Regional Wall Motion and Abnormalities of Electrical Depolarization and Repolarization in Patients After Surgical Repair of Tetralogy of Fallot

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Background—Abnormal depolarization-repolarization in patients with repaired tetralogy of Fallot (TOF) is a risk factor for malignant ventricular tachycardia and sudden death. It is unclear whether ECG abnormalities are associated with abnormal regional right ventricular (RV) function.

Methods and Results—Seventy-four patients (37 patients <18 and 37 >18 years old) who had had TOF repair at 4.0 years old (0.1 to 47 years old) were examined when they were 18.7 years old (1.7 to 61.1 years old), as were 112 control subjects with normal hearts. Regional function was evaluated with tissue Doppler imaging of the RV and left ventricular (LV) free wall and the septum. Myocardial velocities were sampled continuously from base to apex. Synchronous ECG was analyzed for QRS, QT, and JT duration and QRS, QT, and JT dispersion. All 74 TOF patients had normal LV myocardial velocities. Forty-eight patients (24 patients <18 and 24 >18 years old) had reversed myocardial velocities in diastole in the RV free wall, which were associated with reversed systolic myocardial velocities in 22 and additional reverse diastolic myocardial velocities in the septum in 19. Those 48 patients had a longer QRS duration (151±31 versus 124±27 ms) and greater QRS (47±18 versus 29±12 ms), QT (73±27 versus 52±22 ms), and JT (96±31 versus 67±35 ms) dispersion. Compared with normal control subjects, all 74 TOF patients had decreased systolic and diastolic myocardial velocities and a longer isovolumic relaxation time.

Conclusions—RV wall-motion abnormalities are a common finding late after TOF repair and are associated with repolarization-depolarization abnormalities. These data further underscore a likely mechano-electrical interaction as an important part of the pathogenesis of RV disease in these patients. (Circulation. 2001;103:1669-1673.)

Key Words: echocardiography imaging tetralogy of Fallot

Patients with repaired tetralogy of Fallot (TOF) may suffer from sudden unexpected premature death and ventricular dysfunction. Identification of the clinical substrate linked to cardiac arrhythmias and sudden death has been difficult. In an early study, a prolonged QRS duration was associated with an increase in overall heart size and clinical arrhythmia. Although possibly only a surrogate for right ventricular (RV) dilatation, a further link between ECG changes and outcome was established by detailed examination of repolarization and depolarization. The relationship between inhomogeneity of electrical depolarization and repolarization and regional myocardial contraction and diastolic function has not been investigated. The novel technique of tissue Doppler imaging permits quantification of regional function noninvasively.

In this study, we assessed regional RV function in patients after repair of TOF and compared it with the analysis of the ECG to determine whether any association exists between inhomogeneity of ventricular contraction and relaxation and inhomogeneity of electrical depolarization and repolarization.

Methods

Patient Selection

We examined 186 subjects. Seventy-four patients with TOF were studied at age 18.7±12 years (1.7 to 61.1 years), 14.9±9.3 years (0.1 to 41.3 years) after surgical repair. This had been performed at age 4.0±3.9 years (0.1 to 47 years) with various techniques. In 45 patients, a transannular patch had been used to enlarge the RV outflow tract (RVOT); in 17 this was achieved by a subvalvar patch, 8 had undergone atriotomy without the use of an RVOT patch, and 2 each had been repaired by implantation of a homograft or a monocusp valve between the RV and the pulmonary trunk. Of those, 6 had previously undergone a Blalock-Taussig shunt at age 0.1, 0.5, 0.9, 1.9, 3, and 12 years, respectively. At the time of examination, 37 patients were <18 years of age (mean 10.1 years, range 1.5 to 17.7 years), and 37 were >18 years old (mean 27.8 years, range 18.4 to 61 years). The patients represent a consecutive cohort of patients with TOF who were seen in the outpatient departments of Great Ormond Street and Middlesex Hospitals, London, between November 1999 (when tissue Doppler became available at our institutions) and May 2000. Thus, no clinical selection criteria were applied other than routine outpatient follow-up. All but 4 patients were clinically
well. The 4 patients with clinical symptoms had branch pulmonary artery stenosis and were scheduled to undergo further surgery. Data were compared with those from 112 age-matched control subjects who were either being evaluated for an innocent cardiac murmur \( n = 92 \) or volunteered \( n = 20 \) to have their hearts examined by tissue Doppler echocardiography.

**Echocardiography Technique**

Tissue Doppler data were acquired transthoracically at a frame rate between 96 and 132 Hz with a 2.5-MHz transducer interfaced with a system V sector scanner (GE Vingmed). Imaging was performed from an apical 4-chamber view. The myocardial velocities were sampled continuously from base to apex in the free wall of the RV and left ventricle (LV) and in the ventricular septum. Recordings were made simultaneously with the ECG and phonocardiogram and were stored digitally for offline analysis. Echopac software (GE Vingmed) was used to analyze the stored myocardial Doppler data. The peak myocardial velocities during systole (s wave), early diastole (e wave), and late diastole (a wave) were measured at the base, middle, and apical portions of the free walls of the RV and LV and the ventricular septum. The isovolumic relaxation time was measured from the onset of the second heart sound to the beginning of the myocardial e wave. A rigorous definition of wall-motion abnormalities was used. Only those areas showing complete reversal of systolic or diastolic velocity vector were included. The direction of Doppler velocities was color coded with red (flow toward the transducer) and blue (flow away from the transducer) colors, which allows for easy recognition of direction of myocardial velocities. Measurements of the myocardial velocities and the various time intervals were performed on 3 consecutive heartbeats, and the average of the 3 measurements was calculated. Pulsed Doppler studies of the RVOT were performed to assess the systolic pressure gradient across the RVOT and the presence and degree of pulmonary regurgitation. Mild regurgitation was considered to be present if diastolic retrograde flow could be detected under the pulmonary valve, moderate regurgitation if the retrograde flow could be seen in the RV farther apically from the pulmonary valve and in the pulmonary trunk, and severe regurgitation if abnormal retrograde diastolic flow could also be detected in the branch pulmonary arteries.

**Electrocardiograms**

All patients with TOF had a standard 12-lead ECG performed on the day of the echocardiographic examination at a paper speed of 25 mm/s. QT and QRS measurements were made manually as previously described.\(^2\) The end of the T wave was taken at its return to the T-p baseline. When U waves were present, the end of the t wave was taken as the nadir between T and U.\(^3\) Three consecutive cycles were measured, and a mean value was calculated from the 3 values. The JT interval was calculated by subtracting QRS from QT. The QT/QRS/JT dispersion was defined as the difference between the maximum and minimum QT/QRS/JT intervals in any of the 12 ECG leads. The ECGs were evaluated by 1 person (J.S.) who was blinded to the results of the tissue Doppler imaging.

The ECG data for the patients <18 and >18 years old were analyzed separately because of different normal values for QRS duration, depending on age.\(^2,13\)

**Statistical Analysis**

Data obtained by tissue Doppler in the 74 patients and the 112 control subjects and between patients with and without regional wall-motion abnormalities were compared by unpaired \( t \) test, with a value of \( P < 0.05 \) considered to represent a significant difference. \( \chi^2 \) test was performed to compare incidence of abnormalities of regional myocardial velocities in patients with mild, moderate, and severe pulmonary regurgitation and to compare surgical technique. A simple linear regression analysis was performed to examine the relation between age at time of examination and presence or absence of wall-motion abnormalities.

**Results**

**Global RV Function**

Compared with the normal control subjects, patients with repaired TOF had reduced systolic myocardial velocities, indicating a reduced longitudinal RV function, whereas the reduced diastolic myocardial velocities and the prolonged isovolumic relaxation time hint of a reduced diastolic global function (Table 1).

**Regional Function**

All control subjects had the characteristic pattern of myocardial velocities with an apically directed systolic velocity (s wave) and an early (e-wave) and late (a-wave) diastolic velocity directed toward the base of the heart, with a gradual velocity decrease from base to apex (Figure 1). In contrast, reversed s-wave and/or e-wave velocities (Figures 2 and 3) were detected in 48 of 74 patients (65%) with TOF; they were present in 24 of 37 patients <18 years old and 24 of 37 patients >18 years old. Reversed systolic or diastolic myocardial velocities were not present in the LV. Diastolic wall-motion abnormalities were detected in the apex and the middle of the RV free wall, extending to 37% (19% to 55%) of the total length of the RV free wall, and reversed systolic myocardial velocities were found in a similar location, extending to 35% (15% to 50%) of the RV free wall. In 28 of 48 patients with reversed myocardial velocities, these were present in both systole and diastole; 16 of 48 patients had isolated diastolic wall-motion abnormalities, and 2 of 48 had isolated systolic wall-motion abnormalities. In 16 of the 48 patients, reversed myocardial velocities were found in >1 site in both the RV free wall and the ventricular septum, whereas 2 patients had isolated reversed myocardial velocities in the

### TABLE 1. Myocardial Velocities (cm/s) in Patients With Repaired TOF (n=74) and Normal Subjects (n=112)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RV TOF</th>
<th>RV Normal Subjects</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-wave velocity, cm/s</td>
<td>7.1±2.0</td>
<td>11.3±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>560±12.8</td>
<td>48.1±11.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>e-wave velocity, cm/s</td>
<td>9.1±2.9</td>
<td>12.2±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e-deceleration, m·s(^{-1})</td>
<td>1.1±0.5</td>
<td>1.6±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>a-wave velocity, cm/s</td>
<td>4.7±2.2</td>
<td>7.5±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-wave velocity, cm/s</td>
<td>4.1±2.0</td>
<td>7.7±2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>61.4±17.3</td>
<td>53.9±13.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>e-wave velocity, cm/s</td>
<td>5.8±3.8</td>
<td>9.4±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e-deceleration, m·s(^{-1})</td>
<td>1.4±1.5</td>
<td>1.7±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>a-wave velocity, cm/s</td>
<td>2.0±1.6</td>
<td>3.5±2.4</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Apex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-wave velocity, cm/s</td>
<td>1.2±3.2</td>
<td>3.9±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>65.9±15.0</td>
<td>66.5±16.0</td>
<td>NS</td>
</tr>
<tr>
<td>e-wave velocity, cm/s</td>
<td>−2.0±4.6</td>
<td>5.7±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e-deceleration, m·s(^{-1})</td>
<td>1.0±0.5</td>
<td>1.4±0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>a-wave velocity, cm/s</td>
<td>0.2±0.6</td>
<td>0.8±1.6</td>
<td>&lt;0.004</td>
</tr>
</tbody>
</table>

IVRT indicates isovolumetric relaxation time.
ventricular septum. Patients with systolic wall-motion abnormalities had lower peak systolic velocities at the base (6.3±1.9 versus 7.6±2 cm/s, \(P<0.02\)), middle (3.1±1.6 versus 4.6±1.6 cm/s, \(P<0.001\)), and apex (−1.9±0.8 versus 2.2±1 cm/s, \(P<0.001\)) of the RV than those with normal wall motion. Likewise, the peak e-wave velocities were significantly lower in the middle (6.9±4.2 versus 5±2 cm/s, \(P<0.01\)) and apex (−5.5±2 versus 3.3±1.5 cm/s, \(P<0.001\)) of the RV in patients with diastolic regional wall-motion abnormalities than in those with normal diastolic wall motion. There was no correlation between age at time of examination and incidence of wall-motion abnormalities.

Correlation of Regional Function With Hemodynamics
By Doppler criteria, severe pulmonary regurgitation was present in 28 patients, moderate in 25, and mild in 21. Seventy-two patients had a residual RVOT gradient of 23±15 mm Hg (10 to 80 mm Hg), and 2 had no gradient between the RV and the pulmonary trunk. The incidence of reversed myocardial velocities was similar in those with severe (21 of 28 patients, 78%), moderate (14 of 25 patients, 57%), and mild (10 of 21 patients, 48%) pulmonary regurgitation (\(P<0.12\), NS). We found no influence of surgical technique on regional wall-motion abnormalities, which were present in 27 of 45 patients (60%) with a transannular patch, 9 of 17 (53%) with a subvalvar patch, and 3 of 8 (38%) who had been repaired by atriotomy without RV patch (\(P<0.69\), NS). Two patients in whom a monocusp valve had been implanted after removal of the stenotic native pulmonary valve had wall-motion abnormalities, which were also present in 1 of the 2 who had a pulmonary homograft implanted at initial operation.

Correlation of Regional Function With ECG
The 48 patients (24 patients <18 and 24 >18 years old) with repaired TOF and reversed systolic and/or diastolic myocardial velocities was similar in those with severe (21 of 28 patients, 78%), moderate (14 of 25 patients, 57%), and mild (10 of 21 patients, 48%) pulmonary regurgitation (\(P<0.12\), NS). We found no influence of surgical technique on regional wall-motion abnormalities, which were present in 27 of 45 patients (60%) with a transannular patch, 9 of 17 (53%) with a subvalvar patch, and 3 of 8 (38%) who had been repaired by atriotomy without RV patch (\(P<0.69\), NS). Two patients in whom a monocusp valve had been implanted after removal of the stenotic native pulmonary valve had wall-motion abnormalities, which were also present in 1 of the 2 who had a pulmonary homograft implanted at initial operation.
The lack of imaging of the RVOT is a weakness of this study. Although a specific long- or short-axis view would be more appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to appropriate, normal comparative data would be hard to approach. TOF is not seen in its entirety in the apical 4-chamber view chosen in this study, and a tissue Doppler interrogation in this area of the RV is difficult. It is of interest that patients with wall-motion abnormalities also had a greater QRS dispersion. The latter is characteristic of slowed interventricular conduction leading to late electrical activation of some parts of the ventricle and paradoxical late inward motion during diastole in some regions. This is consistent with previous electrophysiological studies that have identified localized areas of slowed conduction in several areas of the RV of these patients. The additional presence of abnormal repolarization in patients with repaired TOF may potentiate the risk for sudden death. Numerous studies have demonstrated that an abnormally long QRS duration alone is not the only marker for identifying patients with repaired TOF at risk for sustained ventricular tachycardia and sudden death and have emphasized the need for assessment of QT and JT dispersion. Abnormal JT dispersion in particular was prevalent in patients with combined systolic and diastolic wall-motion abnormalities in our study, but it should be emphasized that none of our patients experienced clinical ventricular arrhythmias. Although the values of QRS, QT, and JT dispersion are greater in those with wall-motion abnormalities (Table 2), they are less than those reportedly associated with ventricular tachycardia and sudden death.

**Discussion**

Our data show that diastolic and systolic RV wall-motion abnormalities are frequently found in patients late after repair of TOF, even in patients who are clinically well. Global systolic function of the RV is adversely affected by the presence of systolic wall-motion abnormalities, as is the global diastolic function by diastolic wall-motion abnormalities. Furthermore, the association between wall-motion abnormalities and greater QRS, QT, and JT dispersion suggests a link between inhomogeneous electrical depolarization and repolarization and inhomogeneity of RV contraction and relaxation, which may be of relevance to risk of arrhythmia and outcome.

**Tissue Doppler Imaging**

In this study, tissue Doppler imaging was performed along the long axis of the RV, because myocardial velocities can be best assessed in this imaging plane and it best reflects RV contractility because of the myocardial fiber distribution in the RV. Previous studies have demonstrated a good correlation between global function and the peak systolic myocardial velocities at the base of the heart. Because the peak systolic myocardial velocities in the RV free wall were reduced in all sampled segments in the TOF patients compared with normal control subjects, we have evidence of reduced global systolic function in our patients. Perhaps more importantly, tissue Doppler imaging can also provide information on regional systolic function. The regional abnormalities in our patients were found in the apical and middle regions of the RV free wall and the septum. One might expect abnormal regional wall motion to predominate in the RVOT, where many patients with repaired TOF have a ventriculotomy scar or insertion of a noncontractile outflow tract or transannular patch. The RVOT is not seen in its entirety in the apical 4-chamber view chosen in this study, and a tissue Doppler interrogation in this area of the RV is difficult.

**Association Between ECG and Wall-Motion Abnormalities**

It was not the aim of this study to establish a link between RV wall-motion abnormalities and clinical arrhythmias, but our data demonstrate that some of the electrical abnormalities previously linked to the development of clinical arrhythmias are associated with regional abnormalities of the mechanical properties of the RV in repaired TOF. Abnormal depolarization (prolonged QRS duration) and repolarization (JT dispersion) were significantly associated with systolic and diastolic wall-motion abnormalities.

There was no correlation between the QRS duration or QT and JT dispersion and outcome. A link between inhomogeneous electrical depolarization and repolarization and inhomogeneity of RV contraction and relaxation, which may be of relevance to risk of arrhythmia and outcome.
validate, and delineation of patch material from myocardium would be difficult. Nonetheless, this area is particularly important, because it has been identified in some electrophysiological studies to be associated with slowed conduction and initiation of the reentry circuit of ventricular tachycardia. We can only speculate whether, if it is possible to detect them with tissue Doppler imaging, additional wall-motion abnormalities in this area may have affected the results of this study.

In previous studies, a link between electrical abnormalities and RV dilatation per se has been described. It remains unclear from our data whether there is a causal relationship between the regional disturbances of mechanical function and abnormalities of conduction, or vice versa. Furthermore, the primary or additional effect of dynamic volume overload on both factors is not well defined. Interestingly, there was no relationship between severity of pulmonary regurgitation, as defined, and the presence of wall-motion abnormalities. This may merely be a reflection of the relative insensitivity of Doppler methods of assessing pulmonary regurgitation or statistical power in the comparison of relatively small study groups, rather than a robust demonstration of a lack of a link. We made no attempt to measure RV size or pulmonary regurgitation volume, which would clearly be required in future studies of these phenomena.

We did not assess RV function by means other than tissue Doppler imaging, because cardiac catheterization and MRI were not available in these patients, who were almost all without clinical symptoms.

Conclusions
Abnormal diastolic and systolic myocardial velocities of the RV free wall are common and more prevalent in patients with abnormally long QRS duration and QRS and JT dispersion after repair of TOF. This link between abnormal regional contraction and relaxation with abnormal electrical repolarization and depolarization is another manifestation of important mechanoelectrical interactions found in patients after repair of TOF.

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References
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