Effect of age on exercise capacity and cardiac reserve in patients with pulmonary atresia with intact ventricular septum after biventricular repair

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INTRODUCTION

Pulmonary atresia with intact ventricular septum (PAIVS) is an uncommon congenital heart disease (CHD) with variable grades of right ventricular (RV) hypoplasia and tricuspid valve (TV) abnormalities. Management of PAIVS is challenging due to the wide anatomic variations requiring different treatment strategies [1, 2]. RV decompression by means of transcatheter opening of pulmonary valve surgical pulmonary valvotomy or transannular patch is usually the first treatment step after birth if the size of the RV and the TV are adequate and if the coronary circulation is not RV-dependent. In PAIVS patients with mild-to-moderate RV hypoplasia, biventricular repair can usually be achieved although some patients require aortopulmonary shunts early in life [3]. It is generally believed that cardiac function in PAIVS patients is better after biventricular repair than after univentricular repair or the so-called one-and-a-half ventricular repair. However, there is limited evidence to support this [4-8].

In contrast, studies showed that following a biventricular repair, patients with PAIVS still have abnormal RV diastolic function and atrial dilatation, which may negatively influence exercise capacity [5, 9]. It has been reported that peak exercise capacity did not differ between patients with PAIVS after biventricular or univentricular repair [10]. In this study, there was a trend towards...
impaired exercise performance in older patients with PAIVS irrespective of the type of operation. The question then arises as to whether the relatively small and hypertrophied RV in PAIVS is capable of effectively supporting the pulmonary circulation in the long-term. Thus far, detailed studies on biventricular function in PAIVS patients in relation to exercise performance are lacking. Dobutamine stress magnetic resonance imaging (DS-MRI) is an important imaging modality for accurate assessment of cardiac reserve as an early predictor of cardiac dysfunction [11, 12]. Delayed contrast enhancement (DCE)-MRI using gadolinium-based contrast media allows direct visualization of myocardial fibrosis [13].

In the present study, we evaluated exercise capacity and biventricular response to pharmacological stress using DS-MRI in children and young adults with PAIVS after biventricular repair. Furthermore, the presence of myocardial fibrosis was assessed using DCE-MRI.

PATIENTS AND METHODS

The local medical ethics committee approved the study, and informed consent was obtained from all participants and/or parents prior to enrolment. Patients with PAIVS after biventricular repair followed at our institutions, older than 8 years, and with no contra-indication for MRI examination were included in the study. Patients were recruited from the institutional paediatric cardiology database and the national database and DNA data bank of adult patients with a CHD (www.concor.nl) [14]. The database identified 19 eligible patients. Nine patients were excluded for the following reasons; 7 patients refused to participate, one patient was pregnant and one patient had a percutaneous pulmonary valve implantation at this time. Thus, 10 patients between 9 and 42 years of age were included. All patients underwent a symptom-limited cardiopulmonary exercise test with determination of maximum oxygen consumption ($V_{\text{O}_2\max}$) and MRI examination including DCE-MRI and DS-MRI.

Cardiopulmonary exercise test

A symptom-limited cardiopulmonary exercise test, to assess maximal exercise capacity, was performed, according to the Guidelines of the American Thoracic Society [15]. Graded exercise testing on a motor-driven treadmill (Jaeger Oxyconpro, Wuerzburg, Germany) using a modified Bruce protocol was performed in children, and a cycle ergometer (Jaeger Oxyconpro) was used in adults. Continuous heart rate monitoring was done and maximum heart rate (MHR) documented. $V_{\text{O}_2\max}$ was defined as the highest value of oxygen uptake measured twice during the last 15 s of exercise. Oxygen pulse (O$_2$-pulse) was assessed as it is an indirect index of combined cardiopulmonary oxygen transport, and thus stroke volume (SV). Exercise tests were considered valid if the patient reached the anaerobic threshold, defined as having a respiratory exchange ratio (RER) > 1. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman et al. [16]. Impaired exercise capacity was defined as $V_{\text{O}_2\max} < 85\%$ of the predicted values [16].

Magnetic resonance imaging

MRI was performed using an open MRI 1T MRI scanner (Panorama 1T, Philips Medical Systems, Best, Netherlands). Long-axis, 2- and 4-chamber views and short-axis views consisting of 12–14 contiguous slices, covering both the ventricles from the base of the heart to the apex, were acquired using a retrospective electrocardiogram (ECG)-gated steady-state free precession sequence during breath holding at end-expiration. Scan parameters were: repetition time (TR) = 3.2–3.8 ms; echo time (TE) = 1.6–1.9 ms; flip angle (FA) = 50–70°; slice thickness = 8 mm without slice gap; matrix = 160 × 256; field-of-view = 350–400 mm. Temporal resolution was ~25 ms. A retrospective ECG-gated phase-contrast cine sequence with a through-plane velocity encoding was used to assess the flow across pulmonary valve and TV during a breath hold. Scan parameters were: TR = 9 ms, TE = 5 ms, FA = 15–20°, slice thickness = 6–8 mm, matrix = 128 × 256, temporal resolution = 20 ms. Short-axis images were repeated at maximum dobutamine infusion.

Dobutamine infusion

An intravenous line was inserted into the antecubital vein prior to the MRI procedure. Dobutamine was administrated by a digital MRI-compatible infusion pump. After the MRI acquisition at rest, dobutamine was infused in serial incremental doses of 5, 10 and 15 µg/(kg/min) in 3-min stages. Infusions were performed under continuous monitoring with ECG and automated blood pressure measurements. The endpoint for termination of dobutamine infusion was reaching a target heart rate, 85% of age-predicted maximal heart rate (220–age in years) or 15 µg/(kg/min) of dobutamine infusion.

Delayed contrast enhancement MRI

Ten to fifteen minutes after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg), DCE images were acquired in the same orientation as the cine short-axis images using a segmented inversion-recovery gradient-echo pulse sequence. Scan parameters were: TR/TE = 4.01/1.25 ms, FA = 15°, matrix = 208 × 256 and a typical voxel size of 1.6 × 1.3 × 5 mm$^3$, inversion time (TI) = 180–200 ms.

MRI post-processing

All images were analysed on a workstation with an Intel® Pentium® 4 processor (Intel, Santa Clara, CA, USA). Left ventricular (LV) and RV volumes and function were analysed with the software package MASS (Medis, Leiden, Netherlands). Flow velocity-encoded MRI data were analysed using the software package FLOW (Medis).

Vascular contours were drawn for the pulmonary trunk to generate flow versus time curves throughout the cardiac cycle. Peak flow velocity was measured; the presence of pulmonary regurgitation (PR) was assessed and regurgitation fraction (RF) was calculated as percent backward flow over forward flow. The presence of late diastolic forward flow (DDF) in the pulmonary artery was assessed, and late DFF% was defined as percentage of
late DFF over the total pulmonary artery forward flow. Flow versus time curves for TV flow were analysed to assess RV E/A volume ratio.

Biventricular systolic function was assessed by drawing endocardial contours at end-diastole and end-systole in all sections of the cine short-axis data [17]. End-diastolic (EDV) and end-systolic volumes (ESV) were obtained. SVs were calculated by subtracting ESV from EDV. In the presence of significant PR, defined as PR fraction > 20%, the effective RV-SV was calculated, defined as RV-SV minus regurgitant flow, assessed with flow mapping. Ejection fraction (EF) was calculated by dividing SV by EDV × 100%, LV-EF > 50%, and RV-EF > 47% was defined as normal [18]. Cardiac output (CO) was calculated by multiplying SV by HR. All volumetric parameters were indexed for body surface area according to the Mosteller formula: (Height (cm) × weight (kg)/3600). Two observers (S.R. and M.G. with 4 and 15 years of experience in cardiac MRI, respectively) agreed on the presence or absence of DCE in the LV and RV.

**STATISTICAL ANALYSIS**

All statistical testing and data analyses were performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA). The cardiac function parameters at rest and during the maximum pharmacological stress were compared using the paired Student’s t-test in the case of normal distribution or the Wilcoxon test for pairwise comparisons. Variables that were normally distributed are presented as mean and standard deviation; variables with skewed distribution are presented as medians and range. The presence of normal distribution was tested using the Shapiro–Wilk test. Finally, the correlation between the patients’ ages and cardiac work indices during the physical stress, cardiac function parameters at rest and during maximum pharmacological stress was evaluated. The Pearson correlation coefficient was calculated if the variables were normally distributed; otherwise, Spearman rank correlation was calculated. Differences were accepted as statistically significant at P < 0.05.

**RESULTS**

**Patient characteristics**

Characteristics of the patients are displayed in Table 1. All patients were asymptomatic, New York Heart Association (NYHA) class I or II and received no medication. Systolic pulmonary artery pressures at rest were normal in all patients (26 ± 7 mmHg) as assessed by echocardiographic flow velocity measurements of the tricuspid regurgitation.

At birth, all patients had a Z-value of TV diameter of greater than −2.5, and a tripartite or bipartite RV. None of them had RV-dependent coronary circulation, or Ebstein’s malformation of TV.

All patients had a surgical RV outflow tract (RVOT) reconstruction in the neonatal period, nine patients had pulmonary valvotomy and one patient had an RVOT patch. Aortopulmonary shunts were placed in seven patients (70%). Age at complete surgical repair was 2.5 ± 0.5 years. At the time of complete repair, five patients (50%) had an interatrial communication in the form of an atrial septal defect (ASD). Surgical or catheter-directed closure of ASD was performed in all of them at a later stage.

All patients completed the cardiopulmonary exercise test, DCE-MRI and DS-MRI with no adverse events. In particular, none of the patients had episodes of hypotension or sustained arrhythmia, leading to early termination of any test. None of the participants experienced headache, chest pain or palpitations, and no ST-T changes or premature ventricular complexes were recorded on the ECG.

**Cardiopulmonary exercise test**

The cardiopulmonary exercise parameters are summarized in Table 1. All patients achieved an RER > 1, indicating that all patients reached the anaerobic threshold. Median VO2max was 92% of the predicted (range, 60–100%), and median O2-pulse was 97% of the predicted (range, 65–130%). During the exercise test, all patients remained in sinus rhythm and showed an adequate chronotropic response; MHR was 95 ± 2% of the predicted. A strong negative correlation was observed between the patients’ ages and VO2max and O2-pulse (r = −0.72, P = 0.01 and r = −0.74, P = 0.01, respectively; Fig. 1A and B) but not with MHR (r = 0.01, P = 0.9).

**Magnetic resonance imaging**

MRI images of good quality were obtained in all patients at rest and during dobutamine infusion. Data are presented in Table 2. Remarkably, none of the patients showed DCE in RV or LV. All patients had a normal LV and RV systolic function at rest. All patients had a significant PR (RF = 24.7 ± 6.2%) and relatively large RV-EDV. None of the patients had a residual RVOT obstruction (maximum velocity = 2.3 ± 0.7 m/s). Late DFF in the pulmonary artery was present in 70% of the patients and late DFF% strongly correlated with the patients’ age (r = 0.66, P = 0.03). RV E/A volume ratio is negatively correlated with the

**Table 1:** Patients’ characterization and results of the cardiopulmonary exercise test

<table>
<thead>
<tr>
<th>Number of males (%)</th>
<th>10 (3–30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>12 (9–42)</td>
</tr>
<tr>
<td>Median follow-up period after surgical repair (years, range)</td>
<td>11 (8–40)</td>
</tr>
<tr>
<td>NYHA functional classification</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Class I</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Class II</td>
<td>1.1 ± 0.05</td>
</tr>
<tr>
<td>Rest heart rate (bpm)</td>
<td>80 ± 4</td>
</tr>
<tr>
<td>MHR (bpm)</td>
<td>182 ± 4</td>
</tr>
<tr>
<td>MHR (% of predicted)</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Median VO2max (ml/(kg/min), range)</td>
<td>45.2 (19.1–51)</td>
</tr>
<tr>
<td>Median VO2 (%) (% of predicted, range)</td>
<td>92 (60–100)</td>
</tr>
<tr>
<td>Median O2-pulse (ml/beat, range)</td>
<td>10.6 (7–10)</td>
</tr>
<tr>
<td>Median O2-pulse (% of predicted, range)</td>
<td>97 (65–130)</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association; MHR: maximum heart rate; bpm: beats per minute; RER: respiratory exchange rate; VO2max: maximum oxygen consumption; O2-pulse: oxygen pulse.
patients’ ages ($r = 0.65$, $P = 0.04$), indicating impaired RV diastolic function with age.

In response to pharmacological stress, there was an adequate chronotropic response and adequate RV-EF increase. This resulted in a significant increase in RV-SV and RV-CO. LV showed a similar response (Table 2). There was a positive correlation between RV E/A ratio and RV-SV ($r = 0.77$, $P = 0.009$).

There was a negative correlation between the patients’ age and LV-SV, and RV-SV during peak dobutamine infusion ($r = -0.72$, $P = 0.02$ and $r = -0.64$, $P = 0.04$, respectively; Fig. 1C and D), whereas there was no correlation with the other RV or LV function parameters during dobutamine infusion (Table 2).

$V_{O_{2\text{max}}}$ and $O_{2\text{-pulse}}$ during physical exercise correlated with LV-SV response to pharmacological stress ($r = 0.74$, $P = 0.01$ and $r = 0.65$, $P = 0.04$, respectively; Fig. 2A and C) and to RV-SV response ($r = 0.73$, $P = 0.01$ and $r = 0.84$, $P = 0.002$, respectively; Fig. 2B and D) but not to LV-SV at rest ($r = 0.48$, $P = NS$ and $r = 0.34$, $P = NS$, respectively) and to RV-SV at rest ($r = 0.47$, $P = NS$ and $r = 0.39$, $P = NS$, respectively).

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Table 2: Results of DS-MRI and correlation between the patients’ age and cardiac parameters at rest and at maximum dobutamine infusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Stress</th>
<th>$P$-value</th>
<th>Correlation between age and rest parameters</th>
<th>Correlation between age and stress parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>74 ± 8</td>
<td>130 ± 23</td>
<td>&lt;0.001</td>
<td>$r = -0.29$, NS</td>
<td>$r = 0.30$, NS</td>
</tr>
<tr>
<td>RV EDV (ml/m²)</td>
<td>103.4 ± 20.3</td>
<td>99 ± 21.8</td>
<td>NS</td>
<td>$r = -0.20$, NS</td>
<td>$r = -0.33$, NS</td>
</tr>
<tr>
<td>RVESV (ml/m²)</td>
<td>47.4 ± 15.4</td>
<td>32.9 ± 12.9</td>
<td>&lt;0.001</td>
<td>$r = -0.22$, NS</td>
<td>$r = -0.12$, NS</td>
</tr>
<tr>
<td>Effective RV-SV (ml/m²)</td>
<td>42.1 ± 3.4</td>
<td>50 ± 10.1</td>
<td>0.002</td>
<td>$r = 0.52$, NS</td>
<td>$r = -0.73$, 0.01</td>
</tr>
<tr>
<td>RV-EF (%)</td>
<td>53.8 ± 6.6</td>
<td>67.7 ± 8.8</td>
<td>&lt;0.001</td>
<td>$r = -0.06$, NS</td>
<td>$r = -0.09$, NS</td>
</tr>
<tr>
<td>RV-CO (L)</td>
<td>6.2 ± 1.8</td>
<td>9.9 ± 3.9</td>
<td>&lt;0.001</td>
<td>$r = 0.15$, NS</td>
<td>$r = 0.20$, NS</td>
</tr>
<tr>
<td>RV E/A volume ratio</td>
<td>1 ± 0.3</td>
<td>9.3 ± 3.9</td>
<td>&lt;0.001</td>
<td>$r = -0.70$, 0.02</td>
<td>$r = 0.80$, 0.005</td>
</tr>
<tr>
<td>Pulmonary late DFF</td>
<td>7.4 ± 2.3</td>
<td>8.9 ± 1.6</td>
<td>0.39</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PRF (%)</td>
<td>24.7 ± 6.2</td>
<td>34.7 ± 5.6</td>
<td>0.80</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LV EDV (ml/m²)</td>
<td>85.4 ± 10.4</td>
<td>80.2 ± 12.8</td>
<td>NS</td>
<td>$r = -0.52$, NS</td>
<td>$r = -0.67$, NS</td>
</tr>
<tr>
<td>LVEVF (ml/m²)</td>
<td>42.1 ± 6.5</td>
<td>29.9 ± 6.6</td>
<td>&lt;0.001</td>
<td>$r = -0.22$, NS</td>
<td>$r = -0.36$, NS</td>
</tr>
<tr>
<td>LV-SV (ml/m²)</td>
<td>43 ± 8.3</td>
<td>51.5 ± 10.2</td>
<td>0.001</td>
<td>$r = -0.44$, NS</td>
<td>$r = -0.69$, 0.02</td>
</tr>
<tr>
<td>LV-EF (%)</td>
<td>56.5 ± 6.2</td>
<td>68.8 ± 6.4</td>
<td>&lt;0.001</td>
<td>$r = -0.12$, NS</td>
<td>$r = -0.16$, NS</td>
</tr>
<tr>
<td>LV-CO (L)</td>
<td>4.6 ± 0.9</td>
<td>7.5 ± 2.8</td>
<td>0.003</td>
<td>$r = -0.05$, NS</td>
<td>$r = 0.11$, NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD. LV: left ventricle; RV: right ventricle; bpm: beats per minute; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; CO: cardiac output; DFF: diastolic forward flow; PRF: pulmonary regurgitation fraction.
DISCUSSION

Biventricular repair for PAIVS provides satisfactory results in terms of survival and clinical outcomes during early follow-up period. However, comprehensive long-term follow-up studies on RV performance are still limited [1–3, 5].

In the present study in asymptomatic PAIVS patients, we demonstrated that both exercise capacity and biventricular SV response to pharmacological stress decreased with age. Furthermore, we demonstrated that RV diastolic function decreased with age in PAIVS patients correlating well with impaired RV-SV response to pharmacological stress. Finally, we showed a strong correlation between cardiac work indices during physical stress ($V_{O_2 \text{max}}$) and biventricular SV response to pharmacological stress, but not biventricular SV at rest.

Impaired exercise capacity in patients with CHD, even among asymptomatic patients, is a useful predictor for adverse long-term clinical outcomes [19]. In PAIVS patients, few studies are available on exercise capacity evaluation [4, 10].

Our results are in line with the results of Sanghavi et al. [10] who investigated exercise capacity in PAIVS patients after univentricular and biventricular repair. Exercise capacity did not appear to differ between PAIVS patients after biventricular and univentricular repair. However, older PAIVS patients tended to have decreased exercise capacity irrespective of the type of surgical repair. Ekman-Joelsson et al. [4] demonstrated a better exercise capacity in PAIVS patients after biventricular repair when compared with PAIVS patients after univentricular repair. In contrast to our findings, no correlation was found between the patients’ age and exercise capacity, which may be explained by the younger age of their patient cohort. Comparable to our data, both studies showed that cardiac function parameters at rest did not predict exercise capacity in this specific group of patients [4, 10].

In patients with CHD, including children, cardiac reserve can be assessed accurately and safely using DS-MRI, allowing for detection of cardiac dysfunction, which is not present at rest [12, 20]. Thus far, there is no previously published data on cardiac reserve assessment in PAIVS patients after biventricular repair.

In the present study, we demonstrated that with age PAIVS patients failed to increase RV-SV despite adequate increase in RV-EF in response to dobutamine even in the absence of myocardial fibrosis. This could be explained by unfavourable ventricular filling due to impaired RV diastolic function in older PAIVS patients. Deterioration of diastolic function with age is well known and is mainly due to increasing ventricular stiffness [21–23]. In PAIVS patients, impairment of RV diastolic function appears to occur early within the second decade of life. Several causative factors may play a role in the early onset of RV diastolic dysfunction. These include size and dysplasia of the TV, endocardial and myocardial abnormalities of the RV such as major RV hypertrophy, extensive myocardial fibre disarray and endocardial fibroelastosis at the time of birth [3, 24]. Surgical procedures, such as pulmonary valvulotomy or RVOT patch reconstruction, may allow RV growth but probably do not allow normalization of these significant myocardial abnormalities [3, 5, 24].

A recent study in PAIVS patients following biventricular repair showed that the presence of RV myocardial fibrosis using DCE correlated with both the occurrence of late pulmonary DFF and reduced myocardial tissue velocities, indicating impairment of RV diastolic function [25]. In contrast to this study, we were unable to detect any RV or LV myocardial fibrosis by DCE in our group of PAIVS patients. A possible explanation may be that in the study by Liang et al. [25], the majority of patients had an RVOT patch compared with only one patient in our cohort. Furthermore, the DCE acquisition parameters were not

![Figure 2: Correlation between $V_{O_2 \text{max}}$ and biventricular SV response to the pharmacological stress: (A) LV-SV and (B) effective RV-SV. Correlation between $O_2$-pulse and biventricular SV response to the pharmacological stress: (C) LV-SV and (D) effective RV-SV.](https://academic.oup.com/ejcts/article-abstract/42/1/50/355930)
mentioned in the study of Liang et al., which makes it difficult to compare the DCE sequences of the two studies.

We also showed that in older PAIVS patients, LV-SV failed to increase in response to pharmacological stress despite normal contractility. This finding correlated with reduced RV-SV augmentation and could well be explained by reduced LV preload due to impaired RV diastolic function. Although there was no reason to assume significant impairment of LV diastolic function in this PAIVS cohort, we cannot exclude this because LV diastolic function parameters were not measured in the study.

CONCLUSION

In PAIVS patients after biventricular repair, exercise capacity and cardiac reserve decrease with age. These findings are related to impaired diastolic RV function and decreased RV filling during stress, indicating that the function of the RV deteriorates with time. These results indicate that the relatively small and hypertrophied RV at birth may not be capable of maintaining normal ventricular performance in the long-term. This does not imply that long-term prognosis of PAIVS patients after univentricular repair is better than after biventricular repair since comparison of the two treatment strategies was not part of this study.

Conflict of interest: none declared.

REFERENCES