Clinical, Echocardiographic and Humoral Status of Patients Following Repair of Tetralogy of Fallot: Comparison of the Second to the First Decade

Ori Wand MD\(^1\), Zeev Perles MD\(^2\), Azaria J.T. Rein MD\(^2\), Nurit Algur MSc\(^3\) and Amiram Nir MD\(^4\)

\(^1\)Hebrew University-Hadassah Medical School and \(^2\)Pediatric Cardiology Unit, Hadassah Medical Center, Jerusalem, Israel
\(^3\)Biochemistry Laboratory and \(^4\)Pediatric Cardiology Unit, Shaare Zedek Medical Center, Jerusalem, Israel

Key words: tetralogy of Fallot, pulmonary regurgitation, plasma B-type natriuretic peptide, 6 minute walk test

Abstract

Background: Surgical repair of tetralogy of Fallot may leave the patient with pulmonary regurgitation, causing eventual right ventricle dilatation and dysfunction. Predicting clinical deterioration may help to determine the best timing for intervention.

Objectives: To assess whether the clinical and humoral status of patients in the second decade after repair of ToF is worse than that of patients in the first decade after repair.

Methods: Twenty-one patients with repaired ToF underwent clinical assessment, electrocardiogram, echocardiogram and measurement of plasma B-type natriuretic peptide and N-terminal pro-BNP as well as the 6 minute walk distance test. Patients were divided into two groups: group A – less than 10 years after repair (n=10, age < 12 years old), and group B – more than 10 years after repair (n=11, age > 12 years old). The age at repair was similar in both groups.

Results: In all but one patient the distance in the 6 min walk test was less than the minimum for age. RV end-diastolic volume and the 6 min walk test correlated with age. NT-proBNP levels were significantly higher in the ToF group compared to 26 healthy controls (\(P < 0.0001\)) and were inversely correlated with RV ejection fraction. Comparison of the two groups showed no difference in RV end-diastolic volume indexed for body surface area, pulmonary regurgitation severity, right or left ventricular myocardial performance index, RV ejection fraction, QRS duration, or 6 min walk indexed to minimum for age.

Conclusions: In this group of patients with similar age at operation and pulmonary regurgitation severity, most clinical, echocardiographic and humoral parameters were not worse in the second decade after repair of ToF. These data suggest that very early pulmonary valve replacement may not be of benefit.

nt-proBNP = N-terminal pro-BNP

ToF = tetralogy of Fallot

BNP = B-type natriuretic peptide

RV = right ventricle

P = probability

ToF = tetralogy of Fallot

BNP = B-type natriuretic peptide

RV = right ventricle

NT-proBNP = N-terminal pro-BNP

Tetralogy of Fallot is a common cyanotic congenital heart disease. Surgical repair may include right ventriculotomy, which, when performed at an early age, may leave the patient with significant pulmonary regurgitation and residual right ventricular outflow tract obstruction. Long-term pressure and volume overload on the right ventricle may lead to progressive dilatation and functional deterioration of the right ventricle. Many patients eventually need pulmonary valve implantation [1-3]. There are no definite criteria for the timing of valve implantation [4-6]. On one hand, implantation of a valve in a small child may necessitate early replacement of the valve due to growth; on the other hand, delaying implantation may result in irreversible insult to the RV [4]. Assessment of RV size and function is difficult because of the shape of this chamber. B-type natriuretic peptide and the amino terminal segment of its pro-hormone, NT-proBNP, are markers of ventricular distension and of heart failure [7,8] that have been shown to be affected by RV size and function [9-11].

In the present study we performed a comprehensive assessment of patients after repair of ToF. This comprised a clinical evaluation including effort tolerance assessed by a 6 minute walk, anatomic and functional cardiac assessment using echocardiographic examination and humoral status with BNP and NT-proBNP levels. Patients were divided into two groups – those less than 10 years after repair and those 10–20 years after repair.

Patients and Methods

The study was approved by the institutional ethics committee. Informed consent was obtained from participants or their parents. Patients who had undergone surgical repair of ToF were selected. Exclusion criteria included febrile illness in the previous 2 weeks, renal failure, a change in cardiac symptoms in the previous 2 months, invasive procedures performed in the previous 2 months, and history of ToF with pulmonary atresia. The control group for NT-proBNP levels consisted of 26 age-matched children and adolescents with no known heart disease and no acute illness who had undergone complete blood count as part of ambulatory evaluations (before elective surgery, endocrinological workup, etc.). Subjects in the control group had no history of heart disease and no sign of heart disease on physical examination.

Peptide measurements

Blood was taken via peripheral venous puncture after the subject had rested for at least 20 minutes. The blood was collected into tubes containing EDTA. Plasma was separated and stored at -20°C until measured. NT-proBNP was measured by Electrochemiluminescence Immunoassay (Roche, Mannheim, Germany). BNP was measured by automated two-site sandwich immunoassay with the ADVIA Centaur assay (generous donation from Bayer, Tarrytown, NY, USA).
Two-dimensional echocardiographic examination was performed in all patients. The right ventricular systolic pressure was estimated from the tricuspid regurgitation jet velocity as RVp= TR + estimated RAp. Right ventricular dimensions and function were assessed using the prolate ellipsoid algorithm method. The internal margin of the ventricle was traced to calculate the area, and the length of the ventricle was measured. The measurements were made at end-systole and end-diastole. The right ventricular volume was calculated using the formula: right ventricular volume = (8 Π area²) / (3 length) [12]. The internal margin of the right atrium was traced to calculate its area. The measurements were corrected to body surface area. RV ejection fraction was calculated from volume measurements. The degree of pulmonary regurgitation was determined qualitatively. Myocardial Performance Index, a ratio of isovolumic relaxation and contraction times to ejection time, is a measure of both systolic and diastolic function. MPI was assessed using Doppler. Left ventricular function was assessed by M-mode and expressed as shortening fraction.

Six minute walk
The 6 min walk was performed in a straight corridor. Each patient walked up and down the hallway by him/herself. The subjects were told that the purpose of the test was to see how far they could walk in 6 minutes. The test was self-paced and the patient could rest if he/she so wished [13,14].

Statistical analysis
Comparison between two groups was done using the t-test. Comparisons of more than one variable were performed with ANOVA. Non-parametric variables were compared using the Mann-Whitney test. Pearson’s correlation coefficient was calculated to assess the correlation between two variables. Two-tailed significance level was considered when P < 0.05.

Results
The study group comprised 21 patients (15 males and 6 females) aged 5–21 years. The mean age at the time of repair was 1.7 years (range 0.1–5 years). The time since the repair was 2.8–19 years. Eighteen patients (86%) were in New York Heart Association class I, and 3 patients (14%) were in NYHA II. In all but one patient the distance covered in the 6 minute walk was less than the minimum reported for age. The 6 minute walk distance correlated with both age and time from repair (r = 0.49, P < 0.04) and time from repair (r = 0.49, P = 0.04). Eighteen patients had moderate or severe pulmonary regurgitation. Only four patients had elevated right ventricular pressure, as estimated by tricuspid regurgitation velocity. RV end-diastolic volume correlated with both age and time from repair (r = 0.45, P < 0.05). NT-proBNP levels correlated strongly with BNP levels (r = 0.89, P < 0.0001). NT-proBNP levels were significantly higher in the ToF group than in the controls (median: ToF 202 pg/ml, controls 40 pg/ml, P < 0.0002) [Figure 1]. There was no significant age differences between the patients (mean ± SD, 11.6 ± 5.2 years) and the control group (10.8 ± 3.0 years, P > 0.5). In ToF patients, plasma NT-proBNP levels were inversely correlated with right ventricular ejection fraction (r = -0.5, P = 0.02) [Figure 2], but not with RV end-diastolic volume.

Patients were divided according to the time since repair: group A (n=10) – less than 10 years (3.0–9.8 years, mean 6 years) since repair, and group B (n=11) – more than 10 years (10.6–20 years, mean 14). Tables 1 and 2 show comparisons between the two groups. Patients less than 10 years since repair were under the age of 12, and those more than 10 years since repair were older than 12. The age at repair was not different. There was no difference in the RV end-diastolic volume indexed for body surface area, pulmonary regurgitation severity grade, right or left ventricular myocardial performance index, RV ejection fraction or QRS duration.

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MPI = Myocardial Performance Index
NYHA = New York Heart Association
Patients 10–20 years since repair had lower left ventricular shortening fraction, while two of the patients had reduced LV function. Patients 10–20 years after repair had lower NT-proBNP, as expected with age, higher systolic blood pressure and greater 6 minute walk distance, as expected with age. However, 6 minute walk indexed to the published minimum for age [14] was not different.

Discussion

Tetralogy of Fallot is a common congenital heart disease. Surgical repair does not restore normal anatomy and physiology and many patients are left with residual right ventricular outflow obstruction and/or significant pulmonary regurgitation. With time, right ventricular dilatation and dysfunction may ensue. Some patients require pulmonary valve implantation. The timing of this procedure is not well established [4-6]. In this study we performed a comprehensive evaluation of patients after repair of ToF. The evaluation included clinical status, cardiac shape and size, as well as cardiac mechanical and humoral status.

We found that most parameters were not different in the second decade compared to the first decade after repair. Most patients reported no symptoms. However, their exercise capacity was reduced, as also reported by others [15]. Yet the age-indexed 6 minute walk distance was not different between patients less than 10 years since repair and those 10–20 years since repair. The shape of the right ventricle makes it difficult to measure its volume and function. New imaging modalities such as magnetic resonance imaging [16] and three-dimensional echocardiography may prove to be of value in this regard, but they are not commonly available. We applied a detailed method to measure right ventricular volume using two-dimensional echocardiography. We found that the right ventricular volume correlated with age during the first two decades after repair, suggesting no significant dilatation beyond normal growth during this period even in patients with significant pulmonary regurgitation.

BNP and NT-proBNP are markers for cardiac dysfunction. There are extensive data regarding their levels in states of left ventricular dysfunction. Diseases affecting the right ventricle have also been shown to alter the peptide levels [9-11]. We found excellent correlation between NT-proBNP and BNP levels in the patients, strengthening the clinical relevance of the peptide levels. Patients after repair of ToF had higher NT-proBNP levels than controls, a finding consistent with the notion that ToF repair is associated with residual cardiac dysfunction. Similar findings were reported by others [17-20]. In our study, NT-proBNP levels correlated with right ventricular systolic function but not right ventricular volume. This is in agreement with the findings of Dodge-Khatami et al. [18] who, using MRI, found a significant correlation between RV ejection fraction and NT-proBNP in children and young adults, but only a weak correlation with RV volume. They also showed a reduction in NT-proBNP levels following valve placement in these patients. Norozi and colleagues [19] measured NT-proBNP in 50 adults after ToF repair, and echocardiographically assessed right ventricular volume but not function. They found a modest correlation between NT-proBNP levels and RV end-diastolic volume and estimated RV pressure. The lack of correlation between NT-proBNP and right ventricular volume may be due to the relatively limited induction of peptide secretion by RV dilatation compared to LV volume overload [18]. The clinical implication of our findings, as well as those of others, is that significantly elevated NT-proBNP levels should alert the physician to right ventricular dysfunction, which is not easily detected by two-dimensional echocardiography. In our study, older patients had NT-proBNP somewhat lower than younger patients, as expected. The lack of increase in NT-proBNP levels is in accord with the stability of the other measured parameters, suggesting no significant deterioration in the second decade following repair.

Reduction in left ventricular volume and function has been reported in patients long after ToF repair. In our study, left ventricular shortening fraction was lower in older patients due to reduced shortening fraction in two patients. This may or may not be of significance in larger series. The apparent stability of most

Table 1. Demographics and physical findings in patients less and more than 10 years from repair of tetralogy of Fallot

<table>
<thead>
<tr>
<th></th>
<th>&lt; 10 yrs since ToF repair</th>
<th>&gt; 10 yrs since ToF repair</th>
<th>p</th>
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<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>7 (5–11)</td>
<td>16 (13–21)</td>
<td></td>
</tr>
<tr>
<td>Age at operation</td>
<td>1.5 ± 0.8</td>
<td>2.0 ± 1.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean time from</td>
<td>6.0 (3–9.8)</td>
<td>14.4 (10.6–20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>repair (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.77 ± 0.14</td>
<td>1.49 ± 0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>87 ± 17</td>
<td>82 ± 13</td>
<td>0.478</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>97 ± 13</td>
<td>110 ± 6</td>
<td>0.013</td>
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<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diastolic BP</td>
<td>63 ± 11</td>
<td>67 ± 10</td>
<td>0.342</td>
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<tr>
<td>(mmHg)</td>
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Table 2. Humoral, ECG and echocardiographic measurements in patients less and more than 10 years from ToF repair

<table>
<thead>
<tr>
<th></th>
<th>&lt; 10 yrs since ToF repair</th>
<th>&gt; 10 yrs since ToF repair</th>
<th>p</th>
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<tbody>
<tr>
<td>NT-proBNP (median, µg/ml)</td>
<td>234</td>
<td>194</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td>125 ± 25</td>
<td>132 ± 23</td>
<td>0.492</td>
</tr>
<tr>
<td>pulmonary regurgitation grade</td>
<td>3 ± 1.4</td>
<td>3 ± 1.6</td>
<td>1</td>
</tr>
<tr>
<td>RV (mll)</td>
<td>44 ± 31</td>
<td>88 ± 39</td>
<td>0.01</td>
</tr>
<tr>
<td>RVEDV (ml/m²)</td>
<td>58 ± 44</td>
<td>60 ± 27</td>
<td>0.89</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>34 ± 14</td>
<td>39 ± 15</td>
<td>0.46</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>40.1 ± 0.1</td>
<td>30 ± 0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>LVMPI (%)</td>
<td>0.39 ± 0.1</td>
<td>0.44 ± 0.19</td>
<td>0.597</td>
</tr>
<tr>
<td>RVMP (%)</td>
<td>0.26 ± 0.1</td>
<td>0.30 ± 0.21</td>
<td>0.768</td>
</tr>
<tr>
<td>6 min walk/minimum for age</td>
<td>419 ± 117</td>
<td>527 ± 54</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>6 min walk/minimum for age</td>
<td>0.81 ± 0.24</td>
<td>0.83 ± 0.07</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Pulmonary regurgitation grade: 0 = none, 4 = severe.

RVEDV = right ventricular end-diastolic volume, RVEDVI = right ventricular end-diastolic volume indexed for body surface area, RVEF = right ventricular ejection fraction, LVFS = left ventricular shortening fraction, LVMPI = left ventricular myocardial performance index, RVMP = right ventricular myocardial performance index.

LV = left ventricular

LV = left ventricular

LV = left ventricular
measures suggests that very early pulmonary valve replacement may not be of benefit, since it may hasten the need to replace a small-sized implanted valve. Larger, prospective follow-up studies are needed to confirm these data.

Conclusions
Patients after repair of ToF have elevated NT-proBNP levels compared to age-matched controls. Elevated NT-proBNP levels are associated with reduced right ventricular function. In this group of patients with similar age at operation and pulmonary regurgitation severity, most clinical, echocardiographic and humoral parameters were not worse in the second decade after repair of tetralogy of Fallot.

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References

Correspondence: Dr. A. Nir, Pediatric Cardiology Unit, Shaare Ze'dek Medical Center, Jerusalem 94342, Israel.
Phone: (972-308) 685-153
Fax: (972-2) 655-5437
email: amiram@szmc.org.il

There is no kind of dishonesty into which otherwise good people more easily and frequently fall than that of defrauding the government.

Benjamin Franklin (1706-1790), American author, political theorist, politician, printer, scientist, inventor, civic activist, and diplomat. As a scientist he was a major figure in the history of physics for his discoveries and theories regarding electricity. As a political writer and activist he, more than anyone, invented the idea of an American nation, and as a diplomat during the American Revolution, he secured the French alliance that helped to make independence possible. He invented the lightning rod, bifocals, the iron furnace stove (also known as the Franklin stove), a carriage odometer and a musical instrument known as the armonica. He was an early proponent of colonial unity. Many historians hail him as the "First American."