indices, measured before and after pulmonary valve replacement

N=30	Pre-PVR	Post-PVR	P-values	Significance cut-off value
RV EDV (ml)	322±87	215±57	<0.0001 [a]	<0.007
QRS duration (ms)	158±34	153±32	0.002 [a]	<0.021
QRS-T angle (°)	117±34	100±35	0.0004 [a]	<0.014
QT dispersion (ms)	78±27	85±30	0.19	<0.05
T-wave complexity	0.49±0.22	0.44±0.21	0.16	<0.04
T-wave amplitude (μV)	376±121	329±100	0.01 [a]	<0.029
T-wave area (μV s)	43±15	38±13	0.02 [a]	<0.036

PVR = pulmonary valve replacement; RV EDV = right ventricular end-diastolic volume.

[a] Significant P-values after false discovery rate correction, *i.e.*, below the cut-off values provided in the last column.

4. Discussion

In this study we assessed the effects of pulmonary valve replacement in Fallot patients with dilated right ventricles on electrocardiographic indices of repolarization heterogeneity. We found that PVR alters the repolarization process. PVR results in normalization of the spatial QRS-T angle and reduction of T-wave amplitude and area. Furthermore, we analyzed the occurrence of ventricular arrhythmias in these patients. Although the findings are limited by the small number of patients with arrhythmias, the optimal discriminator of patients with severe arrhythmias was a QRS duration >160 ms. No severe arrhythmias were found in patients with RV EDV <220 ml, QRS-T angle <100°, QT dispersion <60 ms or T-wave complexity <0.30.

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In previous studies in Fallot patients late after initial surgical correction, repolarization heterogeneity was implicated as a potential mechanism for arrhythmias [6,21,22]. In the current study, we used a dedicated computer program to enhance the reproducibility and accuracy of ECG analysis. This allowed concomitant calculation of electrocardiographic repolarization indices like the QRS-T angle, T-wave complexity, T-wave amplitude and T-wave area.

4.1. Spatial QRS-T angle

The spatial QRS-T angle comprises properties of both depolarization and repolarization and has prognostic capabilities. Kardys et al. showed that a wide QRS-T angle predicted cardiac death in a general population of more than 6000 men and women older than 55 years [7]. After adjustment for cardiovascular risk factors, hazard ratios of abnormal QRS-T angles for sudden death were 4.6 (CI 2.5–8.5). Zabel et al. showed that the QRS-T angle contributed to the risk stratification of patients after myocardial infarction, independent of classical risk factors [8]. Other studies underscored the prognostic value of the spatial QRS-T angle and the orientation of the T axis [9,23,24].

The large QRS-T spatial angle in our study is related to the right bundle branch block present in most Fallot patients. Subsequently, their right ventricles are mostly activated by the relatively slow myocardial cell-to-cell conduction instead of the specialized conduction system. Consequently, the order of repolarization is no longer predominated by primary factors (differences in action potential duration); instead, secondary factors (the depolarization order resulting from slow cell-to-cell conduction) predominate the repolarization order. The resultant similar order of de- and repolarization in combination with the opposed direction of the de- and repolarizing currents cause large differences in the orientation of the QRS and T vectors, *i.e.*, a wide QRS-T angle.

An increased QRS-T angle may also be caused by a disturbance in the distribution of myocardial action potential durations. Previous studies showed that increased wall stress and hypertrophy have a direct influence on action potential duration [25,26]. In dogs, volume overload leading to eccentric hypertrophy caused interventricular differences in action potential durations and an increased sensitivity to arrhythmogenic medication [26].

Normal values for the QRS-T angle were defined as being smaller than 105° [7,27]. The QRS-T angle in our Fallot patients decreased from 117±34° to 100±35°, denoting a transition from a value outside the normal range to a smaller value within the normal range after PVR. We observed no severe arrhythmias in patients with a QRS-T angle <100°.

4.2. QT dispersion

Previously, Gatzoulis et al. used QT dispersion to refine risk stratification of Fallot patients with a wide QRS complex [6]. All patients with clinically relevant arrhythmias appeared to have a QRS duration of more than 180 ms and a QT dispersion of more than 60 ms. In our patient group the combination of QRS duration and QT dispersion could not be assessed as only four patients had severe arrhythmias. However, we found no ventricular tachycardias in patients with QT dispersion <60 ms. Furthermore, our group of Fallot patients with large RVs had relatively high pre- and postoperative QT dispersion values. Surprisingly, we found no change in QT dispersion after PVR, despite the relatively large right ventricular volume reduction in most patients. This finding is in agreement with the study of Helbing et al. [28], who did not find a correlation between right ventricular volume and QT dispersion in a group of Fallot patients and normal subjects.

Initially, QT dispersion was proposed as a measure of local repolarization differences [29]. However, QT dispersion is strongly dependent on the orientation of the T vector, which represents the summed electromotive forces [30]. The QT interval is shortest in the ECG lead that is perpendicular to the orientation of the last part of the T vector. This shortest QT interval has a large influence on the magnitude of the QT dispersion, calculated as the longest minus the shortest QT interval in any lead. Thus, QT dispersion depends on projections of the *global* T vector on the different lead vectors and does not necessarily represent *local* repolarization differences [30].

4.3. T-wave complexity

T-wave complexity has been shown to yield independent prognostic information in patients with cardiovascular disease [31]. In patients with arrhythmogenic right ventricular dysplasia, higher T-wave complexity is associated with ventricular arrhythmias [32]. Additionally, T-wave complexity is increased in patients with primary repolarization disturbances and can be used to discriminate these patients from healthy individuals [10]. We calculated T-wave complexity by means of singular value decomposition, which is an algebraic algorithm used to characterize the T waves of the eight independent ECG leads I, II and V1–V6. If the eight T waves can be described by only the first few singular values, these T waves are relatively simple as they can be composed from a limited set of basic patterns. The more singular values are needed to accurately describe the T waves, the more complex the T waves. We observed a nonsignificant reduction in T-wave complexity in our relatively small study, which can be interpreted as a trend in the direction of a more normal repolarization. Additionally, patients with a T-wave complexity <0.30 had no severe arrhythmias.

4.4. T-wave amplitude and area

T-wave amplitude and area were related to repolarization heterogeneity in previous studies. In rabbit hearts, T-wave area was strongly correlated to repolarization heterogeneity

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as measured by 7 monophasic action potential electrodes [33]. T-wave amplitude and area were also related to repolarization heterogeneity, measured as the difference in repolarization time between the left and right ventricle in canine hearts [12]. Experiments in preparations of the left ventricular wall mimicked Long QT 1 syndrome and increased repolarization heterogeneity, which was reflected in an increased T-wave amplitude and area [34]. Mathematical simulation studies confirmed these experimental findings [11,35].

In our Fallot patients we measured a decrease in T-wave amplitude and T-wave area after PVR, suggesting a decreased repolarization heterogeneity. The changes in T-wave area and amplitude were more explicit in leads V2 and V3 than in the other ECG leads (Fig. 1a and b). Leads V2 and V3 may display more electrical activity from the right ventricle than the other standard ECG leads due to their proximity to the right ventricle [36,37], underscoring that the observed changes in T-wave amplitude and area were indeed related to changes in the right ventricle. The observed changes in T-wave amplitude and T-wave area suggest decreased repolarization heterogeneity in the right ventricle due to PVR.

4.5. Arrhythmias

The patients with severe arrhythmias had a QRS duration longer than 160 ms. Gatzoulis et al. found that every Fallot patient with symptomatic ventricular arrhythmias had a QRS duration longer than 180 ms [3]. Our study suggests that this criterion should be lowered to ascertain identification of patients with ventricular arrhythmias. The patient who died suddenly had a QRS duration of 164 ms.

Our study was too small to combine electrocardiographic indices of the repolarization with the QRS duration to improve specificity. However, patients with either a QRS-T angle lower than 100°, a QT dispersion lower than 60 ms, a T-wave complexity lower than 0.30 or a RV EDV lower than 220 ml had no severe arrhythmias.

4.6. Limitations

The number of patients with arrhythmias is obviously too small to draw solid conclusions regarding the predictive value of arrhythmias. However, the observed association between normal repolarization indices and the absence of severe ventricular arrhythmias in this relatively small group has a physiological basis. Repolarization heterogeneity may form the substrate for ventricular arrhythmias: as irregular repolarization sequences facilitate the formation of functional barriers, an adversely timed extrastimulus may initiate a re-entry arrhythmia [5].

Furthermore, most electrocardiographic repolarization indices are related to the QRS duration, which in turn is related to RV EDV. This interdependency can be seen as a limitation towards the additional value of repolarization analysis. However, mechanical factors, depolarization and repolarization may all play an intricate role in the process of arrhythmogenesis. A previous study in Fallot patients after total surgical correction registered body surface maps that showed a high similarity between de- and repolarization patterns [38]. Repolarization differences influenced by a smoothly progressing depolarization wavefront do not necessarily increase the susceptibility to arrhythmias. However, in volume overloaded ventricles, fibrosis and mechanically induced changes in conduction velocity may cause patchy, irregular repolarization sequences.

4.7. Conclusions

Normal repolarization indices may be associated with the absence of severe ventricular arrhythmias. Pulmonary valve replacement in Fallot patients with dilated right ventricles has a beneficial effect on electrocardiographic indices of repolarization heterogeneity.

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