Ventricular response to dobutamine stress relates to the change in peak oxygen uptake during the 5-year follow-up in young patients with repaired tetralogy of Fallot

Saskia E. Luijnenburg1,2,3,4, Selma Mekic1, Jochem van den Berg1,2, Rob J. van der Geest5, Adriaan Moelker2, Jolien W. Roos-Hesselink6, Ad J.J.C. Bogers7, Yolanda B. de Rijke8, Jan L.M. Strengers9, Barbara J.M. Mulder4, Hubert W. Vliegen3, and Willem A. Helbing1,2*

1Department of Pediatrics, Division of Cardiology, Erasmus Medical Center—Sophia Children’s Hospital, Sp-2426, PO Box 2060, Rotterdam 3000 CB, The Netherlands; 2Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands; 3Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; 4Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands; 5Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands; 6Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; 7Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, The Netherlands; 8Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, The Netherlands; and 9Department of Pediatrics, Division of Cardiology, University Medical Center—Wilhelmina Children’s Hospital, Utrecht, The Netherlands

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Aims
To evaluate the additional value of dobutamine stress testing in patients with repaired tetralogy of Fallot (TOF) by relating stress imaging parameters at baseline to relevant parameters of clinical condition and right ventricular (RV) size during a serial follow-up.

Methods and results
We prospectively included 27 patients (14 ± 4 years at baseline), who were studied twice with a 5-year interval. Patients underwent cardiovascular magnetic resonance imaging to assess RV systolic and diastolic function at rest and during dobutamine stress. Normal response to dobutamine was defined as a decrease in RV end-systolic volume, and an increase in RV ejection fraction (EF) during stress. Exercise testing and electrocardiography were performed to determine peak oxygen uptake (peak VO2), QRS duration, and QT interval corrected for heart rate (QTc) interval. RV volumes, QRS duration, and QTc interval increased significantly from baseline to follow-up; peak VO2 tended to decrease (95 ± 20–89 ± 14%, P = 0.086). Response to dobutamine was normal in 26 of 27 patients and remained stable during the follow-up [relative increase in RV EF during stress: +25 ± 9% (baseline) vs. +27 ± 10% (follow-up)]. A smaller relative increase in RV EF during stress at baseline related to a larger relative decrease in peak VO2 during the follow-up (r = 0.59, P = 0.004). No significant associations were found with the relative increase in QRS duration, QTc interval, or RV end-diastolic volume during a 5-year follow-up.

Conclusion
In a young TOF population, response to dobutamine stress was normal and remained stable during the 5-year follow-up. A smaller increase in RV EF during stress at baseline was predictive for a larger decrease in peak VO2 during the 5-year follow-up.

Keywords
tetralogy of Fallot • dobutamine stress • cardiovascular magnetic resonance imaging • exercise capacity • serial follow-up

Introduction
Residual pulmonary regurgitation (PR) is an important cause of long-term morbidity in patients after repair of tetralogy of Fallot (TOF).1–5 Patients with severe PR are often treated with pulmonary valve replacement (PVR), but the optimal timing to perform a PVR remains subject for debate. Preoperative thresholds for cardiovascular magnetic resonance (CMR) imaging parameters have been

* Corresponding author. Tel: +31 10 7036264; Fax: +31 10 7036772, Email: w.a.helbing@erasmusmc.nl
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established,6–9 and clinical predictors for adverse outcomes have been recognized.2,5,10–13 Since many of these factors interact, it remains difficult to predict the course of right ventricular (RV) deterioration and clinical condition over time in asymptomatic TOF patients.

CMR imaging during physical or pharmacological stress has been proposed as an additional tool in the early diagnosis of RV dysfunction, since its prognostic value has been proven in patients with coronary artery disease.14,15 Furthermore, in patients with a systemic RV, the inability to decrease RV end-systolic volume (ESV) or to increase RV ejection fraction (EF) during stress was predictive for future cardiac events.16 Various studies have revealed abnormal responses to stress in TOF patients,17–20 but the prognostic value in these patients is yet undetermined.

Our aim was to evaluate the additional value of dobutamine stress testing in patients with repaired TOF by relating stress imaging parameters at baseline to relevant parameters of clinical condition and RV size during a serial follow-up.

Methods

Patients

We conducted a prospective serial follow-up study, for which the inclusion criteria were: (i) surgical repair of TOF without associated cardiac lesions, (ii) corrective surgery at an age of 24 months or younger, and (iii) transatrial–transpulmonary approach to repair. Patients with a residual ventricular septal defect or significant residual pulmonary valve stenosis (echo-Doppler mean gradient > 30 mmHg) were excluded, as were patients with a homograft. Patients with tricuspid regurgitation (TR) were not excluded. Fifty-one patients participated in the baseline study between September 2002 and June 2004.21 Thirty-nine patients agreed to participate in the follow-up study between September 2007 and March 2010. At both time points, patients underwent CMR imaging at rest and during low-dose dobutamine stress, cardiopulmonary exercise testing, 12-lead electrocardiography (ECG), and N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment.

CMR imaging parameters and NT-proBNP levels were compared with groups of healthy controls within our centre: controls–CMR (n = 20): 11 males (55%), 27.0 ± 3.3 years; controls–NT-proBNP (n = 27): 19 males (70%), 19.3 ± 4.3 years. Controls were healthy volunteers without cardiac symptoms.

The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. Our study protocol was approved by the local Ethical Committee; all participants, and if required their parents, gave written informed consent before inclusion in the study.

Cardiovascular magnetic resonance imaging

CMR imaging was performed using a 1.5-T system (General Electric Medical Systems, Milwaukee, WI, USA). An eight-channel phased-array cardiac surface coil was placed on top and beneath the chest. All patients were monitored by vector cardiogram gating and respiratory monitoring. All images were obtained during breath-hold in end-expiration. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in a short-axis orientation. Flow measurements in the pulmonary artery were performed in the main pulmonary artery, just above the level of the original valve tips, if recognizable, or approximately halfway the original valve annulus level and the pulmonary artery bifurcation. Care was taken to be perpendicular to an area of relatively laminar flow at a level away from the valve leaflets and the pulmonary bifurcation. A velocity-encoded CMR imaging sequence was used. All scans were repeated during continuous infusion of dobutamine hydrochloride at 7.5 μg/kg/min, as described previously.21 Dobutamine infusion was decreased to 5.0 μg/kg/min, if any of the following events occurred: an increase of >50% or a decrease of >20% in heart rate or systolic blood pressure, or diastolic blood pressure. The test was discontinued if serious rhythm disturbances were seen, or if the patient experienced a significant discomfort.

Analysis was performed on an Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial borders of both ventricles were manually traced in end-diastole and -systole. Endocardial borders of the RV were defined in all phases and all slices of the short-axis set using a previously described semi-automated full cardiac cycle contour detection method.22 Contours were manually corrected if necessary. Papillary muscles and trabeculations were included in the ventricular cavity. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. The variability of our MR measurements has been reported previously.23 Time volume curves for the RV were acquired by summation of the volumes of every slice of each phase; additionally, RV time volume change curves were reconstructed. All RV data sets were analyzed by a single observer (S.M.) and supervised by another observer (S.L.), who also analyzed all left ventricle (LV) data sets and had 4 years of experience in cardiac contour tracing.

The following parameters were assessed, as has been reported previously: (i) end-diastolic volume (EDV); (ii) ESV; (iii) stroke volume (SV); (iv) EF; (v) early filling fraction, defined as an increase in ventricular volume during the first one-third of diastole, expressed as the percentage of ventricular SV; (vi) deceleration time (Dt), which is the time from the early peak filling rate to the extrapolation point of deceleration of flow to the baseline; (vii) atrial filling fraction, defined as the increase in ventricular volume after the onset of atrial contraction, expressed as the percentage of ventricular SV; (viii) and early-to-atrial (E/A) filling volume ratio. RV effective SV (effSV) was calculated to correct for PR: RVeff.SV = RVSV − PR volume. Volumes were indexed (i) for body surface area, and Dt for the RR interval.

A normal stress response was defined as the ability to decrease RVESVi during stress and to increase RVEFi during stress. The decrease in RVESVi and increase in RVEFi during stress were expressed as relative changes, compared with the value at rest: relative change in RVESVi and increase in RVEFi during stress were expressed as relative changes, compared with the value at rest: relative change in RVESVi = [(RVESVi(stress) − RVESVi(rest)) × 100%], and the relative change in RVEFi = [(RVEFi(stress) − RVEFi(rest)) × 100%].

Clinical parameters

A standardized 12-lead ECG was obtained to determine QRS duration and QT interval corrected for heart rate (QTC).

Blood samples were drawn from a peripheral vein after 30 min rest in a supine position. Plasma and serum were separated immediately after sample collection and stored at −80°C. NT-proBNP was measured using a Cobas E411 immunoanalyzer (Roche Diagnostics, Mannheim, Germany); coefficient of variation <2.55%.

Patients performed a maximal bicycle exercise test on a Jaeger Oxycon Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 10–20 W per minute. Tests were regarded as maximal when the respiratory quotient at peak exercise was ≥1.05. Peak workload and peak oxygen uptake (peak VO2) were recorded and expressed as percentages of the predicted values.24,25 The ventilatory response-to-carbon dioxide production (VE/VO2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.
Statistical analysis
Continuous data were tested for normality with the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean (± standard deviation) and non-normally distributed data as median (range). Differences between groups of patients were evaluated using the Student t-test, paired t-test, or with non-parametric tests, as appropriate. Categorical data are expressed as counts (percentages); differences between groups of patients were evaluated with the χ² test, Fisher’s exact test, or McNemar test. To test the potential additional value of stress imaging parameters on relevant outcome parameters, correlations were assessed using linear regression analysis. The relative change in RVESVi during stress and the relative change in RVEF during stress were defined as independent variables. The change in parameters of clinical condition and RV size during the 5-year follow-up were defined as dependent variables.

Analysis was performed using the SPSS statistical software package version 17.0 (SPSS, Inc., Chicago, IL, USA). A P-value of <0.05 was considered to indicate statistical significance.

Results
Stress imaging data were incomplete in 3 of 39 patients, and 9 other patients had undergone PVR during the 5-year follow-up period. They were excluded from our serial follow-up analysis, and results are therefore given for the remaining 27 patients who had not undergone PVR (referred to as ‘non-PVR’ patients).

TR was not an exclusion criterion, but significant TR was limited in this young patient population. In only three patients, TR of >5 and <10% on CMR imaging was reported.

In three patients (11%), dobutamine infusion was decreased to 5.0 μg/kg/min, because of an increase in the heart rate of >50%. This was well tolerated and the study protocol was completed with a dobutamine dosage of 5.0 μg/kg/min. No serious adverse effects to dobutamine were observed. Characteristics of the patients are displayed in Table 1.

Cardiovascular magnetic resonance imaging
Response to dobutamine
For the parameters of systolic function, the response to dobutamine stress was similar at both time points: a decrease in biventricular EDVi and biventricular ESVi was observed during dobutamine stress, as well as an increase in heart rate, biventricular SVi, RVEff.SVi, and biventricular EF (Table 2). No major changes were observed in RV diastolic functional parameters during dobutamine stress, except for an increase in RV Dt.

At baseline, all patients were able to increase RVEF and to decrease RVESVi during dobutamine stress. At follow-up, only one patient was unable to increase RVEF and to decrease RVESVi during dobutamine stress.

Follow-up period
The relative increase in RVEF during dobutamine stress and the relative decrease in RVESVi during dobutamine stress remained unchanged during the 5-year follow-up; relative increase in RVEF during stress: +25 ± 9% (baseline) vs. +27 ± 10% (follow-up), not significant; relative decrease in RVESVi during stress: −30 ± 10% (baseline) vs. −32 ± 10% (follow-up), not significant.

RV volumes and PR fraction increased significantly during the 5-year follow-up; resting RVEF remained unchanged (Table 2).

Clinical parameters
QRS duration and the QTc interval increased significantly during the 5-year follow-up (Table 1). Exercise capacity was adequate at both time points, but peak VO₂ tended to decrease during the follow-up [peak VO₂: 40 ± 8 mL/kg/min (baseline) to 37 ± 9 mL/kg/min (follow-up), P = 0.051; or 95 ± 20% (baseline) to 89 ± 14% (follow-up), P = 0.086]. NT-proBNP levels remained unchanged during the follow-up, but were higher than in healthy controls (NT-proBNP: 13 ± 10 pmol/L (patients at follow-up) vs. 4 ± 2 pmol/L (controls); P < 0.001).

Correlations
At both time points, a larger decrease in RVESVi during stress related to a larger increase in RVEF during stress (Figure 1A) (both time points: r = −0.72, P < 0.001). Both parameters were used as independent variables to test associations with changes in clinical parameters and RV size during the 5-year follow-up.

A smaller relative increase in RVEF during stress at baseline was significantly associated with a larger decrease in peak VO₂ during the 5-year follow-up [relative change in peak VO₂: (((peak VO₂follow-up − peak VO₂baseline)/peak VO₂baseline) × 100%)]
There were no significant associations, however, between the relative increase in RVEF during stress at baseline and the relative increase in QRS duration or QTc interval during the 5-year follow-up, nor were there significant associations between the relative decrease in RVESVi during stress at baseline and the relative increase in RVEF during stress at follow-up. This patient was 14 years old, his PR was 48%, RVEDVi 187 mL/m2, and RVEF 48%. His peak VO2 had decreased from 90 to 70% of predicted values and QRS duration or QTc interval during the 5-year follow-up, he experienced a significant, increase in RV size, QRS duration, and QTc interval during the follow-up period. Furthermore, peak VO2 tended to decrease during these 5 years. NT-proBNP levels were higher than in healthy controls and remained stable during the follow-up.

Early diagnosis of RV dysfunction in asymptomatic patients after TOF repair remains a challenge and new parameter has been studied to improve decision-making with regard to timing of PVR. Stress imaging might be useful in this process, as its prognostic value has been proven in patients with other types of congenital heart disease. In aortic regurgitation, a lesion that bears a striking resemblance to PR, preserved LV contractile reserve has been related to favourable follow-up results. In patients with a systemic RV, the inability to decrease RVESV or increase RVEF during stress was predictive for adverse cardiac events (e.g. hospitalization for heart failure, cardiac surgery, aborted cardiac arrest, or death) after 8-year follow-up. In our study, with the shorter follow-up, only one patient showed no decrease in RVESVi and no increase in RVEDVi during the 5-year follow-up (r = −0.22, P = 0.28), or between the relative decrease in RVESVi during stress at baseline and the relative increase in resting RVEDVi during the follow-up (r = 0.26, P = 0.20).

**Discussion**

This serial prospective follow-up study demonstrated that, in a young population of patients with repaired TOF and moderate amounts of PR, response to dobutamine stress was good and remained stable during the 5-year follow-up. A smaller increase in RVEF during dobutamine stress at baseline was predictive for a larger decrease in peak VO2 during the 5-year follow-up. Since several studies have established the prognostic value of peak VO2 with regard to adverse outcomes and mortality in patients with congenital heart disease, this finding is of additional value in the follow-up of TOF patients. Clinical condition was adequate in these patients at both time points, although there was a limited, but statistically significant, increase in RV size, QRS duration, and QTc interval during the follow-up period. Furthermore, peak VO2 tended to decrease during these 5 years. NT-proBNP levels were higher than in healthy controls and remained stable during the follow-up.

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**Table 2 Results of CMR imaging parameters at rest and during dobutamine stress for patients and healthy controls**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (N = 20)</th>
<th>Patients (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Follow-up</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>69 (± 11)</td>
<td>78 (± 12)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>30 (± 16)</td>
</tr>
<tr>
<td></td>
<td>RV</td>
<td></td>
</tr>
<tr>
<td>EDV (mL/m2)</td>
<td>97 (± 18)</td>
<td>136 (± 34)§</td>
</tr>
<tr>
<td>ESV (mL/m2)</td>
<td>45 (± 11)</td>
<td>69 (± 21)§</td>
</tr>
<tr>
<td>SV (mL/m2)</td>
<td>52 (± 9)</td>
<td>67 (± 15)§</td>
</tr>
<tr>
<td>EF (mL/m2)</td>
<td>52 (± 9)</td>
<td>46 (± 7)§</td>
</tr>
<tr>
<td>EF (%)</td>
<td>54 (± 5)</td>
<td>50 (± 6)§</td>
</tr>
<tr>
<td></td>
<td>LV</td>
<td></td>
</tr>
<tr>
<td>EDV (mL/m2)</td>
<td>90 (± 14)</td>
<td>81 (± 10)‡‡</td>
</tr>
<tr>
<td>ESV (mL/m2)</td>
<td>38 (± 7)</td>
<td>35 (± 6)</td>
</tr>
<tr>
<td>SV (mL/m2)</td>
<td>52 (± 9)</td>
<td>47 (± 6)‡‡</td>
</tr>
<tr>
<td>EF (%)</td>
<td>58 (± 4)</td>
<td>57 (± 4)</td>
</tr>
<tr>
<td>Early filling fraction (%)</td>
<td>42 (± 11)</td>
<td>38 (± 11)</td>
</tr>
<tr>
<td>Atrial filling fraction (%)</td>
<td>28 (± 9)</td>
<td>33 (± 12)</td>
</tr>
<tr>
<td>E/A volume ratio</td>
<td>1.6 (± 0.6)</td>
<td>1.5 (± 1.2)</td>
</tr>
<tr>
<td>DT/RR interval ratio</td>
<td>0.14 (± 0.05)</td>
<td>0.23 (± 0.09)§</td>
</tr>
</tbody>
</table>

Results are given as mean (standard deviation).

DT, deceleration time; E/A volume ratio, ratio of early-to-atrial filling volume; EDV, end-diastolic volume; EF, ejection fraction; Eff.SV, effective stroke volume; ESV, end-systolic volume; HR, heart rate; LV, left ventricle; CMR, cardiovascular magnetic resonance; PR, pulmonary regurgitation; RV, right ventricle; SV, stroke volume.

Significantly different between baseline and follow-up: *P < 0.01/**P < 0.005.
Significantly different between rest and dobutamine stress: †P < 0.01/‡P < 0.05.
Significantly different between patients and healthy controls: ‡‡P < 0.01/[‡]P < 0.05.
The normal response to dobutamine stress in our TOF patients is in agreement with recently reported results of Parish et al., who demonstrated a decrease in RVESVi and an increase in RVEF with a dobutamine dosage of 10 μg/kg/min in their TOF patients. In a small number of their TOF population, an increase to a dobutamine dosage of 20 μg/kg/min resulted in either lack of further reduction or even increase in RVESVi, and a significant worsening of the increase in RVEF during stress. A limitation to their study is the lack of clinical outcome parameters. Further research is warranted to determine the optimal dobutamine dosage in TOF patients.

Since no hard endpoints were reached in our young TOF population during the follow-up period, we evaluated the additional value of stress testing by assessing relevant relations between stress imaging parameters and parameters that have been shown to have prognostic relevance in the TOF population. These included parameters of RV size, exercise test results, ECG parameters, and NT-proBNP levels. At both time points, we found several significant cross-sectional relations between the relative increase in RVEF during stress or the relative decrease in RVESVi during stress, and parameters of RV size and clinical condition (e.g. RVESVi, QRS duration, QTc interval, and NT-proBNP level) (data not shown). However, we were unable to find a significant correlation between the relative increase in RVEF during stress at baseline and that in resting RVESVi during the 5-year follow-up (r = 0.22, P = 0.28), or between the relative decrease in RVESVi during stress at baseline and the relative increase in resting RVESVi during the follow-up (r = 0.26, P = 0.20). The small number of patients may have limited statistical power, and further studies are needed to establish if the relation is present.

**Limitations**

The main limitation of this study is the lack of hard endpoints. Surrogate markers were explored by means of detailed evaluation of clinical status, CMR imaging measurements, exercise testing, ECGs, and NT-proBNP levels.

Our study has been performed in young TOF patients operated on according to current surgical strategies. Our results may therefore not be representative for older TOF patients.

Our patient population is most likely biased towards patients with a more favourable outcome, since patients who underwent PVR during the follow-up were excluded. This may have influenced our results. Additional analyses in the nine excluded patients who underwent PVR after the baseline study (data not shown) demonstrated a significantly smaller decrease in RVESVi during dobutamine stress at baseline than in our 27 non-PVR patients [relative decrease in RVESVi at baseline: −20 ± 11% (pre-PVR patients) vs. −30 ± 10% (non-PVR patients), P = 0.016]. This may indicate that stress imaging may be of additional value in the decision-making regarding PVR. This should be confirmed in larger studies.
Conclusions

In a young TOF population, operated on according to current surgical strategies, the response to dobutamine stress is normal and remained normal during the 5-year follow-up in the majority of the patients. A smaller increase in RVEF during dobutamine stress at baseline was predictive for a larger decrease in peak VO₂ during the 5-year follow-up. Since peak VO₂ is an important surrogate marker for late deterioration, this indicates the potential additional value of dobutamine stress imaging in the follow-up of TOF patients.

Conflict of interest: none declared.

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