



Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance

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KEYWORDS

Tetralogy of Fallot;
Right ventricle;
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Aims Correct timing of pulmonary valve replacement (PVR) is crucial for preventing complications of pulmonary regurgitation and right ventricular (RV) dilatation after repair of tetralogy of Fallot. We sought to assess the remodelling of the RV after early PVR in children, using cardiovascular magnetic resonance (CMR).

Methods and results Twenty children with severe pulmonary regurgitation and RV dilatation and mean age 13.9 ± 3 years underwent CMR evaluation 5.6 \pm 1.8 months before and 5.9 \pm 0.6 months after PVR. PVR was performed when the RV end-diastolic volume exceeded 150 mL/m², as measured by CMR. The time interval between primary repair and PVR was 12 \pm 3 years. Post-operative CMR demonstrated a significant reduction of the RV end-diastolic volume from 189.8 \pm 33.4 to 108.7 \pm 25.8 mL/m² ($P < 0.0001$), of the RV end-systolic volume from 102.4 \pm 27.3 to 58.2 \pm 16.3 mL/m² ($P < 0.0001$), and of the RV mass from 48.7 \pm 12.3 to 35.8 \pm 7.7 g/m² ($P < 0.0001$). The RV ejection fraction did not change significantly.

Conclusion Prompt RV remodelling, with reduction of RV volume and mass, is observed after performing PVR if the RV end-diastolic volume exceeds 150 mL/m². Early PVR may prevent the detrimental complications of severe pulmonary regurgitation.

Introduction

The long-term survival and the quality of life of patients after repair of tetralogy of Fallot are excellent.¹ However, long-term morbidity with potential lethal complications, such as arrhythmias and sudden death, are common.² Pulmonary valve regurgitation secondary to transannular patching, commissurotomy of the pulmonary valve, or pulmonary conduit failure is the most common residual finding during mid- to long-term follow-up and the most frequent reason for re-operation.^{1,3} Previously considered a benign lesion, recently severe pulmonary regurgitation has been recognized to have deleterious effects on the right ventricular (RV) function.⁴ Presently, pulmonary valve replacement (PVR) is considered to be critical for preservation of RV function.^{2,5} Although the significance of chronic RV volume overload is well recognized, the debate about the optimal timing for PVR remains unsolved.

With this prospective study, we sought to assess the RV remodelling after early PVR using cardiovascular magnetic resonance (CMR) in children with chronic pulmonary regurgitation after repair of tetralogy of Fallot.

Methods

Patient population

Between August 2002 and March 2004, 28 children with tetralogy of Fallot underwent PVR for severe pulmonary regurgitation in our institution. Twenty patients could be evaluated by CMR pre- and post-operatively and were included in the study. The remaining eight patients could not be recruited, because four were referred for surgery from another institution and did not have any pre-operative CMR examination, two had intracardiac devices, one had a cochlear implant, and another one was lost to follow-up. Detailed patient's characteristics are shown in *Table 1*. Severe pulmonary valve regurgitation was the main reason for PVR in all cases; pulmonary stenosis was not present in any patient. Thirteen patients were in functional NYHA Class I, and seven in NYHA Class II. Thirteen patients (65%) showed ventricular arrhythmias during a pre-operative 24 h-ECG recording, classified as Low

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Table 1 Patient demographics and surgical techniques

Patients	20
Diagnosis	
Tetralogy of Fallot	17
DORV (Fallot type)	2
Absent pulmonary valve (Fallot type)	1
Surgical correction	
Age at primary repair (years)	1.9 ± 1.1
Primary surgical technique used	
Monocusp homograft patch	11
Transannular patch	7
Aortic homograft valved conduit	2
Pulmonary valve replacement	
Age at PVR (years)	13.9 ± 3
Weight (kg)	41.9 ± 18.7
Time interval TR/PVR (years)	12 ± 3

DORV, double outlet right ventricle; TR, total repair; PVR, pulmonary valve replacement.

grade 4a in three children and Low grade 1 in 10. A right bundle branch block was present in 18 of 20 patients (90%), with a mean QRS-duration of 150 ± 18 ms.

Methods

This is a prospective study for assessment of the remodelling of the right ventricle after PVR. Pre-operatively, patients were primarily evaluated by echocardiography. CMR was then performed in patients with evidence of severe pulmonary regurgitation and RV dilatation at echocardiography. Post-operatively, CMR was the primary investigation technique, as CMR is at present considered to be the tool of choice for evaluation of the RV volume.^{6,7} CMR evaluation was performed 5.6 ± 1.8 months before and 5.9 ± 0.6 months after PVR. Echocardiography with assessment of RV dimensions and function was repeated within a median interval of 1 day (range 1–77 days) before and 6 months (range 4–8 months) after PVR.

PVR was indicated in the presence of severe pulmonary valve regurgitation and RV dilatation both at CMR and echocardiography and of a RV end-diastolic volume exceeding 150 mL/m² and/or more than double the end-diastolic volume of the left ventricle (LV) as measured by CMR, independent of the clinical status of the patient. The value of RV end-diastolic volume >150 mL/m² was defined on the basis of CMR data reported for adults with chronic pulmonary valve regurgitation and adapted for the paediatric age group and corresponded to 150% of the normal upper limit for RV end-diastolic volume in children, which is 100 mL/m².^{8,9} Remodelling of the RV was defined by significant changes in RV volume, mass, and function.

Permission to proceed with this study was granted by our institutional Ethics Review Board. Informed consent was obtained from all patients.

Surgical technique

Cardiopulmonary bypass was established using external iliac vessel cannulation prior to repeat sternotomy, with limb cooling to 16°C. Minimum dissection was performed to separate the heart from the sternum and to free the right side of the heart. When the procedure was limited to the reconstruction of the RV outflow tract, including enlargement of the pulmonary arteries, it was performed on a beating, continuously perfused heart. If a concomitant procedure was necessary, a more complete dissection of the heart was

performed: the aorta was cross-clamped and cardioplegia given to obtain cardiac arrest. The RV outflow tract was opened longitudinally and the bifurcation was completely transected. Patch enlargement of the intrapericardial part of the pulmonary artery was performed as needed. A valved conduit was sutured on the pulmonary bifurcation with a running prolene suture. Proximally, the graft was inserted on the conal septum and then the infundibulum was modelled to fit the inlay part of the conduit. A reduction plasty of the dilated RV infundibulum was performed if necessary and consisted in complete resection of the old infundibular patch. At times, a purse-string stitch was placed inside the RV outflow tract proximal to the graft and tightened to further reduce the size discrepancy. Post-operatively, prophylactic acetyl-salicylic acid in a dose of 3–5 mg/kg/day was given to all patients during 6 months to prevent formation of thrombotic clots on the conduit valve.¹⁰

Cardiac magnetic resonance

Image acquisition

CMR studies were performed with a 1.5 T System (Signa MR/I Echo Speed; General Electric Medical Systems, Milwaukee, WI, USA), using a phased-array cardiac coil. The CMR protocol included cine steady-state free precession sequences in the axial plane for evaluation of the anatomy and in short axis planes to assess the ventricular volumes and mass. Velocity-encoded phase contrast sequences were performed for calculation of blood flow velocity and volume in the main pulmonary artery. Contrast-enhanced CMR angiography was performed for assessment of the anatomy of the pulmonary arteries. The images were acquired during breath holding in all patients.

Ventricular volumes were measured from a multi-section image set of 10–12 contiguous slices parallel to the plane of the atrio-ventricular valves (ventricular short axis), covering the full length of both ventricles.¹¹ The acquisition parameters of the steady-state free precession images were TE minimum, flip angle 45°, bandwidth 125 kHz, matrix 224 × 224, number of excitations 1, field of view 30–45 cm, slice thickness 6–8 mm with 1–2 mm gap depending on the body size, and retrospective gating with 20 images reconstructed per cardiac cycle.

Velocity mapping was performed in a double oblique plane perpendicular to the main pulmonary artery. The images were acquired halfway between the pulmonary valve and the pulmonary bifurcation. Acquisition parameters were TE minimum, flip angle 15°, matrix 256 × 128, bandwidth 31.25 kHz, views per segment 4–6 depending on the heart rate, number of excitations 1, slice thickness 4 mm, field of view adequate for patient's size, and retrospective electrocardiographic gating. Twenty phases per cardiac cycle were reconstructed by a standard interpolation technique.¹² The upper velocity range was set 25% higher than the expected peak velocity, on the basis of Doppler echocardiography, to optimize measurement accuracy while avoiding aliasing.

Image analysis

All images were analysed off-line on a commercially available workstation (SUN Microsystems Inc., Mountain View, CA, USA).

The volumetric data of the ventricles and RV mass were calculated with the MASS software package (Magnetic Resonance Analytical Software System Version 4.0, MEDIS, Medical Imaging Systems, Leiden, The Netherlands). The endocardial contours were traced manually as previously described.¹¹ For RV mass calculation, the epicardial and endocardial contours were traced in the end-systolic phase; the moderator band and the trabeculations were included into the mass. We chose the end-systolic phase for more reliable delineation of the RV free wall, which in children in the end-diastolic phase would be very thin to be traced consistently. The myocardial volume mass was multiplied by the specific density of the myocardium (1.05 g/m³). The RV ejection fraction was calculated as RV end-diastolic volume – RV end-systolic volume/RV

end-diastolic volume $\times 100$. A RV ejection fraction $>50\%$ was considered as normal.¹³ Flow data were analysed with the FLOW V2.0 software package (MEDIS, Medical Imaging Systems, by tracing the contours of the main pulmonary artery in each time frame.¹⁴

Echocardiography

Pre- and post-operative echocardiographic assessment was performed with a Sonos 5500 ultrasound imaging system (Philips Medical Systems, Andover, MN, USA) in the generally accepted standard views. The RV dimensions were evaluated by measuring the RV diameter on the two-dimensional images in the four-chamber view. The degree of pulmonary regurgitation was evaluated semi-quantitatively using colour Doppler and pulsed-wave Doppler mapping. Pulmonary regurgitation was classified as severe (retrograde diastolic flow into the branch pulmonary arteries), moderate (retrograde diastolic flow in the main pulmonary artery), and mild (regurgitant jet detectable in the RV outflow tract but no retrograde diastolic flow in pulmonary trunk).¹⁵ The contractility of the right ventricle was described qualitatively by the cardiologist performing echocardiography.

Statistics

Descriptive data are presented as mean \pm SD or median (range) as appropriate. All ventricular volumetric data and mass were indexed for body surface area. The sample size of the study was determined after preliminary analysis of the results of 20 patients, which showed already significant results; power calculation demonstrated a power of 0.9 for detecting a volume difference of 30 mL/m², which we considered medical relevant. The two-tailed paired Student's *t*-test was used to compare the intra-individual pre-operative and post-operative data, without adjustment for multiplicity, as this was judged not appropriate.¹⁶ A *P*-value less than 0.05 was considered statistically significant.

The results of 10 randomly selected patients, five pre-operatively and five post-operatively, were used for calculation of the intra- and inter-observer variability by determining the mean difference (SD) and the limits of agreement between measurements.¹⁷ The intra-observer variability was assessed by comparison of ventricular volume measurements by one observer (E.R.V.) on two separate occasions, at least 3 months apart. The inter-observer variability was assessed by comparison of the results of two independent observers (E.R.V. and C.J.K.).

Results

Surgical results

PVR consisted in insertion of a bovine jugular vein valved conduit (Contegra®, Medtronic Inc., Minneapolis, MN, USA) in 18 patients and of an aortic homograft and a pulmonary homograft in one patient each. Concomitant surgical procedures were performed in 11 patients, including closure of a residual ventricular septal defect in three patients, augmentation of the pulmonary bifurcation in four, augmentation of the left pulmonary artery in two, and augmentation of the right pulmonary artery in two. A reduction plasty of the RV was performed in five patients. The mean cardiopulmonary bypass time was 124 \pm 59 min. Aortic cross-clamping and cardioplegia were needed in two patients with a residual ventricular septal defect. PVR was performed without mortality in all 20 patients. Peri-operative morbidity occurred in five patients (25%), including intra-operative bleeding in two, post-operative pneumonia in two, and a postpericardiotomy syndrome in one. None of these complications prolonged the length of hospitalization (mean 10 \pm 1.4 days).

Haemodynamic results

Cardiovascular magnetic resonance

The haemodynamic changes after PVR are summarized in Table 2. Pre-operatively, all patients presented moderate-to-severe pulmonary regurgitation with corresponding severe RV dilatation. Six months after PVR, a significant reduction of the RV dimensions ($P < 0.0001$) was observed in all patients and a significant reduction of RV mass ($P < 0.0001$) was measured in 19 of 20 patients (Figure 1). In one patient, the images obtained were of insufficient quality for determining RV mass. The RV ejection fraction remained unchanged. Normalization of the RV end-diastolic volume to a value <105 mL/m² occurred in 8 of 12 patients (66%), who presented with a pre-operative end-diastolic volume <200 mL/m²; in two cases, a RV reduction plasty was performed. In contrast, in eight patients with a pre-operative end-diastolic volume ≥ 200 mL/m², normalization of RV dimensions occurred in only one, who underwent RV reduction plasty.

CMR also demonstrated a post-operative increase of the LV end-diastolic volume and a trend towards improvement of the pre-operative slightly reduced LV ejection fraction (Table 2).

Echocardiography

Pre-operatively, severe pulmonary regurgitation and significant RV dilatation, with RV diameters larger than LV diameters (mean 40.9 \pm 6.3 vs. 38.3 \pm 4.6 mm), were observed in all patients. Similar to the CMR results, a significant reduction of the RV dimensions was measured post-operatively; the mean RV end-diastolic diameter decreased from 40.9 \pm 6.3 to 33.9 \pm 6.7 mm ($P < 0.0001$) after PVR. Pre-operatively, the RV function was judged as normal in 17 patients and as diminished in three. After PVR, normal RV function was described in all but one patient. Moderate tricuspid regurgitation was found in five of 20 patients pre-operatively and in one of 20 post-operatively.

Arrhythmias

Ventricular arrhythmias were recorded in 13 patients pre-operatively and improved post-operatively in seven

Table 2 CMR data before and after PVR

Variables (<i>n</i> = 20)	Before PVR	After PVR	<i>P</i> -values
RVEDV (mL/m ²)	189.8 \pm 33.4	108.7 \pm 25.8	<0.0001
RVESV (mL/m ²)	102.4 \pm 27.3	58.2 \pm 16.3	<0.0001
RV mass (g/m ²)	48.7 \pm 12.3	35.8 \pm 7.7	<0.0001
RV-EF (%)	46.9 \pm 7.3	44.6 \pm 9.0	0.37
LVEDV (mL/m ²)	77.3 \pm 10.1	84.1 \pm 12.0	0.007
LVESV (mL/m ²)	36.7 \pm 7.4	40.1 \pm 15.3	0.32
LV-EF (%)	53.1 \pm 5.8	56.3 \pm 6.8	0.068
MPA netflow (mL/min)	3878 \pm 2088	4499 \pm 1575	0.063
PR (%)	48.6 \pm 14.3	9.1 \pm 7.9	<0.0001

EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MPA, main pulmonary artery; PR, pulmonary regurgitation; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.

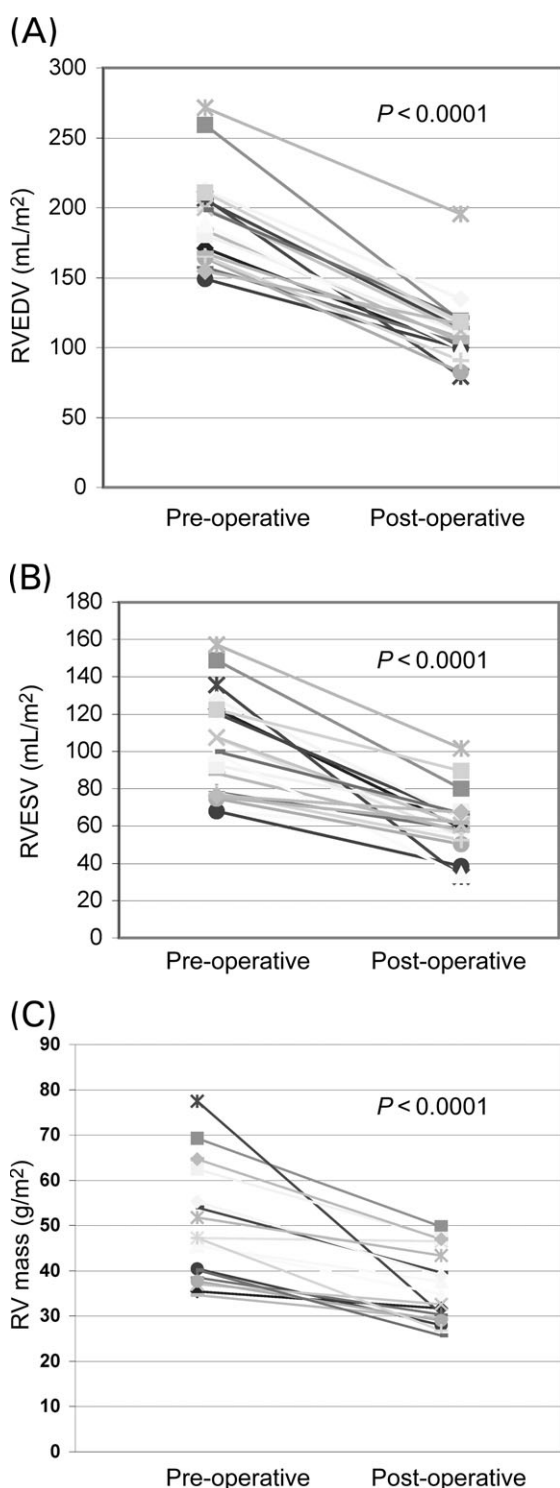


Figure 1 Changes in right ventricular end-diastolic volume (A), end-systolic volume (B), and right ventricular mass (C) before and after PVR in 20 patients.

of them. Particularly, two of the three patients with arrhythmias Lown Class 4a totally normalized (Lown Class 0) and one improved into Lown Class I.

In the 18 children with right bundle branch block, post-operative QRS duration did not change significantly, as measured by standard ECG (150 ± 18 ms pre-operatively vs. 148 ± 17 ms post-operatively).

Valve function

Echocardiography demonstrated a good function of the valved graft in all patients. Colour Doppler showed no pulmonary regurgitation in four, trivial regurgitation in 14, and mild regurgitation in two patients. Flow acceleration within the RV outflow tract, with a mean velocity of 270 ± 10 cm/s, was measured using spectral Doppler in 13 patients.

CMR detected regurgitant flow in the pulmonary conduit in seven patients, with a mean regurgitation fraction of $9.2 \pm 7.3\%$.

Intra- and inter-observer variability

Intra- and inter-observer variability is summarized in Table 3. Normalized to the mean value of the volume data, the mean difference corresponded to a variability range from <1 to 5% for intra-observer measurements and from <1 to 13% for inter-observer measurements. Inter-observer variability was slightly higher for measurements of the RV volumes than for measurements of the LV volumes.

Discussion

Pulmonary valve regurgitation is a frequent residual finding after repair of tetralogy of Fallot, resulting in RV dilatation, RV failure, and arrhythmias, which determine long-term morbidity and prognosis.⁵ PVR enables volume unloading of the right ventricle, which may be essential for preserving ventricular function and for enhancing the clinical status of the patient. However, the optimal timing for PVR remains unclear.

The haemodynamic effects of PVR have been reported in adults and in children, by assessing functional class, exercise tolerance, and volumetric changes at echocardiography and nuclear angiocardigraphy.^{4,13,18,19} Two authors used CMR for assessing ventricular volumetric and functional changes after valve replacement in adults.^{8,20} This study reports the use of CMR to demonstrate remodelling of the RV after PVR in children, by describing the changes occurring in RV volume, mass, and function.

Timing PVR and ventricular remodelling

Clinical symptoms, including exercise intolerance, onset of ventricular arrhythmias, and echocardiographic findings such as progressive RV dilatation and onset of tricuspid regurgitation, have been used so far as indicators for re-intervention.²¹ However, Therrien *et al.*¹³ suggested that post-operative RV resizing after PVR may not occur in all patients, if PVR was performed on the basis of clinical symptoms. Other authors demonstrated that in spite of good clinical conditions, mild or moderate pulmonary regurgitation has considerable negative effects on global RV performance and cardiac reserve and that RV contractile function is reduced in relation to the degree of pulmonary regurgitation.^{22,23} The clinical experience teaches us that children may develop clinical symptoms later, when the ventricular function is already seriously impaired. Moreover, CMR is the first imaging modality providing exact quantification of regurgitant volume and RV ventricular volume and mass. This information may allow us to look

Table 3 Intra- and inter-observer variability of CMR measurements

Variables (<i>n</i> = 10)	Intra-observer variability		Inter-observer variability	
	Mean difference \pm SD	Limits of agreement	Mean difference \pm SD	Limits of agreement
RVEDV (mL/m ²)	5.5 \pm 8.8	-11.8/+22.8	-8.2 \pm 4.7	-17.4/+1
RVESV (mL/m ²)	1.8 \pm 11.4	-20.6/+24.2	-13.8 \pm 11	-35.4/+7.8
LVEDV (mL/m ²)	0.9 \pm 9.4	-17.5/+19.3	-1.9 \pm 2.7	-7.1/+3.4
LVESV (mL/m ²)	1.7 \pm 3	-4.2/+7.6	-0.5 \pm 3	-6.4/+5.4

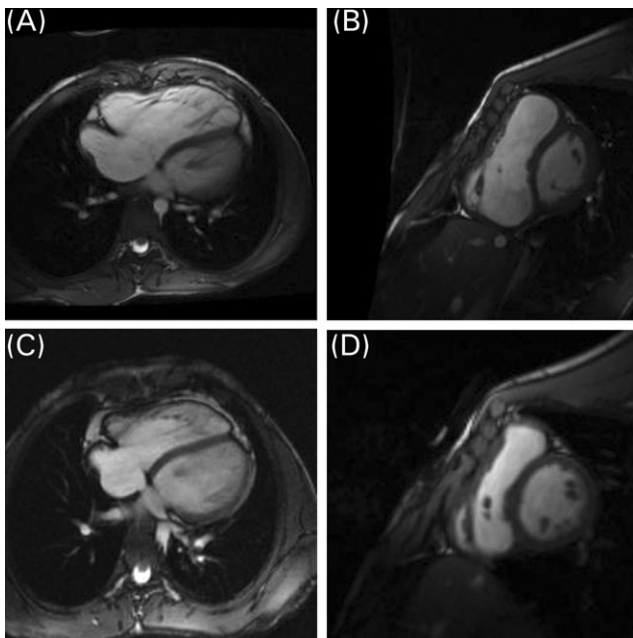


Figure 2 Steady-state free precession images showing a dilated right ventricle in the long- (A) and short-axes (B) pre-operatively and a reduction of RV dimensions post-operatively in the long- (C) and short-axes (D). Note the flat interventricular septum on the end-diastolic pre-operative short-axis image (B) secondary to volume overload of the right ventricle.

for new quantitative indicators for PVR and facilitate the management of these patients.³

Our data demonstrate that remodelling of the right ventricle can be achieved within 6 months post-operatively, if PVR is performed in a timely fashion (Figure 2). Using a RV end-diastolic volume >150 mL/m² as indication for PVR, we observed not only a significant reduction of the RV volume but also a decrease in RV mass, which may represent a better indicator for remodelling. RV mass is independent of loading conditions and of surgical interventions such as RV reduction plasty, because in this technique, only fibrous tissue or patch material, but no cardiac muscle, is resected in the RV outflow tract. The RV ejection fraction did not show any changes after PVR. However, the pre-operative data may represent an overestimation of the effective ejection fraction, because a regurgitation of the pulmonary or tricuspid valve leads to an increase of the end-diastolic volume and therefore to a higher ejection fraction. Thus, if the effects of regurgitation on the measurement of ejection fraction are taken into consideration, the real RV output may have improved after valve replacement.⁸ In addition, the post-operative increase in LV end-diastolic volume and

the trend towards improvement of the LV function may reflect an enhanced RV output, increased net-flow in the main pulmonary artery, and a more favourable right-to-left ventricular interaction.²⁴

Surgical considerations

PVR was performed with no mortality and negligible morbidity. In our institution, the choice of the valved conduit to be inserted is determined by the availability of the different grafts. For this reason, most patients received a bovine jugular vein graft, which can be stored and is available in different sizes. After implantation of a bovine jugular vein graft, CMR and echocardiography showed an excellent function of the inserted valved conduit. In this group of patients, with a relatively large body size, and by empirically giving prophylactic acetylsalicylic acid, we did not observe any of the described graft-related complications, such as thrombus formation or pseudo-aneurysm.^{10,25,26} The flow acceleration in the RV outflow tract observed in 13 of 20 patients was clinically insignificant and related rather to the tubular geometry of the conduit inserted on the top of a dilated right ventricle than to a valve dysfunction or a supravalvar stenosis.²⁶ Nevertheless, caution is required for optimizing indication for PVR, because an ideal graft is yet to be found and patients receiving one of the existing valves or valved conduits most likely require repeated valve surgeries during a lifetime. As reported by others, concomitant surgical procedures were needed at the time of PVR to correct other abnormalities in the majority of the patients.^{3,4} Additional residual findings, including obstruction of the pulmonary arteries, stenosis of the pulmonary valve, residual shunts, and severe tricuspid valve regurgitation, may enhance the negative effects on the right ventricle by additional pressure and/or volume overload.²² Thus, early timing of PVR may be crucial in these selected but frequent cases.

Reproducibility

The intra- and inter-observer variability indicates a good reproducibility of the CMR volume measurements. Our results are within the variability range of 5–15% previously reported in the literature, but single cases show limits of agreement of as high as 24 mL/m².^{7,27} This variability can be accepted in this study group as, in contrast to the accepted validation studies, we did not evaluate normal-shaped ventricles, and in children, breath-holding may not be always optimally performed, thus the image quality may not be always maximal. As reported in other studies, a higher variability was found for RV volume measurements

than for LV volume measurements, owing to the complex geometry of the right ventricle and the difficulties in defining the correct plane of the tricuspid valve in the most basal slice and in delineating the RV endocardial border and owing to the thin RV free wall, the increased trabeculations, and other structures such as the moderator band.^{27,28} Nevertheless, CMR still offers a superior reproducibility when compared with echocardiography, because CMR is not dependent on suitable acoustic window for echo or geometric assumption.²⁸

Limitations

The most important limitation of this study is the lack of a control group. We could demonstrate that prompt remodelling of the RV is observed in children, if PVR is performed in patients with a RV end-diastolic volume >150 mL/m². Even though we used a higher cut-off in children than in the one proposed for the adult population, our data indicate that we are not operating too late.⁸ However, we could not provide evidence for or against a hypothesis that delayed cardiac surgery would not result in similar remodelling. Nevertheless, the fact that none of the patients with a pre-operative RV end-diastolic volume >200 mL/m² showed normalization of the RV volume within 6 months may be an helpful indicator for defining an upper limit for re-intervention. Further prospective CMR studies comparing different timing for valve replacement and providing longer follow-up may help to understand the influence of pulmonary regurgitation on RV haemodynamics over time and to define clearer limits for intervention. Moreover, long-term results of new valved conduits used for reconstruction of the RV outflow tract would help to unburden the concerns existing about the need for repeated pulmonary valve surgery.

Conclusions

In children, prompt remodelling of the right ventricle, with reduction of RV volume and mass, is observed after performing PVR if the RV end-diastolic volume exceeds 150 mL/m². Early PVR is safe and may prevent the detrimental complications of severe pulmonary regurgitation, affecting the long-term prognosis of patients after repair of tetralogy of Fallot.

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Conflict of interest: none declared.

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