Ventricular interaction in children after repair of tetralogy of Fallot: a longitudinal echocardiographic study

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Received 26 October 2008; accepted after revision 7 March 2009; online publish-ahead-of-print 31 March 2009

Aims Progressive right ventricular (RV) dilation due to pulmonary regurgitation (PR) after repair of tetralogy of Fallot (TOF) may impair left ventricular (LV) filling. Our aim was to analyse long-term time courses of M-mode LV and RV measurements and to relate these to the degree of PR.

Methods and results Retrospective longitudinal cohort of children (n = 88) after repair of TOF followed by serial echocardiography over 9 years. LV and RV diameters were expressed by z-scores based on normal paediatric reference values. Time courses of LV and RV diameter z-scores, degree of PR, and influence of co-variables were analysed using mixed regression models. LV diameter z-scores were significantly lowered before repair, increased after surgery, but fell again over time; thus, mean LV diameters were significantly lower than normal population means at all times. LV diameter z-scores correlated negatively with RV dilation and degree of PR. Notably, they were significantly higher in patients with previous shunts. After pulmonary valve replacement, LV diameter z-scores recovered to normal, whereas RV diameter z-scores remained abnormal.

Conclusion Our results confirm progressive adverse RV–LV interaction in the long-term post-operative follow-up of TOF. The use of z-scores facilitated the analysis of time courses of LV and RV diameters.

KEYWORDS Tetralogy of Fallot; Pulmonary regurgitation; Longitudinal course; Ventricular interaction; Echocardiography

Introduction

For decades, repair of tetralogy of Fallot (TOF) has been performed successfully, with post-operative children usually living a life free of major symptoms. In the long-term, however, residual lesions in the right ventricular (RV) outflow tract frequently cause complications.¹⁻³ The most important problem is pulmonary regurgitation (PR) that increases over time leading to RV dilation and dysfunction.⁴⁻⁵ Severe RV dilation may also contribute to shape changes of the left ventricle (LV), thereby causing cardiac dysfunction by LV underfilling.⁶⁻⁸ Recently, adverse RV–LV interaction has been confirmed by magnetic resonance imaging (MRI) studies.⁹⁻¹⁵ MRI could also demonstrate short-term improvement of LV stroke volume after pulmonary valve replacement (PVR).

To the best of our knowledge, there are no longitudinal data on RV–LV interaction after repair of TOF in childhood. Thus, the objective of our study was to assess longitudinal time courses of M-mode measurements of LV and RV obtained from a cohort of children after repair of TOF. Our hypothesis was that RV overload resulting from PR would have a progressive negative effect on LV diameters. To account for growth, ventricular diameters were normalized using z-scores based on published paediatric reference values adjusted to body surface area.¹⁶

Specific study aims were to: (i) describe longitudinal time courses of LV and RV diameters, (ii) examine the correlation between time courses of LV and RV diameters and the degree of PR, and (iii) determine the influence of co-variables (gender, previous systemic to pulmonary shunt, mode of repair, and presence of ventricular septum defect (VSD) patch leak on LV and RV time courses).

Methods

Study design

The study design was a retrospective longitudinal cohort study performed in a tertiary care paediatric cardiology centre (Division of Paediatric Cardiology, Department of Paediatric and Adolescent
Patients
Consecutive children with TOF who had undergone repair between 1981 and 2001 were identified. The study population consisted of 107 patients with TOF born between 1978 and 2001. Patients who had <3 years of longitudinal post-operative follow-up (follow-up in other centres, surgery [re-operation, PVR] within 3 years) were excluded (n = 19) resulting in a study cohort of n = 88.

Study period
Echocardiographic follow-up data between 1983 and 2005 were evaluated. Patients were followed until adulthood or were still under follow-up at the end of the study period. All 88 patients had longitudinal data for at least 3 years following repair, 80 patients for 5 years, 72 patients for 7 years, and 52 patients for 9 years.

Echocardiography
Serial echocardiographic examinations were performed using the Advanced Technology Laboratories (MAK 600) (1983–88) and GE Vingmed System FiVe (GE Vingmed Ultrasound A/S Norway) (1988–2005) systems. Transducers were used depending on the age of the child: 7.5 MHz—<6 months; 5 MHz—6 months—6 years; 3 MHz—older than 6 years. From 1993 onwards, all echocardiographic measurements were transferred online into a computerized database (EchoPac System GE) at the time of examination.

Over the last 20 years, all echocardiographic examinations were performed according to a standardized protocol, including M-mode, two-dimensional, and Doppler, which guarantees consistency of data. There were two experienced operators in the first decade; a third trained operator was included in the second decade. No formal studies of concurrent inter-observer variability were performed but there was a good agreement between the ultrasound operators during longitudinal follow-up.

Ventricular diameters [left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), and right ventricular end-diastolic diameter (RVEDD)] were measured from the left parasternal long-axis view in M-mode.17 PR was assessed from left parasternal long-axis view and tricuspid regurgitation from apical four-chamber view. Valve regurgitations were determined using colour flow mapping and Doppler. PR was graded as follows: absent = small flame below the pulmonary valve; moderate = jet in the right ventricular outflow tract (RVOT) with retrograde diastolic flow in the pulmonary artery, or severe = retrograde diastolic flow in both pulmonary artery branches. VSD patch leaks were also documented (left parasternal long-axis view, apical four- and five-chamber views).

Clinical parameters
The following clinical parameters were obtained retrospectively from patient’s medical records for the purposes of the study: age, weight, height, and body surface area at each examination; gender, occurrence of hypoxicemic spells, pre-operative β-blocker treatment, prior palliative surgery (systemic to pulmonary shunt), coronary artery anomaly, mode of repair; transannular patch, RVOT patch, homograft, infundibulecmy; VSD patch leak, RVOT aneurysms, aortic regurgitation, need for PVR, and dates of all ECHO examinations and operations.

Calculation of z-scores
LVEDD, LVESD, and RVEDD measurements were expressed by z-scores using published paediatric reference values indexed to body surface area.16 Z-scores were calculated by the following formula: z-score = (patient value — normal population mean)/normal population standard deviation. Z-scores express the deviation of the patient’s ventricular diameters from mean diameters in normal children with the same body surface area. They allow assessing deviations independent of cardiac and somatic growth. A z-score of zero corresponds to the normal population mean. Positive z-scores indicate ventricular diameters larger and negative z-scores indicate ventricular diameters smaller than the normal population mean. Z-scores outside ±2 are outside the normal range. The graphs display longitudinal measurements over time after repair. Z-scores are presented as means and standard errors of the mean.

Follow-up schedule
For the purpose of comparing time courses between patients, follow-up examinations performed within defined time windows around the following time points were used for the analysis: pre-operative measurement (using the last echocardiographic examination before repair), 1 year after repair (using the echocardiographic examination closest to 1 year after surgery, but accepting any examination between 0.25 and <2 years), 3 years after repair (2 to <4 years), 5 years after repair (4 to <6 years), 7 years after repair (6 to <8 years), and 9 years after repair (8 to <10 years). Because of the limited follow-up data beyond 9 years after repair, analyses were restricted to an observation period of 9 years.

Time courses in patients requiring PVR (n = 14; 16%) were evaluated separately in a similar fashion. Time points after PVR were specified as follows: pre-operative measurement (last examination before re-operation), 1 year after re-operation (0.5 to <1.5 years), 2 years after re-operation (1.5 to <2.5 years), and 3 years after re-operation (2.5 to <3.5 years).

Statistical analysis
Correlations between LV and RV diameter z-scores, degree of PR (at latest follow-up), and the influence of co-variables, such as gender, previous systemic to pulmonary shunt, mode of repair, and presence of residual VSD patch leak, were analysed using mixed multiple regression models. Ultrasound operators were entered as a variable into the longitudinal model to account for intra- and inter-observer variability. The association between LV and RV diameter z-scores and the need for PVR were analysed using a generalized estimating equation model. Statistical analysis was performed using SPSS for Windows version 12.0 and SAS version 8.2.

Results
Clinical characteristics of the 88 children included in the study cohort are presented in Table 1. Notably, 24% of the study cohort had undergone a two-stage repair with a systemic to pulmonary shunt as a first palliative operation. In this two-stage repair group, VSD patch leak was present in 33% and there were no large RVOT aneurysms or more than trivial aortic regurgitation.

Figure 1 presents LV and RV diameter z-scores before and after repair of TOF in the overall study cohort. LVEDD and LVESD z-scores were significantly decreased before repair, raised after surgery, but fell again over time. Thus, at all times, both LVEDD and LVESD in the study cohort were significantly smaller than respective normal population means. After repair, RVEDD significantly increased beyond normal range reaching a plateau at a z-score of +5 at 7
years post-operatively. There were trends for negative correlations between time courses of both LVEDD and LVESD z-scores and RVEDD z-scores. Figure 2 demonstrates the negative correlation between LVEDD z-scores and RVEDD z-scores pre-operatively and at all time points from 1 to 9 years follow-up.

PR was the most important factor affecting both LV and RV diameters. As can be seen from Table 2, the degree of PR increased over time after repair. Although 95% of patients had no PR before repair, 18% had none/mild PR, 52% moderate, and 30% severe PR already 1 year after surgery. At 7 and 9 years follow-up, 48% and 43% of patients had developed severe PR, respectively. The lower percentage of patients exhibiting severe PR at 9 years follow-up is explained by the omission of patients who had undergone PVR in the meanwhile.

Figure 3 shows time courses of LV and RV diameter z-scores stratified by the degree of PR at latest follow-up (PR none—moderate vs. PR severe). Time courses of both LVEDD (P = 0.03) and LVESD (P = 0.01) z-scores were indirectly correlated with the degree of PR, whereas time courses of RVEDD z-scores were directly correlated with the degree of PR (P < 0.001).

A further variable significantly associated with time course of LVEDD z-score was the presence of a systemic to pulmonary shunt prior to TOF repair (Figure 4). In patients with previous shunts, LVEDD was significantly higher compared with those without shunt (P = 0.012) and reached normal population means by 7 years after repair. Time courses of LVESD z-scores showed a similar trend. None of the other variables tested (gender, mode of repair, and presence of VSD patch leak) showed a significant association with time courses of LV and RV diameter z-scores in regression models.

Fourteen patients (16%) required PVR a median of 8.9 years (minimum 6.4; maximum 12.0 years) after repair of TOF. Variables associated with requirement for PVR were the increase in RVEDD (P = 0.017) and the degree of PR (P = 0.06). Time courses of LVEDD, LVESD, and RVEDD z-scores before and after PVR are presented in Figure 5. Mean LVEDD and LVESD recovered after PVR and reached normal population means within 3 years. Mean RVEDD decreased significantly over time, but the mean z-score was still +4 above the normal population mean 3 years after PVR.

**Discussion**

After repair of TOF in childhood, the major long-term complication is PR resulting in RV volume overload. Our longitudinal follow-up study, which was performed in a large cohort of children for 9 years, demonstrated an inverse relationship between progressive RV dilation and a decrease in LV diameters. Thus, our results confirm progressive negative RV–LV interaction in this population.

**Right and left ventricular interaction, degree of pulmonary regurgitation**

Prior to repair of TOF, both LVEDD and LVESD were significantly decreased compared with normal (the pre-operative pathophysiology of TOF is characterized by reduced pulmonary blood flow, hence an untrained LV). After repair, LV diameters showed catch-up growth 1 year post-operatively, but decreased again over time. At any time, LV diameters in

**Table 1** Patient characteristics

<table>
<thead>
<tr>
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<th>n = 88</th>
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<tbody>
<tr>
<td>Female</td>
<td>38 (43%)</td>
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<tr>
<td>Hypoxemic spells</td>
<td>45 (51%)</td>
</tr>
<tr>
<td>Pre-operative β-blocker treatment</td>
<td>26 (29%)</td>
</tr>
<tr>
<td>Systemic to pulmonary shunt</td>
<td>21 (24%)</td>
</tr>
<tr>
<td>Age at repair surgery</td>
<td>1.7 years (0.1; 9.0)*</td>
</tr>
<tr>
<td>Mode of repair surgery</td>
<td>Transannular patch 42 (48%)</td>
</tr>
<tr>
<td></td>
<td>Right ventricular outflow tract patch 29 (33%)</td>
</tr>
<tr>
<td></td>
<td>Homograft 12 (13%)</td>
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<tr>
<td></td>
<td>Infundibulotomy 5 (6%)</td>
</tr>
<tr>
<td></td>
<td>Residual VSD patch leak 21 (24%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary valve replacement (PVR) 14 (16%)</td>
</tr>
<tr>
<td></td>
<td>Age at PVR 12.0 years (7.0; 17.5)*</td>
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*Median (minimum; maximum).

Figure 1 Time course of ventricular diameters before and after repair of tetralogy of Fallot (overall cohort). Data (mean and standard error of mean) presented as z-scores. Horizontal lines at zero = normal population mean; horizontal lines at ±2 standard deviations = upper/lower reference limits. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RVEDD, right ventricular end-diastolic diameter; 0, before surgery.

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study patients were significantly smaller than those of healthy children. LVEDD was more decreased than LVESD. Time courses of both LVEDD and LVESD were negatively correlated with the course of RVEDD and the degree of PR.

This progressive decrease of LV diameters is explained by adverse diastolic RV–LV interaction.\textsuperscript{14,18} Diastolic ventricular interaction means that the volume of one ventricle is indirectly influenced by the volume of the other ventricle. Such interaction is normally negligible, but it is accentuated in both RV volume and pressure overload.\textsuperscript{6–8} The anatomic basis of this adverse diastolic RV–LV interaction is the continuity of muscle fibres between the two ventricles and the ventricular septum. Increased filling of the RV impairs LV compliance, and the LV diastolic pressure–volume curve shifts to the left.\textsuperscript{19} In our population, LVEDD was more impaired than LVESD, suggesting that the diastolic function of LV, namely LV filling, is more affected by RV volume overload. A rise in LV filling pressure may potentially aggravate PR by raising diastolic pulmonary artery pressure.\textsuperscript{19}

Diastolic RV–LV interaction may also add to some extent to the exercise intolerance reported by some children with PR. In case of RV volume overload, the LV is not ‘circular’ and LV volume is reduced. Despite normal end-diastolic fibre length and normal fibre shortening, the ejection fraction is reduced. This paradoxical finding is the result of the process of shape change prior to ventricular ejection early in the systole. Of total fibre shortening, only 80–95% is actually devoted to ventricular ejection.\textsuperscript{19} However, due to the retrospective design of our study, we are not able to provide data on ejection fraction.

Two-stage repair with prior shunt, left ventricle

LVEDD \textit{z}-scores were significantly higher in children who had undergone a two-stage repair with prior shunt (24% of the total study cohort) and reached normal population means by 7 years after repair. Time courses of LVESD \textit{z}-scores showed a similar trend. This finding is not confounded by other factors since children with prior shunts or without had

![Figure 2](image_url)

\textit{Figure 2} Graphical display of right and left ventricular interaction. Left ventricular end-diastolic diameter \textit{z}-scores (\textit{x}-axis) and right ventricular end-diastolic diameter \textit{z}-scores (\textit{y}-axis). The bold line represents correlation at all follow-up time points at 1, 3, 5, 7, and 9 years, 0 indicates before surgery.

![Figure 3](image_url)

\textit{Figure 3} Time course of ventricular diameters, stratified by the degree of pulmonary regurgitation. Dotted line with triangles = patients with none/mild/moderate pulmonary regurgitation; full line with squares = patients with severe pulmonary regurgitation at their latest follow-up. Abbreviations as in \textit{Figure 1}.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
Time after repair surgery & Pre-OP (%) & 1 year (%) & 3 years (%) & 5 years (%) & 7 years (%) & 9 years (%) \\
\hline
None PR & 95 & 10 & 4 & 3 & 5 & 2 \\
Mild PR & 1 & 8 & 12 & 15 & 7 & 16 \\
Moderate PR & 3 & 52 & 39 & 46 & 40 & 39 \\
Severe PR & 1 & 30 & 45 & 36 & 48 & 43 \\
\hline
\end{tabular}
\caption{Degree of pulmonary regurgitation during follow-up after repair of tetralogy of Fallot}
\end{table}

Pre-OP, before repair surgery; PR, pulmonary regurgitation.
similar frequencies of transannular patch and of exhibiting severe PR at latest follow-up. 47.5% of children with prior shunts and 48% of children with primary repair had received a transannular patch. The percentage of patients exhibiting severe PR at latest follow-up was 52% in the former and 48% in the latter group, therefore it is rather unlikely that mode of surgery and degree of PR could account for the observed higher LVEDD z-scores in the group with prior shunt. One may speculate, whether larger LV diameters in children with prior shunts may be explained by larger peripheral pulmonary arteries and a better trained LV maintaining better LV filling in spite of progressive RV dilation.20

Left ventricle after pulmonary valve replacement

After PVR, LVEDD and LVESD increased to normal sizes while RVEDD decreased but remained significantly abnormal. This recovery of LV diameters could theoretically contribute to improved exercise tolerance by allowing better LV filling and increased stroke volume. MRI studies performed 1 year after percutaneous pulmonary valve implantation in a cohort of children and adults showed a reduction in RV end-diastolic volume and an increase in LV end-diastolic volume.21 However, despite an increase in stroke volume and improvement of symptoms, significant changes in maximal exercise capacity could not be documented.

The incomplete resolution of RV dilation in our patient population indicates that PVR was probably undertaken too late.22 This may be explained by the fact that in the early years of the study, the indication for PVR was mainly based on the presence of clinical symptoms. Currently, the most accurate method to assess the degree of PR and RV size is cardiac MRI, which is the main tool for deciding about the requirement of PVR.10,13,22,23 Whether the use of cardiac MRI for optimal timing of PVR will improve future long-term outcome requires further studies. Echocardiographic measurement of RV function remains challenging even with the advanced ECHO techniques. M-mode measurements of LV and RV diameters (LVEDD, LVESD, and RVEDD), however, are standardized, consistent, and more readily available than cardiac MRI, particularly in younger children who cannot co-operate with breath holding. From our data, we conclude that time courses of LV and RV diameter z-scores and, especially, ‘RV–LV interaction’ are of utility in the follow-up after repair of TOF. Such serial measurements may be regarded as another ‘puzzle stone’ in the decision-making process for the optimal timing of PVR as demonstrated in Figure 2.
Limitations and strengths

Finally, limitations but also strengths of our study deserve to be mentioned. As to the former: the reader might note rather high RVEDD z-scores observed in our study. These are explained by the measurement of RVEDD in M-modes from the parasternal long-axis view and not from the para-

sternal short-axis view. In the parasternal long-axis view, it is, in fact, the often enlarged RVOT which is measured. This methodical approach, although consistent, may also partly explain the finding of still enlarged RV diameters after PVR. In our institution, PVR was not always combined with reconstruction of the RVOT. Current surgical concepts do not only focus on valve replacement but include also ven-

tricular remodelling to improve the RV function. The increasing use of MRI and application of modern ECHO tech-

iques for the assessment of RV function and morphology will help to select those patients who will benefit from such an approach.24

Strengths of our study are both the longitudinal design using serial measurements over 9 years and the consistency of echocardiographic data obtained in our ECHO unit by applying standardized protocols. Moreover, only the use of z-scores allows appropriate presentation and analysis of serial data in a growing paediatric cohort.

Conclusion

After repair of TOF, LV diameters are significantly smaller compared with LV diameters of normal children. The pro-

gressive decrease in LV diameters is negatively correlated with RV dilation and the degree of PR. Our longitudinal data confirm the adverse RV–LV interaction after repair of TOF in childhood.

We suggest that LV and RV diameter z-scores and, especially, the assessment of RV–LV interaction are intro-

duced into the regular echocardiographic follow-up after repair of TOF. Such serial time courses of LV and RV diam-

eters, mainly their relative changes over time, could be of utility in the scenario of decision-making about the require-

ment of PVR.

Conflict of interest: none declared.

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