CONGENITAL HEART DISEASE

ECG predictors of ventricular arrhythmias and biventricular size and wall mass in tetralogy of Fallot with pulmonary regurgitation

W A Helbing, A W Roest, R A Niezen, H W Vliegen, M G Hazekamp, J Ottenkamp, A de Roos, E E van der Wall

Background: In patients with the tetralogy of Fallot, QRS prolongation predicts malignant ventricular arrhythmias. QRS prolongation may result from right ventricular dilatation. The relation of ECG markers to biventricular wall mass and volumes has not been assessed.

Objective: To investigate the relations of surface ECG markers of depolarisation and repolarisation to right and left ventricular volume and biventricular wall mass.

Methods: 37 Fallot patients (mean (SD) age 17 (9) years) were studied 14 (8) years after surgical repair; 34 had important pulmonary regurgitation. Left and right ventricular size was assessed from tomographic magnetic resonance imaging (MRI), and the amount of pulmonary regurgitation by velocity mapping MRI. QT, QRS, and JT duration and interlead dispersion markers were derived from a standard 12 lead ECG.

Results: Mean QRS duration was significantly prolonged (133 (31) vs 91 (11) ms in controls), as were dispersion of QRS (36 (17) vs 20 (6) ms), QT interval (87 (48) vs 42 (20) ms), and JT interval (93 (48) vs 42 (19) ms). Biventricular volumes were increased (right ventricular end diastolic volume, 129 (41) vs 70 (9) ml/m²; left ventricular end diastolic volume, 83 (16) vs 69 (10) ml/m²), as was right ventricular wall mass (24 (7) vs 17 (2) g/m²). QRS duration correlated best with right ventricular mass (r = 0.55, p < 0.01).

Conclusions: In patients operated on for tetralogy of Fallot and with pulmonary regurgitation, ECG predictors of ventricular arrhythmias are influenced by several mechanical factors that may occur simultaneously. These include increased right ventricular volume, but also increases in left ventricular volume and in right and left ventricular wall mass.

Tetralogy of Fallot is the most common type of cyanotic congenital heart disease, occurring in approximately 2700 newborns each year in the USA.¹ Surgical correction now has a low mortality, and long term survival is good.¹ Nevertheless, patients operated on for tetralogy of Fallot are at increased risk of sudden death, which is often attributed to the development of ventricular arrhythmias.² Several risk factors for ventricular arrhythmias have been identified in these patients. These factors—which may be interrelated—include, among others, residual haemodynamic abnormalities (for example, diminished right ventricular function, increased right ventricular systolic pressure, and pulmonary regurgitation), residual electrophysiological abnormalities (inducible sustained ventricular tachycardia, conduction defects, abnormalities of dispersion of depolarisation and repolarisation), and surgical variables (transatrial or transventricular approach, age at operation).² ³ ⁴ ⁵

Despite these well recognised risk factors, the prediction of the occurrence of malignant ventricular arrhythmias has been cumbersome.³ Recently, prolongation (and prolongation rate) of the QRS duration—particularly a QRS duration of more than 170 ms in children and more than 180 ms in adults—has been established as a sensitive predictor of life threatening ventricular arrhythmias in patients operated on for tetralogy of Fallot.⁶ ⁷ ⁸ A direct relation between QRS duration and right ventricular size and function has been suggested. This relation would have various clinical implications, including the need for the development of strategies to prevent right ventricular dilatation after surgical repair of tetralogy of Fallot. From available studies it remains unclear whether QRS duration is an adequate marker of right ventricular dilatation. Furthermore, QRS duration may be influenced by factors other than right ventricular volume.⁹ ¹⁰

Magnetic resonance imaging is an excellent non-invasive technique for assessing the size of geometrically complex heart chambers, particularly the right ventricle.¹¹ ¹² In this study we aimed to assess the value of QRS prolongation as a marker of right ventricular dilatation, and also to assess the relation of surface ECG markers of depolarisation and repolarisation to left ventricular volume and biventricular wall mass.

METHODS

Study subjects

Magnetic resonance imaging (MRI) results from 37 patients who had undergone complete repair of the tetralogy of Fallot at a mean (SD) age of 17 (9) years (19 male, 18 female), and from 37 healthy volunteers matched for age and sex, were studied retrospectively (table 1). The adults in this group were consecutive patients referred for magnetic resonance evaluation of pulmonary regurgitation and ventricular function. The paediatric patients were randomly selected from the institutional database.¹³ ¹⁴

Patients were included in the study only if recent ECG data were available (not more than two months from the time of the MRI study). Thirty four patients had residual pulmonary regurgitation, and three had residual pulmonary stenosis with Doppler gradients of 40, 70, and 75 mm Hg, respectively. We excluded patients with known residual intracardiac shunting.

The baseline characteristics of all the patients are given in table 1. Restrictive right ventricular diastolic function was
measured flows. Volume flow out of or back into the right
planes for velocity mapping, perpendicular to the direction of
mine the position of the ventricles and the orientation of the
MRI studies were done using a Gyroscan S15 or NT15
Magnetic resonance imaging
controls was taking drugs affecting ECG parameters.
healthy controls, matched for age and sex. None of the healthy
of the QRS complex to the end of the T wave.
U waves, if present, were
calculated as the maximum (QRS, QT, or JT) minus the mini-
duration were measured manually on recordings of all 12
leads. Rate correction was performed with Bazett’s formula,
for lead II and for maximum and mean QRS, QT, and JT meas-
ments (irrespective of lead). Interlead dispersion was calculated as the maximum (QRS, QT, or JT) minus the mini-
imum interval, derived from at least 11 recordings. The end of the T wave was defined as the point where it crossed the iso-
electric baseline, or where the tangent of the downward slope
of the T wave crossed the baseline. U waves, if present, were
not included in the measurements. In case of a U wave the end
point of the T wave was measured at the nadir of the T and U
wave. The JT interval was defined as the interval from the end
of the QRS complex to the end of the T wave.
ECG data of the patients were compared with those of
healthy controls, matched for age and sex. None of the healthy
controls was taking drugs affecting ECG parameters.
Electrocardiography
Standard 12 lead ECGs, recorded at 25 mm/s, were analysed by
one observer (WAH), blinded to the clinical history and the
results of MRI studies and the 24 hour ECGs. QT, QRS, and JT
duration were measured manually on recordings of all 12
leads. Rate correction was performed with Bazett’s formula,
for lead II and for maximum and mean QRS, QT, and JT meas-

ments. Interlead dispersion was calculated as the maximum (QRS, QT, or JT) minus the mini-
imum interval, derived from at least 11 recordings. The end of the T wave was defined as the point where it crossed the iso-
electric baseline, or where the tangent of the downward slope
of the T wave crossed the baseline. U waves, if present, were
not included in the measurements. In case of a U wave the end
point of the T wave was measured at the nadir of the T and U
wave. The JT interval was defined as the interval from the end
of the QRS complex to the end of the T wave.

Ventricular volumes and mass
Ventricular volumes were calculated by summation of ventricular cavity areas, assessed by manual tracing of the
endocardial border on a stack of gradient echo image sections of a specific time frame, and multiplied by section thickness with correction for the interslice gap. Papillary muscles and the moderator band were not included in the ventricular area. Epicardial contours were drawn on end systolic frames to determine ventricular wall mass. The interventricular septum was considered to be part of the left ventricular wall. Ventricu-
lar wall volume was calculated as myocardial area (epicardial

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>Male/female [n]</td>
<td>19/18</td>
</tr>
<tr>
<td>Age at study (years)</td>
<td>16.8 (9), range 6–33</td>
</tr>
<tr>
<td>Children (age &lt;18 years) [n=24]</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Adults [n=13]</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.7 (0.49)</td>
</tr>
<tr>
<td>Age at operative repair (years)</td>
<td>4.5 (3)</td>
</tr>
<tr>
<td>Time of follow up (years)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Right ventriculotomy [n]</td>
<td>10</td>
</tr>
<tr>
<td>Transannular patch [n]</td>
<td>13</td>
</tr>
<tr>
<td>Restrictive RV filling pattern [n]</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary stenosis (&gt;30 mm Hg) [n]</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary regurgitation [n]</td>
<td>34</td>
</tr>
<tr>
<td>Functional state at time of study</td>
<td>NYHA class I [n]</td>
</tr>
<tr>
<td></td>
<td>NYHA class II [n]</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association functional class; RV, right ventricular.
indicate significance. A probability value of $p < 0.05$ was considered to be significant for all statistical tests. All analyses were performed using the SPSS-PC statistical software package.

Magnetic resonance imaging

The MRI results are given in Table 3. Compared with controls, right ventricular volumes were increased ($p < 0.01/0.001$). The right ventricular ejection fraction was decreased ($p < 0.01/0.05$) and right ventricular wall mass increased ($p < 0.05$). The left ventricle in the patients was also enlarged ($p < 0.01$), and the ejection fraction decreased ($p < 0.01$). Left ventricular wall mass of the patients did not differ from that of the controls. Among the 34 patients with pulmonary regurgitation, the regurgitant fraction ranged from 4% to 70%.

Correlations

Correlations between ECG findings and MRI measurements in the Fallot patients are given in Table 4 and Figure 1. QRS duration correlated significantly with right ventricular end diastolic volume, end systolic volume, right ventricular wall mass, left ventricular volumes, left ventricular wall mass, percentage pulmonary regurgitation, age, and body surface area. The best correlation was with right ventricular wall mass ($r = 0.53$, $p < 0.01$). A significant correlation was also noted between rate corrected mean JT interval and biventricular volumes and wall mass. Correlation between QTc and MRI measurements, age, and body surface area did not reach significance; the same was noted for dispersion of QRS, QT, and JT.

There was no significant difference between any of the ECG findings in the patients with restrictive right ventricular physiology and those without. Indices of ventricular size and function did not differ between those patients with and without restrictive right ventricles. Correlations with MRI calculations did not differ statistically between ECG measurements derived from lead II, or from maximum or mean ECG measurements.

DISCUSSION

Our study involved a relatively young group of patients operated on for tetralogy of Fallot. Most of the surgery had been done using recent techniques, avoiding right ventriculotomy. Thirty four patients had pulmonary regurgitation, and right ventricular size was increased. QRS duration encompassed the entire spectrum commonly found in these patients. We found a significant correlation between surface ECG QRS duration and right ventricular volumes. This correlation also exists between QRS duration and right ventricular wall mass. However, in the present group, in whom an increased left ventricular size and diminished left ventricular ejection fraction were observed, QRS duration also correlated with left ventricular size and wall mass.

### Table 2: ECG results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT (n)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVT (n)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cRBBB (n)</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>133 (36)</td>
<td>91 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>437 (28)</td>
<td>421 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>JTc (ms)</td>
<td>292 (26)</td>
<td>320 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>36 (17)</td>
<td>20 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QTd (ms)</td>
<td>87 (48)</td>
<td>42 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>JTd (ms)</td>
<td>93 (48)</td>
<td>42 (19)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD); *range.

cRBBB, complete right bundle branch block; JTc, rate corrected JT interval; JTd, JT dispersion; QRSd, QRS dispersion; QTd, QT dispersion; QRS, rate corrected QTC interval; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Stroke volume was defined as end diastolic (maximum ventricular) volume minus end systolic (minimum) volume. Ejection fraction was calculated as stroke volume divided by end diastolic volume. Ventricular volume indexes were calculated as volume divided by the body surface area.

### Table 3: Results of magnetic resonance measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EDV (ml/m²)</td>
<td>129 (41)</td>
<td>70 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV ESV (ml/m²)</td>
<td>64 (30)</td>
<td>32 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>49 (10)</td>
<td>68 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV mass (g/m²)</td>
<td>24 (7)</td>
<td>17 (2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV EDV (ml/m²)</td>
<td>83 (16)</td>
<td>69 (10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV ESV (ml/m²)</td>
<td>45 (15)</td>
<td>20 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>50 (11)</td>
<td>70 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>51 (13)</td>
<td>54 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>PR (%) RV SV (range)</td>
<td>39 (21)</td>
<td>0 (–70)</td>
<td></td>
</tr>
</tbody>
</table>

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricular; PR, pulmonary regurgitation; RV, right ventricular; SV, stroke volume.

### Table 4: Correlation (linear regression analysis) of ECG findings and magnetic resonance measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>RV EDV</th>
<th>RV ESV</th>
<th>RV mass</th>
<th>LV EDV</th>
<th>LV ESV</th>
<th>LV mass</th>
<th>PR</th>
<th>Age</th>
<th>BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS</td>
<td>0.49</td>
<td>-0.01</td>
<td>0.47</td>
<td>-0.01</td>
<td>0.55</td>
<td>-0.01</td>
<td>0.43</td>
<td>0.15</td>
<td>0.45</td>
</tr>
<tr>
<td>JTc</td>
<td>-0.48</td>
<td>0.01</td>
<td>-0.48</td>
<td>0.01</td>
<td>-0.40</td>
<td>0.04</td>
<td>-0.44</td>
<td>-0.01</td>
<td>-0.45</td>
</tr>
</tbody>
</table>

BSA, body surface area; EDV, end diastolic volume; JTc, rate corrected JT interval; LV, left ventricular; PR, pulmonary regurgitation; RV, right ventricular.
The observed negative correlation between JTc duration and biventricular volumes is compatible with previous observations of decreased repolarisation duration with increased mechanical stress. Abnormalities of dispersion of depolarisation and repolarisation (increase in dispersion of QRS, QT, and JT) were present in our Fallot patients. These variables could not be related to ventricular size or wall mass. Restrictive right ventricular physiology has been related to a reduced risk of ventricular arrhythmias in adult Fallot patients. This has been explained on the basis of a decrease in right ventricular size caused by impairment of filling and a subsequent reduction in the amount of pulmonary regurgitation with restrictive right ventricular function. In our study, we could not relate ECG characteristics to restrictive right ventricular diastolic functional abnormalities.

Documented ventricular arrhythmias occurred in only two patients (5.4%). This low incidence of ventricular arrhythmias prevented us from assessing potentially “critical” ventricular volumes or wall mass that might predict the occurrence of malignant arrhythmias.

**Previous studies of mechanoelectrical interaction in tetralogy of Fallot**

Arrhythmias of ventricular origin occur with an incidence of 0.5–6% in patients who have undergone complete repair of tetralogy of Fallot. In these patients, delayed conduction (as evidenced by prolonged QRS duration) often occurring directly postoperatively, and increased inhomogeneity of repolarisation (increased dispersion markers) provide the basis for re-entry tachycardias, which increase the risk of sudden death. Re-entry circuits may include a ventricular septal defect patch, right ventricular outflow patches, and ventricular scars. Furthermore, residual haemodynamic problems, such as pulmonary stenosis or regurgitation and decreased right ventricular ejection fraction, have been associated with an increased risk of ventricular ectopic activity and with inducible ventricular arrhythmias. In many of the studies on this subject, accurate measurements of ventricular volumes or wall mass were not available. The relation between residual haemodynamic problems and ventricular arrhythmias has been explained by mechanoelectrical interaction, which has been defined as the development of potentially arrhythmogenic electrophysiological changes caused by alterations in the loading conditions of the cardiac chambers. Recently, studies by Gatzoulis and colleagues and Berul and associates showed an increased risk of ventricular tachycardias in Fallot patients with a prolonged QRS duration (> 170 ms in children or > 180 ms in adults, respectively). A significant correlation (r = 0.43) between QRS duration and echocardiographic right ventricular long axis length was established. This relation between QRS duration and right ventricular size was also demonstrated by Balaji and
colleagues, but could not be confirmed in another echocardiographic study. Abd El Rahman and co-workers, using three dimensional echocardiography, established a correlation with QRS duration for right ventricular end diastolic volume of $r = 0.61$, and for end systolic volume of $r = 0.51$. In these studies, relations between QRS duration and other mechanical factors could not be established.

Using MRI as the gold standard technique, we confirmed that QRS duration correlates with right ventricular volumes. However, it is unlikely that right ventricular dilatation alone is the cause of QRS prolongation or ventricular arrhythmias. Previous studies have shown a clear relation between QRS duration and left ventricular volumes and wall mass. Our studies confirm these findings. We showed that QRS duration also correlates with right ventricular and left ventricular wall mass in patients operated on for tetralogy of Fallot. The occurrence of ventricular arrhythmias is not increased by chronic ventricular dilatation alone, but when it is combined with regional differences in stretch and contractility. These regional differences may be promoted by myocardial hypertrophy, which results in areas of slow conduction or unidirectional block. It is conceivable that the combination of right ventricular volume overload and left ventricular function abnormalities—may be present with important pulmonary regurgitation—may further enhance regional differences in stretch and contractility.

These factors, particularly the influence of right ventricular wall mass, have been difficult to assess in previous studies of patients with tetralogy of Fallot using conventional imaging techniques. In the present study, we did not aim to assess a direct link between ventricular size, wall mass, and clinical arrhythmias. However, our results may call into question the concept that the increased risk of ventricular arrhythmias in patients with tetralogy of Fallot results from right ventricular dilatation alone. This is in accordance with results of a recent large multicentre study in adult patients, in which it was concluded from circumstantial evidence rather than direct measurements that chronic pulmonary regurgitation was associated with sustained ventricular arrhythmias. A QRS duration of more than 180 ms was a clear risk factor for ventricular tachycardia and sudden death, as was a rapid rate of shortening of QRS duration. This is in accordance with a combined effect of ventricular size and enhancement of regional differences in stretch and contractility as risk factors for ventricular arrhythmias. Elaborating on this concept, Vogel and colleagues recently showed an association between regional right ventricular wall motion abnormalities and repolarisation–depolarisation disturbances in patients with tetralogy of Fallot. However, wall motion abnormalities could not be correlated with wall mass or the amount of pulmonary regurgitation.

**Clinical implications**

The findings of our study show that ventricular depolarisation and repolarisation in patients operated on for tetralogy of Fallot and with pulmonary regurgitation are influenced by several mechanical factors that may occur simultaneously. These include not only increased right ventricular volumes but also increased left ventricular volumes and right ventricular and left ventricular wall mass. These factors may contribute to electrical inhomogeneity, thus promoting the substrate for re-entry tachycardias. At the same time, biventricular volumes and wall mass may also influence the haemodynamic response to ventricular tachycardias. Thus QRS prolongation should be considered a surrogate risk factor for ventricular arrhythmias, itself influenced by multiple factors. Which of these factors is most important is not evident. Of note, we were able to show a significant correlation between QRS and JTc duration with left ventricular mass, although left ventricular mass in the patients did not differ from that in the healthy controls.

Further evaluation, including assessment of dispersion markers and of haemodynamic factors such as right ventricular and left ventricular function, and the severity of pulmonary regurgitation, is mandatory in the presence of important QRS prolongation after repair of tetralogy of Fallot. Such a strategy, which may have to be combined with electrophysiological studies, should help to distinguish those patients who require surgical relief of haemodynamic abnormalities from those who may be managed with antiarrhythmic drugs or an implantable cardioverter-defibrillator to prevent life threatening ventricular arrhythmias.

**Conclusions**

In patients operated on for tetralogy of Fallot, ECG predictors of ventricular arrhythmias are influenced not only by right ventricular volumes but also by left ventricular volumes and wall mass.

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**IMAGES IN CARDIOLOGY..........................................................**

**Left anterior descending and circumflex coronary artery spasm after right coronary artery stent implantation**

A 47 year old woman with variant angina and recurrent ischaemic episodes, despite aggressive medical treatment, was referred to our attention. Coronary angiography showed a normal left coronary artery and significant obstruction of the middle portion of the right coronary artery (upper panel, centre), that was successfully treated with stent implantation (lower panel, centre). At the end of the procedure, the patient complained of chest pain associated with ST segment elevation in the anterior precordial leads. Repeated angiography showed absence of residual stenosis with normal run-off of the right coronary artery, but a localised spasm in the middle portion of both circumflex and left anterior descending coronary arteries (upper panel, right). Spasms were promptly relieved by intracoronary glyceryl trinitrate (lower panel, right).

The possibility that coronary stretching, caused by stent deployment, could trigger coronary spasm in remote coronary arteries has to be taken into account during coronary interventions in the presence of acute post-procedural ischaemia.

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Left anterior descending and circumflex coronary artery spasm after right coronary artery stent implantation
F Versaci, A Gaspardone and I Proietti

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