Exercise capacity and ventricular function in patients treated for isolated pulmonary valve stenosis or tetralogy of Fallot

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A R T I C L E   I N F O

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A B S T R A C T

Background: We hypothesized 1) that long-term ventricular outcome and exercise capacity would be better in patients with isolated pulmonary valve stenosis (PS) treated with balloon pulmonary valvuloplasty (BPV) than in patients operated for tetralogy of Fallot (TOF), and 2) that ventricular outcome and exercise capacity would not be different in PS patients and healthy controls.

Methods: We included 21 PS patients after BPV (16.2±5.2 years) and 21 patients operated for TOF (16.6±5.6 years), matching them for gender, age at treatment, and age at study. Patients underwent cardiovascular magnetic resonance (CMR) imaging, exercise testing, 12-lead ECG and 24-hour Holter monitoring for assessment of right ventricular (RV) size and function, pulmonary regurgitation (PR), exercise capacity and electrocardiographic status. Healthy controls for CMR imaging and exercise testing were matched for gender and age at study.

Results: RV volumes and PR percentage were significantly larger in TOF patients than in PS patients; biventricular ejection fraction (EF) was not different. PR was mild in most PS patients. RV end-systolic volume was significantly larger in PS patients than in healthy controls; RVEF was significantly lower. Both patient groups had similar exercise test results. Peak workload and VO2 max. were significantly lower in PS patients than in healthy controls.

Conclusions: Longstanding mild PR in PS patients can lead to an enlarged RV, reduced RV function and reduced exercise capacity. Despite more PR and larger RV volumes in TOF patients, exercise capacity and biventricular function are similar in both patient groups.

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1. Introduction

Residual pulmonary regurgitation (PR) often occurs after treatment for congenital heart disease (CHD), particularly after repair of tetralogy of Fallot (TOF) [1–4] and isolated pulmonary valve stenosis (PS) [5–8]. The effects of severe PR on right ventricular (RV) function and clinical outcome include RV dilatation, decreased right and left ventricular (LV) function, reduction of exercise capacity, arrhythmias, and increased risk of sudden cardiac death [1–3,9,10]. A pulmonary valve replacement (PVR) is often considered in patients treated for TOF, but the best time for performing a PVR is still uncertain, especially in patients with asymptomatic PR [11–15].

Before corrective treatment, the RV is subjected to pressure overload in both types of CHD. In TOF patients, this is combined with hypoxemia caused by a right-to-left shunt at the ventricular level (ventricular septal defect (VSD)). Treatment options also differ significantly: TOF patients undergo a surgical repair in early childhood, whereas patients with isolated PS are now treated with percutaneous balloon pulmonary valvuloplasty (BPV) [16]. These factors may add to differences in long-term outcome with respect to RV function and clinical status.

Long-term outcome in patients after treatment for isolated PS has been studied less extensively than in patients after repair of TOF and most reports in PS patients focus primarily on results of residual pulmonary valve (PV) peak gradients. Results at long-term follow-up are excellent in the majority of the patients, although mild PR is often reported. While most studies have used echocardiography in their evaluation of long-term outcome in patients treated for isolated PS [5–8], very few have used the current gold standard technique for
assessing RV size and function, i.e. cardiovascular magnetic resonance (CMR) imaging [17].

This study was therefore based on two hypotheses: 1) we hypothesized that long-term ventricular function, exercise capacity and clinical status would be better in patients treated for isolated PS than in patients treated for TOF. 2) We hypothesized that ventricular function, exercise capacity and clinical status in PS patients would not differ from those in healthy controls.

To test these hypotheses, we compared the long-term outcome in PS patients after BPV with those in a matched group of TOF patients and in a matched group of healthy controls.

2. Methods

2.1. Patients

The study population of the PS patients consisted of patients who underwent balloon pulmonary valvuloplasty for isolated pulmonary valve stenosis at the Erasmus Medical Center between 1990 and 1995. Thirty patients could be identified from the medical records of the Departments of Pediatric Cardiology and Cardiothoracic Surgery; 21 agreed to participate in the current study. They underwent CMR imaging, exercise testing, echocardiography, 12-lead electrocardiography (ECG), and 24-hour Holter monitoring. These PS patients were compared to patients after repair of tetralogy of Fallot. Patients with TOF undergo the aforementioned tests as part of routine clinical care in our center. TOF patients were randomly selected from the clinical database and were matched to the PS patients for gender, age at treatment, and age at study. Medical records were reviewed for patient characteristics.

Healthy controls, who were matched for gender and age at study, were randomly selected from our databases of healthy volunteers, who had participated in a study to obtain normal values of biventricular function with CMR imaging or in a study to obtain normal values of exercise capacity. Since not all healthy controls had undergone both tests, 2 separate control groups were composed: one for results of CMR imaging and the other for results of exercise testing.

The research study was approved by the local Ethical Committee; all patients, and if required, their parents, gave informed consent.

2.2. Echocardiography

Conventional echocardiography was carried out, consisting of transthoracic M-mode and two-dimensional echocardiography, as well as pulsed-wave and continuous-wave Doppler measurements, using an ultrasound Philips Sonos 5500 (Philips Medical Systems, Best, the Netherlands). The maximum peak gradient across the PV was determined using Doppler measurements and calculated using the modified Bernoulli equation (\(Ap = 4 \times \sqrt{V_{max}^2})\). PR was semi-quantitatively classified as none, mild, moderate or severe, according to the length, the width and the localization of the regurgitant flow [18].

2.3. CMR image acquisition

CMR imaging was performed using a 1.5 Tesla system (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array cardiac surface coil. Standard localizer imaging planes were acquired to plan a short axis set and flow measurements of the pulmonary valve. The short axis set, using steady-state free precession cine imaging, was acquired from base to apex. Typical imaging parameters were: repetition time 3.5 msec., echo time 1.5 msec., flip angle 45°, slice thickness 8–9 mm., inter-slice gap 0–1 mm., field of view 320×240 mm., and matrix 160×128 mm. Flow measurements were performed perpendicular to flow. Typical imaging parameters were: repetition time 4.8 msec., echo time 2.6 msec., flip angle 18°, slice thickness 7 mm., inter-slice gap 0 mm., field of view 290×220 mm., and matrix 256×128 mm. Velocity encoding was set at 150 cm/s, and was increased whenever phase aliasing occurred. All images were obtained during breath-hold in end-expiration.

2.4. CMR analysis

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages QMass (version 5.2) and QFLOW (version 3.2) (Medis Medical Imaging Systems, Leiden, the Netherlands).

The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the left ventricular mass. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml [19].

The following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass. Pulmonary regurgitation (in milliliters) was normalized for systolic SV in the main pulmonary artery and was expressed as a percentage. Additionally, RV effective stroke volume (ef.SV) was calculated to correct for PR: RVef.SV = RVSV – PR volume. Results were indexed for body surface area (BSA). To minimize observer variability, all data sets were analyzed by the same observer (SEI).

2.5. Exercise test

Patients performed a maximal bicycle exercise test on a Jaeger Oxymox Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 15–20 W per minute. Patients were encouraged to perform until exhaustion. Tests were regarded as maximal when the respiratory quotient (RQ) at peak exercise was ≥ 1.05. The following parameters were recorded: peak heart rate, peak workload, peak oxygen uptake (\(V_O_2_{max}\)), anaerobic threshold (AT), and the ventilatory response to carbon dioxide production (VE/\(V_CO_2\)). The AT was determined using the V-slope method [20]. The VE/\(V_CO_2\) slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

2.6. Electrocardiography

A standardized 12-lead ECG was obtained to determine rhythm status, QRS duration and QT interval corrected for heart rate. A 24-hour Holter monitoring was performed in patients on a day with usual activities.

2.7. Statistical analysis

Data are expressed as mean ± standard deviation, as median (range) or as counts (percentages). Differences in continuous data between groups of patients were evaluated using the Student’s t-test, paired t-test or with nonparametric tests. Differences in categorical data between groups of patients were evaluated with the chi-square or Fisher exact test.

Analysis was performed using the SPSS statistical software package version 15.0 (SPSS, Inc., Chicago, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

3. Results

The patient characteristics are displayed in Table 1. There were no significant differences in height, weight, and BSA between the 2 patient groups, who were matched for gender, age at treatment and age at study. NYHA class was not significantly different between the PS and TOF patients.

In 7 TOF patients, a palliative shunt had been placed before corrective surgery (33%); 14 TOF patients had corrective surgery with the use of a transannular patch (70%). In 4 patients with TOF, additional surgery had been performed after the initial surgery and before participation in the study. This included closure of a residual VSD in 3 patients and additional relief of pulmonary stenosis in all 4. Three patients with isolated PS had undergone a re-intervention after BPV and before participation in the study. One PS patient first underwent a repeat BPV, but eventually a surgical relief of the repeat pulmonary stenosis was needed twice. One other PS patient underwent closure of a persistent ductus arteriosus: another had surgical repair of moderate tricuspid regurgitation.

The pulmonary valve peak gradient before treatment was significantly higher in PS patients than in TOF patients (83 ± 21 mm Hg (PS patients) vs. 63 ± 20 mm Hg (TOF patients), p = 0.004) (Table 1). The PV peak gradient significantly decreased immediately after treatment in both patient groups, and decreased even further at long-term follow-up in PS patients. The PV peak gradient immediately after treatment was not significantly different between PS patients and TOF patients. Even so, the PV peak gradient at long-term follow-up was not significantly different between the patient groups.

At long-term follow-up, 20 PS patients (55%) and all TOF patients had pulmonary regurgitation; this was predominantly classified as mild or moderate in PS patients, and as moderate or severe in TOF patients.

3.1. CMR imaging

PR percentage was significantly higher in TOF patients than in PS patients (PR: 30 ± 13% (TOF patients) vs. 10 ± 10% (PS patients),
Results of 24-hour Holter recordings were available for all PS patients and 11 TOF patients. There were no significant differences in mean, minimal or maximal heart rate, and total supraventricular premature beats. The median number of total ventricular premature beats (VPB) was higher in TOF patients than in PS patients, although this was not statistically significant (number of VPBs: 2 (0–7341) (TOF patients) vs. 1 (0–890) (PS patients), p = 0.07). One PS patient had 1 run of ventricular tachycardia (VT), consisting of 5 heart beats. Another PS patient had 2 runs of supraventricular tachycardia (SVT), consisting of 13 heart beats in total. None of the TOF patients showed runs of VT or SVT.

4. Discussion

Our results show that adolescent patients with isolated pulmonary valve stenosis and tetralogy of Fallot, whose age at treatment, duration of follow-up, and residual RV outflow gradient were similar, have similar clinical outcomes (NYHA class, and exercise performance). Although clinical condition, as assessed using the NYHA class, was good in the majority of the patients, exercise performance was significantly reduced in both patient groups. Residual PR in the PS

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study population and results of echocardiography.</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>PS patients (N=21)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 ± 13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 ± 20</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.62 (± 0.33)</td>
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<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>Class II</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Age at treatment (yrs)</td>
<td>3.6 (± 4.2)</td>
</tr>
<tr>
<td>Age at study (yrs)</td>
<td>16.2 (± 5.2)</td>
</tr>
<tr>
<td>Interval between treatment and study (yrs)</td>
<td>12.6 (± 2.1)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>PV peak gradient before treatment (mmHg)</td>
<td>83 (± 21)*</td>
</tr>
<tr>
<td>PV peak gradient immediately after treatment (mmHg)</td>
<td>26 (± 10)†</td>
</tr>
<tr>
<td>PV peak gradient at long-term follow-up (mmHg)</td>
<td>15 (± 11)‡</td>
</tr>
</tbody>
</table>

Reported data are expressed as mean (SD) or as counts (percentages).
* Significant difference between PS patients and TOF patients.
† Significant difference between results before treatment and immediately after treatment.
‡ Significant difference between results immediately after treatment and at long-term follow-up.

| Abbreviations: PS = pulmonary stenosis; TOF = tetralogy of Fallot; BSA = body surface area; NYHA = New York Heart Association; PV = pulmonary valve. |

p<0.001 (Table 2). Right ventricular volumes (EDV, ESV, and SV) and mass were also significantly larger in TOF patients than in PS patients (RVEDV: 131 ± 29 ml/m² (TOF patients) vs. 101 ± 20 ml/m² (PS patients), p = 0.001; RVESV: 66 ± 20 ml/m² (TOF patients) vs. 51 ± 15 ml/m² (PS patients), p = 0.009). RV effective SV, biventricular EF and LV volumes and mass were not significantly different between the 2 patient groups.

RVESV was significantly larger in PS patients than in healthy controls, and RVEF was significantly lower (RVESV: 51 ± 15 ml/m² (PS patients) vs. 41 ± 9 ml/m² (healthy controls), p = 0.02; RVEF: 50 ± 6% (PS patients) vs. 54 ± 3% (healthy controls), p = 0.02). RVEDV was larger in PS patients than in healthy controls, but this was not statistically significant (RVEDV: 101 ± 20 ml/m² (PS patients) vs. 90 ± 18 ml/m² (healthy controls), p = 0.09). All other parameters were not significantly different between PS patients and healthy controls.

3.2. Exercise test

The exercise test results are given in Table 3. None of the parameters was significantly different between PS patients and TOF patients. Peak heart rate, peak workload, VO₂ max., and the AT were significantly lower in PS patients than in healthy controls (VO₂ max.: 36 ± 10 ml/kg/min (PS patients) vs. 44 ± 7 ml/kg/min (healthy controls), p = 0.004). The VE/VO₂ slope was not significantly different between PS patients and healthy controls.

3.3. Electrocardiography

12-lead ECG data were available for all patients. All patients were in sinus rhythm. The QRS duration was significantly longer in TOF patients than in PS patients (127 ± 23 ms. (TOF patients) vs. 95 ± 20 ms. (PS patients), p<0.001). A complete right-bundle branch block (RBBB) was significantly more present in TOF patients than in PS patients (a complete RBBB in 15 TOF patients (71%) vs. 1 PS patient (5%), p<0.001). The heart rate, PQ time, and QT time corrected for heart rate were not significantly different.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results of CMR imaging.</th>
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<tr>
<td>Parameter</td>
<td>PS patients (N=19)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>16.2 (± 5.2)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.62 (± 0.31)</td>
</tr>
<tr>
<td>PR (%)</td>
<td>10 (± 10)§</td>
</tr>
</tbody>
</table>

Reported data are expressed as mean (SD).
* Significant difference between PS patients and TOF patients.
† Significant difference between PS patients and healthy controls.
§ Significant difference between results immediately after treatment and at long-term follow-up.

Results of exercise testing.

| Parameter | PS patients (N=19) | TOF patients (N=21) |
|---------|------------------------------------------------------------------------|
| Age (years) | 16.2 (± 5.2) | 16.6 (± 5.6) |
| Height (cm) | 165 (± 13) | 159 (± 13) |
| Peak heart rate (beats/min) | 176 (± 15)* | 181 (± 12) |
| Peak workload (Watt) | 142 (± 40)* | 138 (± 34) |

Reported data are expressed as mean (SD).
* Significant difference between PS patients and healthy controls.
group was mild, with a mean PR percentage of 10 ± 10% versus 30 ± 13% in the TOF group. Considering the differences in techniques used to relieve the RV outflow stenosis, it was not unexpected to find more PR after treatment for TOF than for isolated PS. Although RV volumes were significantly larger in TOF patients than in PS patients, LV size, RV effective SV, and biventricular function were not significantly different. Despite the minimal residual RV outflow stenosis and mild PR in the PS group, CMR imaging revealed a larger RVEF and a lower RVEF in the PS group compared with the results in healthy controls.

Relatively few studies have reported on the long-term clinical outcome after BPV for isolated PS. Our study confirms that PR is generally mild in PS patients at follow-up after BPV [5–8]: only 3 PS patients in our study had a PR percentage >20%. RV enlargement has been considered uncommon in PS patients after BPV. Assessment of RV dimensions in most previous studies, however, has been done using echocardiography [5,7,21]. Recently, Harrild et al. studied PS patients after BPV using CMR imaging and reported that mild PR and mild RV dilatation were often present at long-term follow-up, but that severe PR and severe RV dilatation were very uncommon [17]. Our own results demonstrated that longstanding mild PR in PS patients is associated with an increase in RVEF and a decrease in global RV function. Furthermore, our PS patients had a reduced exercise capacity. These results confirm those of the study by Harrild et al., who also found a reduced VO2 max. in PS patients.

Although results of exercise testing in patients after repair of TOF are available in the literature, their results differ considerably [10,11,22]. In adults operated on for TOF, VO2 max. has varied between 58% and 80% of predicted values [10,22]. Age at operation and duration of follow-up are important factors to consider. The good results in our TOF group might be explained by our patients’ relatively young age at surgery and young age at study relative to those of the TOF patients described in earlier studies. A younger age at surgery has been recognized to be related to a more favorable clinical outcome [3].

In contrast with our second hypothesis, exercise performance in PS patients was significantly lower than in healthy controls. This might in part be explained by impaired chronotrophy, since the maximal heart rate was significantly lower than in healthy controls. It is striking that the TOF patients in our study had similar results on exercise testing as PS patients, despite significantly higher amounts of PR. A similar result was also found in a study by Yetman et al., who compared a group of pediatric PS patients after surgical valvulotomy with a matched group of TOF patients [23]. Remarkably, exercise capacity was more severely impaired in the PS patients in Yetman’s study than it was in the TOF patients. The authors argued that this might result from diastolic RV restriction in TOF patients, which was suggested to improve exercise capacity, as reported by Gatzoulis et al. [24]. This has however, not been confirmed either in pediatric and adolescent TOF patients who were operated on at a younger age or in a recent study in adult TOF patients [22,25].

In recent years, an abnormal ventilatory response to exercise, as assessed by an elevated VE/VCO2 slope, has been shown to be a powerful predictor of cardiac-related mortality in patients with CHD [10,26]. Our results were comparable to the results reported by Giardini et al., who found a VE/VCO2 slope of 31 ± 5 in their total group of TOF patients [10]. In our study however, the VE/VCO2 slope was not significantly different between PS patients and healthy controls and was also not different between the 2 patient groups.

Our study confirms the adverse effects of longstanding PR. At the same time, exercise performance and ventricular function were comparable between the PS and TOF group, despite important differences in RV dimensions. Based on the fact that exercise capacity was similar in both patient groups, the relatively short hypoxic period before corrective surgery doesn’t seem to have a negative influence on exercise capacity in these TOF patients at the current follow-up duration. It seems therefore that other factors have more impact on exercise capacity, like for example the amount of PR or global RV function. PR percentage was not correlated with peak oxygen uptake or the VE/VCO2 slope however, although the limited number of patients in the study is a factor to consider. The similar biventricular function in our PS and TOF patients might be an explanation for their similar exercise test results.

A recent functional analysis of 3 components of the RV in adolescent TOF patients by Bodhey et al., demonstrated that the ejection fraction of the apical trabecular component, which provides the major ejective momentum, is maintained in patients with slight to moderate ventricular dysfunction [27]. In TOF patients operated on at a young age, RV contractile reserve is also well preserved [28]. These findings suggest that RV myocardial performance may be well maintained in TOF patients operated on at a young age, despite enlarged RV size. The RV may therefore be well suited to perform its role of maintaining LV preload in this situation.

It might be speculated that long-term prognosis in TOF patients eventually will be worse than in PS patients, since TOF patients already have a more severe RV dilatation at this follow-up duration. Previous studies have suggested that there is a threshold for the dimension of the RVEDV, above which the RV does not recover completely, even if a PVR is performed [11,12,14,15].

Arrhythmias are an important problem in patients with residual PR, particularly in patients with TOF [9,29]. Significant ventricular arrhythmias in PS patients are uncommon [30], which is in agreement with our results. A QRS duration of >180 ms and an older age at repair are associated with a higher risk of ventricular tachycardia and sudden death [9]. Dietl et al. reported a significant reduction in ventricular arrhythmias in TOF patients who had had a transatrial repair than in those who had had a transventricular repair [29]. Significant ventricular arrhythmias in our TOF patients were uncommon. This relates to the mild QRS prolongation, young age at repair and transatrial surgical repair in most of the patients. None of our patients had a QRS duration >180 msec.

5. Limitations

No echocardiographic data was available for 10 TOF patients before treatment and for 2 TOF patients immediately after treatment, in all of whom the assessment of RV outflow gradients had been based on results from cardiac catheterizations. Particularly, the significant difference in PV peak gradient before treatment between PS patients and TOF patients should therefore be interpreted with caution.

In some of the older TOF patients, data from exercise testing and 24-hour Holter monitoring were missing. Since exercise capacity might be better preserved at a younger age, this may have resulted in an overestimation of the exercise capacity in the TOF patients.

We studied children, adolescents and young adults treated at a young age. Our results are therefore representative for patients with a similar age and follow-up-duration.

Since we only had small patient groups, a limited statistical power is a factor to consider.

6. Future perspectives

Assessment of RV volumes and function with CMR imaging in patients treated with BPV for isolated PS has hardly been done before. We found that PS patients had a larger RV, a lower RV function, and a lower exercise capacity than healthy controls, although their clinical condition was excellent. Since we only had a small PS patient group, results should be confirmed in larger studies. Serial follow-up studies in PS patients are necessary to evaluate the degree of progression of their PR and RV dilatation and to see how this influences their clinical condition and exercise capacity later in life.

Serial follow-up data might also be useful to evaluate whether certain parameters, like PR percentage and RV dilatation, might be more progressive in the TOF group and to see how this would then influence biventricular function and exercise capacity at longer term follow-up.
7. Conclusion

In contrast to our hypothesis, pediatric and adolescent patients with isolated pulmonary valve stenosis have a lower exercise capacity, a larger right ventricle and a lower RV function than healthy controls, although their clinical condition is excellent. However, exercise performance and biventricular function are similar to those in patients with tetralogy of Fallot, despite more severe pulmonary regurgitation and larger RV volumes in Fallot patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical publishing in the International Journal of Cardiology [31,32].

References