Non-invasive diagnosis and follow-up of right ventricular overload

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III

Predicting outcome of pulmonary valve replacement in adult tetralogy of Fallot patients

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Abstract

Background

Predicting changes in right ventricular (RV) size and function after pulmonary valve replacement (PVR) is important for timely reintervention in adult tetralogy of Fallot patients.

Methods

We analyzed the influence of pulmonary regurgitation severity and RV size and function before PVR on the outcome of RV size and function after PVR in 27 adult Fallot patients who had cardiac magnetic resonance imaging before and after PVR. RV dimensions were indexed for body surface area.

Results

Pulmonary regurgitation (48% ± 11% of RV stroke volume) was not related to RV dimensions and function before PVR. Moreover, severity of pulmonary regurgitation did not influence changes in RV dimensions after PVR. The indexed RV end-systolic volume before PVR (median, 98 $mL \cdot m^{-2}$; range, 52 - 235 $mL \cdot m^{-2}$) best predicted the indexed RV end-systolic volume after PVR (median, 59 $mL \cdot m^{-2}$; range, 24 - 132 $mL \cdot m^{-2}$, r=0.78, P<0.001) and the indexed RV end-diastolic volume after PVR (mean, 107 $mL \cdot m^{-2}$; range, 70 - 170 $mL \cdot m^{-2}$, r=0.73, P<0.001). Baseline RV ejection fraction corrected for valvular insufficiencies and shunting (21% ± 7%) best predicted the RV ejection fraction after PVR (43% ± 10%, r=0.77, P<0.001).

Conclusions

Timing of PVR should be based on indexed RV end-systolic volume and corrected RV ejection fraction rather than on severity of pulmonary regurgitation.

Introduction

Tetralogy of Fallot is a common form of cyanotic heart disease [1]. Correction in infancy offers good long-term results with minimal morbidity [2]. In most Fallot patients, however, residual pulmonary regurgitation, stenosis, or both, is present after total correction, the degree and duration of which determine size and function of the right ventricle (RV) [3-5]. Increased RV end-diastolic and end-systolic volumes are associated with diminished RV function and increased arrhythmia propensity [6, 7]. For patients with a dilated RV caused by significant pulmonary valve regurgitation, pulmonary valve replacement (PVR) has been proven to be beneficial with respect to reverse remodeling of the RV and a decrease in QRS duration [8, 9]. PVR is therefore the therapy of choice in patients with pulmonary regurgitation, a dilated RV, and risk factors for developing arrhythmias [10]. Although PVR is associated with low mortality, its intrinsic morbidity and the preferred use of non-mechanical valve substitutes in younger patients have led to an ongoing debate about the optimal timing of this intervention [11-17]. PVR is clearly indicated when patients become symptomatic or at risk for (fatal) arrhythmias [18]. Hence, PVR should preferably be performed before the right ventricle is dilated beyond a "point of no return," yet no sooner than necessary. Timing of PVR during this arbitrary time interval is therefore dependent both on patient features and the preference of the team of specialists involved. Because the shape of the RV cannot be described by a simple geometric model, adequate volumetric calculations of the RV have only become feasible in recent years with the advent of multiplanar magnetic resonance imaging [19]. Using Simpson's rule for analysis of serial tomographic slices acquired at the end of RV systole and diastole, RV volumes and function can be calculated reliably [20]. Considering the PVR-related reduction in RV volumes and improvement of ejection fraction, it would be of great interest to be able to predict the outcome of PVR for individual patients with respect to the degree of improvement in RV size and function [8, 13]. Despite overt evidence of benefit of PVR in groups of Fallot patients, lack of unequivocal data for individuals has led our group to analyze which cardiac magnetic resonance (CMR) imaging measurements of RV size and function best predict the degree of improvement in RV dimensions and function after PVR.

Methods

Patients

The CMR studies were part of a study protocol for preoperative and postoperative evaluation that had been previously approved by the Institutional Review Board. All data used were from patients who gave their informed consent.

Data on patients' surgical history are presented in Table 1. CMR imaging was available in 27 patients before and after PVR from a group of 31 consecutive adult Fallot patients who underwent operation. Total surgical correction of tetralogy of Fallot had been performed at a median age of 5.6 years (range, 1.3 - 13.2 years). At the time of the study, all patients had significant pulmonary regurgitation and a dilated right ventricle. All patients received an orthotopically implanted cryopreserved pulmonary homograft using normothermic or moderately hypothermic cardiopulmonary bypass. Residual RV outflow tract obstruction was relieved by resection of infundibular muscular tissue in two patients or augmentation with the implanted homograft itself in two other patients. An aneurysmatic RV outflow tract was corrected during the same operation in two patients. Other associated procedures were closure of a residual atrial defect in one patient and ventricular septal defects in three (one had been closed before), tricuspid valve repair in one, or annuloplasty or both in six others, if necessary. Residual pulmonary artery stenosis was relieved in one patient. All interventions were performed by a team of surgeons specialized in congenital heart disease. All patients were assessed for validity according to New York Heart Association (NYHA) class by the principal cardiologist both before and after PVR (within 1–4 weeks of the CMR studies) during outpatient visits. CMR studies were conducted at a median of 4.8 months (range, 0.7 - 15.4 months) before PVR. A similar CMR study was made for follow-up at a median of 7.3 months (range, 4.4 - 19.7 months).

Table 1: Patients' historical surgical data

n = 27, 17 (63%) male	n	%
History of palliative surgery	12	44.4
Use of RV patch	1	3.7
Use of transannular patch	13	48.1
APC patch only	6	22.2
No patch	7	25.9
Transatrial VSD closure	4	14.8
Transventricular VSD closure	21	77.8
VSD not closed	2	3.7

RV = right ventricle, APC = common pulmonary artery, VSD = ventricular septal defect

CMR Imaging

CMR imaging was performed as previously described [8]. In brief, these studies were performed on a 1.5 Tesla scanner (NT15 Gyroscan, Philips, Best, The Netherlands). Short-axis images of the heart were acquired with a multiphase, electrocardiogram-triggered, multi-shot echoplanar gradient echo technique during breath holds. We used a slice thickness of 10 mm and a 0.8 mm - 1.0 mm section gap. The flip angle was 30 degrees, and echo time was 5 to 10 ms. Between 18 and 25 frames per cycle resulted in a temporal resolution of 22 to 35 ms. Volumetric and functional RV measurements were derived from these studies, and differences between measurements over time were calculated. Variables were indexed for body surface area. Variables selected as end points of interest after PVR were indexed RV end-diastolic volume ($mL \cdot m^{-2}$), indexed RV end-systolic volume ($mL \cdot m^{-2}$), and RV ejection fraction (%). Also calculated was the so-called corrected RV ejection fraction (%), which corrects for pulmonary regurgitation, tricuspid regurgitation, and residual shunting (which equals net pulmonary forward flow/RV end-diastolic volume). Because surgery corrects such regurgitation and shunting, RV ejection fraction no longer needs correction after PVR. We tested the relationship between each of these variables before and after PVR. We also assessed the influence of severity of pulmonary regurgitation (as a percentage of RV stroke volume) on RV dimensions and function. We further evaluated consequences of postoperative pulmonary valve gradients (maximum and mean as seen with transthoracic echocardiography) as well as RV pressures (tricuspid regurgitation gradient estimated right atrial pressure).

Statistical Analysis

The SPSS 12.0.1 (SPSS Inc, Chicago, IL) software for Windows (Microsoft Inc, Redmond, WA) was used for data analysis. Assessment of the association between two continuous variables was performed with a correlation analysis. When two groups of patients were compared for differences in a factor described by a continuous variable, use was made of a two-tailed independent t-test or a Mann-Whitney test. Correlations are shown in parentheses. Values of $P<0.05$ were considered to be statistically significant. Baseline indexed RV end-systolic volume, baseline RV end-diastolic volume, baseline uncorrected RV ejection fraction, baseline corrected RV ejection fraction, and pulmonary regurgitation severity were entered in a multiple linear regression model, and a backward selection procedure (removed if $P>0.10$) was performed to determine the most significant predictor(s) of RV size and function after PVR. Additional logistic regression analysis was performed, incorporating the same baseline variables of pulmonary regurgitation and RV size and function, to construct a model for prediction of outcome below a cutoff value of RV end-systolic volume.

Results

CMR images were assessable for indexed RV end-diastolic volume, indexed RV end-systolic volume, and RV ejection fraction in all 27 patients. Measurements of corrected RV ejection fraction and pulmonary regurgitation severity were obtained in 26 patients because one CMR study showed artifacts. Mean patient age at the time of PVR was 30.8 ± 8.2 years. Median patient age at the time of palliation (n=12) was 2.0 years (range, 0.2 - 6.4 years), and mean patient age at the time of total correction was 5.6 ± 2.8 years. Pulmonary valve replacement had a clinically relevant result, reflected by mean patient NYHA class change from 2.0 ± 0.6 before PVR to 1.3 ± 0.3 after PVR (P<0.001).

Pulmonary Regurgitation

As summarized in Table 2, baseline pulmonary regurgitation as percentage of RV stroke volume (48% ± 11%) was not correlated with baseline indexed RV end-systolic volume (median, 98 mL·m^{-2}; range, 52 - 235 mL·m^{-2}), baseline indexed RV end-diastolic volume (median, 166 mL·m^{-2}; range, 113 - 290 mL·m^{-2}), or baseline RV ejection fraction (42% ± 11%). Moreover, pulmonary regurgitation severity was not related to the significant postoperative decrease in indexed RV end-diastolic volume (66 ± 30 mL·m^{-2}) or the decrease in indexed RV end-systolic volume (40 ± 26 mL·m^{-2}).

Right Ventricular Volumes

Indexed RV end-systolic volume and indexed RV end-diastolic volume were closely related before PVR (r=0.91, P<0.001). After PVR, indexed RV end-systolic volume (median, 59 mL·m^{-2}; range, 24 - 132 mL·m^{-2}) remained closely associated (r =0.77, P<0.001) with indexed RV end-diastolic volume (109 ± 26 mL·m^{-2}). Linear regression analysis defined baseline indexed RV end-systolic volume as the best predictor of both indexed RV end-systolic and indexed RV end-diastolic volume after PVR (Figure 1). Prediction of outcome of indexed RV end-systolic volume (mL·m^{-2}) was defined by 17.3 + [0.45·baseline indexed RV end-systolic

Table 2: Baseline RV size and function in relation to PR severity (n=26)

	PR as % of RV stroke volume	
Indexed RV end-systolic volume	r=0.14	P=0.50
Indexed RV end-diastolic volume	r=0.16	P=0.42
RV ejection fraction	r=-0.04	P=0.84

RV = right ventricular, PR = pulmonary regurgitation

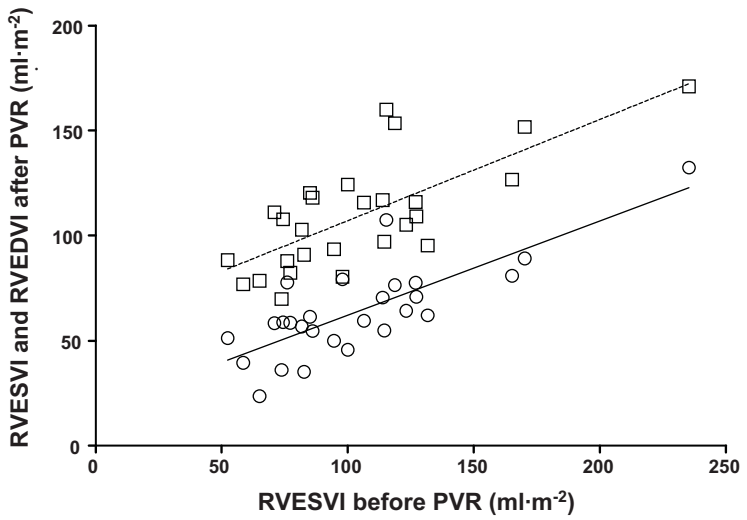

Figure 1
Baseline indexed right ventricular end-systolic volume (RVESVI) is an excellent predictor of indexed RV end-systolic volume and end-diastolic volume (RVEDVI) after pulmonary valve replacement (PVR). Open circles=postoperative RVESVI plotted against baseline RVESVI. Predicted postoperative RVESVI=17.3 + [0.45·baseline RVESVI] (n=27, r=0.78, P<0.001). Open squares=postoperative RVEDVI plotted against baseline RVESVI.
Predicted postoperative RVEDVI=58.8 + [0.49·baseline RVESVI] (n=27, r=0.73, P<0.001).

volume] (r=0.78, *P*<0.001). Prediction of outcome of indexed RV end-diastolic volume (mL·m^{-2}) was defined by 58.8 + [0.49·baseline indexed RV end-systolic volume] (r=0.73, *P*<0.001). An indexed RV end-systolic volume of less than 60 mL·m^{-2} was reached in 14 patients. Binary logistic regression analysis correctly identified patients who did or did not reach an indexed RV end-systolic volume of 60 mL·m^{-2} in 92.3% of cases with the following formula: predicted indexed RV end-systolic volume after PVR = -3.3 + [0.3·baseline indexed RV end-systolic volume] - [0.16·baseline indexed RV end-diastolic volume]. Patients with an outcome of indexed RV end-systolic volume of less than 60 mL·m^{-2} after PVR also had a lower mean indexed RV end-diastolic volume after PVR (97 ± 17 mL·m^{-2} versus 123 ± 29 mL·m^{-2}, *P*<0.01) and better mean RV ejection fraction after PVR (0.50 ± 0.07, versus 0.36 ± 0.06, *P*<0.001) than patients with an outcome of indexed RV end-systolic volume exceeding 60 mL·m^{-2} (n=13). Preoperative characteristics of patients with an indexed RV end-systolic volume after PVR above or below 60 mL·m^{-2} are summarized in Table 3.

Table 3: Baseline right ventricular volume and corrected right ventricular ejection fraction determine right ventricular end-systolic volume after pulmonary valve replacement

	RVESVI < 60 mL·m^{-2} (n=14)	RVESVI > 60 mL·m^{-2} (n=13)	
	Mean ± SD	Mean ± SD	*P*
RVESVI	81 ± 18	130 ± 41	0.001
RVEDVI	157 ± 24	196 ± 50	0.020
Corrected RVEF	25 ± 5	17 ± 7	0.002

RV = right ventricular, PVR = pulmonary valve replacement, RVESVI = indexed right ventricular end-systolic volume, RVEDVI = indexed right ventricular end-diastolic volume, RVEF = right ventricular ejection fraction

Right Ventricular Function Before and After Pulmonary Valve Replacement

RV ejection fraction did not change significantly after PVR, increasing from a 42% ± 10% to 43% ± 10% (P=0.30). The change from baseline mean corrected RV ejection fraction to uncorrected RV ejection fraction after PVR was considerable with 22% ± 6% (P<0.001). According to regression analysis, RV ejection fraction after PVR was best predicted by 21.6 + [1.02 · baseline corrected RV ejection fraction] (r = 0.77, P<0.001). Results are illustrated in Figure 2. After PVR, uncorrected RV ejection fraction was no longer different from corrected RV ejection fraction (0.43 ± 0.10 versus 0.42 ± 0.10, P=0.65).

Right Ventricular Pressure Load After Pulmonary Valve Replacement

Echocardiography was available in 26 patients within a median of 3 months (range, 0.3 - 8 months) after PVR. Tricuspid regurgitation in 23 patients was grade I or lower, and three patients had grade II residual tricuspid regurgitation. The median peak pulmonary valve gradient was 16.5 mmHg (range, 4.0 - 43.0 mmHg), and the median of the mean pulmonary valve gradient was 8.3 mmHg (range, 2.0 - 23.0 mmHg). The median peak RV pressure (tricuspid valve gradient + estimated right atrial pressure) was 35.0 mmHg (range, 23.0 - 78.5 mmHg). The calculated median pulmonary artery systolic pressure, which was calculated as [tricuspid valve gradient + estimated right atrial pressure] - mean pulmonary valve gradient, was 27.0 mmHg (range, 9.0 - 71.5 mmHg). One patient needed percutaneous balloon dilatation of a residual pulmonary artery stenosis. Pulmonary arterial hypertension developed in one patient a few weeks after PVR through recanalization of an old Potts shunt. This shunt was closed with a percutaneous intervention. An effect of higher pulmonary valve gradients or estimated pulmonary artery systolic pressures toward increased RV size or decreased RV function after PVR could not be found.

Left Ventricular Size and Function

Indexed left ventricular end-systolic volume did not change after PVR, from 40 ± 18 mL·m^{-2} to 39 ± 11 mL·m^{-2} (P=0.71). Similarly, indexed left ventricular end-diastolic volume remained unchanged, from 89 ± 31 mL·m^{-2} to 87 ± 18 mL·m^{-2} (P=0.76). Hence, left ventricular ejection fraction remained essentially unchanged after PVR, from 56% ± 12% to 55% ± 9% (P=0.87).

Discussion

Our results show that the right ventricle improved in dimensions and function after PVR in all 27 Fallot patients. Although our group previously reported a similar outcome, we were now able to demonstrate that changes in RV size and function after PVR are proportionate to baseline status [8]. It is important to realize that after PVR, patients may thus experience a large decrease in both RV end-diastolic and end-systolic volume as well as an increase in corrected RV ejection fraction, whereas absolute RV measurements of size and function may not normalize. Similar results have been reported by Therrien and colleagues [13] and Dave

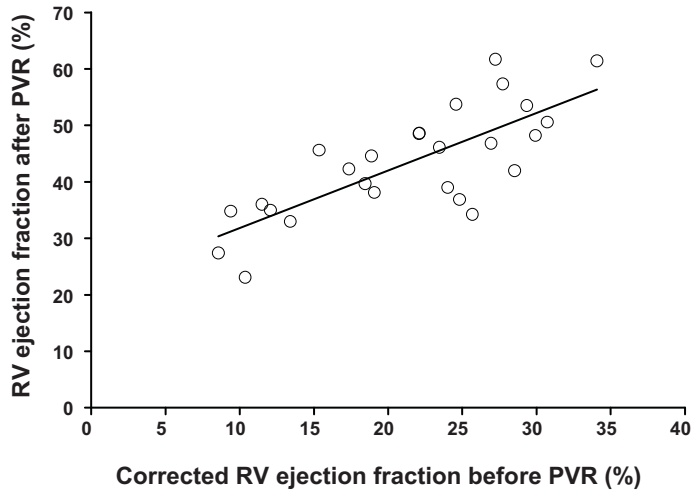

Figure 2

Baseline corrected right ventricular (RV) ejection fraction is the best predictor of RV ejection fraction after pulmonary valve replacement (PVR). Predicted RV ejection fraction after PVR=21.6 + [1.02·baseline corrected RV ejection fraction] (n=26, r=0.77, P<0.001).

and colleagues [17], suggesting that PVR should be performed before an indexed RV end-diastolic volume of 150 - 170 mL·m^{-2} is reached. Despite overt evidence of the importance of pulmonary regurgitation in adult Fallot patients, RV dimensions and function may vary greatly in patients with the same degree of pulmonary regurgitation [4]. And although pulmonary regurgitation is held responsible for RV dilatation and decrease of RV function over time, the absence of overt influence of pulmonary regurgitation severity on RV size or function before or after PVR strongly suggests that pulmonary regurgitation severity should not be the variable of primary consideration in deciding when to perform pulmonary valve replacement in adult Fallot patients [5, 10]. Rather, when pulmonary regurgitation is present, we should focus on variables of RV size and function that indicate how the individual's RV is coping with the burden of pulmonary regurgitation, and at the same time predict change in RV size and function if PVR were performed. Our results suggest that RV end-systolic volume and corrected RV ejection fraction are the most important measurements of RV size and function to assess. Baseline corrected RV ejection fraction had the closest relation with RV ejection fraction after PVR in our group. This can be explained by the fact that pulmonary regurgitation, tricuspid regurgitation, and shunting over a residual ventricular septal defect may all lead to a compensatory increase in RV stroke volume to maintain net pulmonary forward flow with each heartbeat. Hence, without correction for regurgitation and shunting, RV ejection fraction overestimates true RV performance. To evaluate the true RV performance and possible benefit of PVR for the patient, it has therefore been suggested that the corrected RV ejection fraction should be used in the preoperative situation [8]. Several reports have addressed changes in RV volumes after PVR, rendering different cut-off values for indexed RV end-systolic and end-diastolic volumes [13, 14, 17]. Indexed RV end-systolic volume is probably the most important preoperative measure of RV dimensions and function because it incorporates both RV volume overload and systolic function, variables strongly related to clinical status [5]. Five patients in our study returned to an indexed RV end-systolic volume within normal limits [21]. Ideally, lifelong optimal management of a Fallot patient would prevent important RV dilatation while preserving RV systolic function. That such management still requires repeated surgical intervention implies that the pursuit of optimal RV hemodynamics may not be successful in most patients [22]. Perhaps it is therefore more realistic to strive towards a near-normal RV size and function in adult Fallot patients that have not had the benefit of current surgical techniques and medical management. In our group, little over half of patients reached an indexed RV end-systolic volume of less than 60 mL·m^{-2}, which was associated with a better RV ejection fraction and a lower indexed RV end-diastolic volume. Preoperative cut-off values likely to result in a favorable outcome are therefore an

indexed RV end-systolic volume of 100 mL·m^{-2} and a corrected RV ejection fraction that exceeds 20%. The strong relation between indexed RV end-diastolic volume and indexed RV end-systolic volume, both before and after PVR, likely reflects ventricular adaptation in response to increased wall stress and volume loading. RV fibrosis might explain why in some patients RV dimensions regressed less, and RV ejection fraction remained impaired [23]. Although changes in surgical practice and techniques now allow for total correction much earlier in life, mostly with a transatrial approach, and with less need for prior palliation, we believe that our cohort of patients still represents an important part of adult Fallot patients who require long term management, and probably repeat PVR in time to come.

Conclusion

In patients with important pulmonary regurgitation, timing of pulmonary valve replacement should be based on indexed right ventricular end-systolic volume and corrected right ventricular ejection fraction rather than on severity of pulmonary regurgitation.

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