Clinical Outcomes of Surgical Pulmonary Valve Replacement After Repair of Tetralogy of Fallot and Potential Prognostic Value of Preoperative Cardiopulmonary Exercise Testing

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Background—Indications for surgical pulmonary valve replacement (PVR) after repair of tetralogy of Fallot have recently been broadened to include asymptomatic patients.

Methods and Results—The outcomes of PVR in adults after repair of tetralogy of Fallot at a single tertiary center were retrospectively studied. Preoperative cardiopulmonary exercise testing was included. Mortality was the primary outcome measure. In total, 221 PVRs were performed in 220 patients (130 male patients; median age, 32 years; range, 16–64 years). Homografts were used in 117 patients, xenografts in 103 patients, and a mechanical valve in 1 patient. Early (30-day) mortality was 2%. Overall survival was 97% at 1 year, 96% at 3 years, and 92% at 10 years. Survival after PVR in the later era (2005–2010; n=156) was significantly better compared with survival in the earlier era (1993–2004; n=65; 99% versus 94% at 1 year and 98% versus 92% at 3 years, respectively; P=0.019). Earlier era patients were more symptomatic preoperatively (P=0.036) with a lower preoperative peak oxygen consumption (peak $\dot{V}O_2$; P<0.001). Freedom from redo surgical or transcatheter PVR was 98% at 5 years and 96% at 10 years for the whole cohort. Peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO2$ slope (ratio of minute ventilation to carbon dioxide production), and heart rate reserve during cardiopulmonary exercise testing predicted risk of early mortality when analyzed with logistic regression analysis; peak $\dot{V}O_2$ emerged as the strongest predictor on multivariable analysis (odds ratio, 0.65 per 1 $mL \cdot kg^{-1} \cdot min^{-1}$; P=0.041).

Conclusions—PVR after repair of tetralogy of Fallot has a low and improving mortality, with a low need for reintervention. Preoperative cardiopulmonary exercise testing predicts surgical outcome and should therefore be included in the routine assessment of these patients. **(*Circulation*. 2014;129:18-27.)**

Key Words: exercise test ■ heart defects, congenital ■ surgery ■ survival ■ tetralogy of Fallot

The outcome for patients with tetralogy of Fallot has improved dramatically since the introduction of surgical repair.[1,2] Pulmonary regurgitation, a common sequela of repair, may be well tolerated for decades. It is known, however, to have long-term detrimental effects, including exercise intolerance, progressive right ventricular (RV) dilatation and dysfunction, ventricular and atrial tachycardia, congestive heart failure, and sudden cardiac death.[3,4] Implantation of a competent pulmonary valve is commonly undertaken to avoid these adverse clinical outcomes. Cardiopulmonary exercise (CPEX) testing to assess objective exercise tolerance has been proposed as a potential tool for optimal timing of pulmonary valve replacement (PVR) because symptoms are often volunteered late by patients and are preceded by impairment in CPEX testing results. Indeed, CPEX testing has recently become part of routine medical surveillance of these patients in our center. In other disease settings, impaired CPEX performance is associated with a higher perioperative surgical risk,[5,6] but the association between baseline peak oxygen uptake and surgical risk has not been explored to date in a large cohort of adults with previous repair of tetralogy of Fallot (rTOF) undergoing PVR.

Clinical Perspective on p 27

In this study, we therefore examined contemporary outcomes of rTOF patients undergoing surgical PVR in a single tertiary center, with particular reference to preoperative baseline CPEX testing and its potential prognostic value.

Methods

All rTOF patients who underwent surgical PVR between January 1993 and December 2010 under the care of the adult congenital heart service at the Royal Brompton Hospital, London, UK, were included. Patients were identified from our surgical database, and their hospital

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Table 1. Characteristics of 220 Repaired Tetralogy of Fallot Patients Undergoing 221 PVRs at the Royal Brompton Hospital Between 1993 and 2010

Parameter*	
Male, n (%)	128 (58)
Age at PVR, y	32.0 (25.0–40.0)
Age at palliative surgery, y	2.7±4.2
TOF with associated lesions	20
Pulmonary atresia	11
Absent pulmonary valve	5
Atrioventricular septal defect	2
Absent left pulmonary artery	1
Partial anomalous pulmonary venous return	1
Previous palliative operation, n (%)	74 (34)
Blalock-Taussig shunt	43
Waterston shunt	20
Potts shunt	1
Central shunt	2
Brock procedure	5
Open pulmonary valvotomy	2
Nature of repair (n=210), n (%)	
Use of conduit	19 (9)
Use of RVOT patch	57 (27)
Use of transannular patch	108 (51)
Sternotomies before PVR (1/2/3), n†	187/31/3
Previous pulmonary valve replacement, n (%)	12 (5)
Preoperative clinical status	
PVR for predominant regurgitation/stenosis/both, n	178/36/7
Symptoms, %‡	
NYHA class I/II/III/IV	41/48/11/1
Diuretic use	25
Signs and symptoms of decompensated heart failure	5
Patient reported shortness of breath on exertion/fatigue	56
Arrhythmia (VT/established AF/AT/PPM for AV block‡)	21 (12/6/25/8)
Syncope (confirmed VT/AT/undocumented arrhythmia)	10 (45/18/36)
Electrocardiogram	
QRS duration (mean), ms	156±25
Preoperative cardiopulmonary exercise testing, n=154	
Peak $\dot{V}O_2$, mL·kg^{-1}·min^{-1}	23±8
Percent predicted peak $\dot{V}O_2$	65±18
Peak $\dot{V}O_2$ ≤70% predicted, %	38
Echocardiography (n=159)	
LV function grade 1/2/3/4, %§	87/11/1/2
RV function grade 1/2/3/4, % §	17/50/28/5
More than mild TR, %	11
Preoperative CMR	
RV end diastolic volume index (n=99), mL/m^2	156±45
RV end systolic volume index (n=99), mL/m^2	87±34
RV:LV end diastolic volume ratio (n=130)	2.1:1
RV ejection fraction (n=132), %	45±9
Pulmonary regurgitant fraction (n=136), %	39±12

AF indicates atrial fibrillation; AT, atrial tachycardia; AV block, atrioventricular conduction block; CMR, cardiac magnetic resonance; LV, left ventricular; NYHA, New York Heart Association; peak $\dot{V}O_2$, peak oxygen consumption; PPM, permanent pacemaker; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; VT, ventricular tachycardia (sustained ≥30-second duration, syncopal or presyncopal).

*Data are presented as median (interquartile range) or mean±SD. Percentages are rounded to the nearest whole integer.

†For all 221 operations.

‡Subsets not mutually exclusive.

§Echocardiographic grade: 1=good, 2=mildly impaired, 3=moderately impaired, 4=severely impaired.

records were examined. Because this was a retrospective analysis of data collected for routine clinical care, individual informed consent was not required (UK National Research Ethics Service guidance). The study was locally registered and approved.

Data recorded included demographics; information on previous surgical palliations and repairs; details of the surgical procedure, including the type of prosthesis used; preoperative New York Heart Association (NYHA) class; QRS duration from 12-lead surface ECGs; and ventricular function assessed by transthoracic echocardiography. Deaths were identified from the hospital database, automatically updated by the Office for National Statistics, which registers all UK deaths.

Preoperative CPEX testing was performed using a symptom-limited graded treadmill exercise. Peak oxygen uptake (peak $\dot{V}O_2$), ratio of minute ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$), and anaerobic threshold were assessed. Tests were excluded from subsequent analysis if the respiratory quotient value was <1 (n=7). Heart rate reserve was calculated as peak pulse rate on exercise minus resting pulse rate.

The primary outcome measure of the study was all-cause mortality. Early death was defined as death within 30 days of surgery. The secondary outcome measure was need for further pulmonary valve intervention, whether surgical or percutaneous. Follow-up was to the latest clinic visit. To assess the potential impact of surgical era, the earlier era was defined as the period between 1993 and 2004 (n=62), and the later era was the period between 2005 and 2010 (n=159), the latter coinciding with a marked increase in annual surgical volumes of PVR at our center.

Results are presented as mean and standard deviation if normally distributed or as median and interquartile range if not normally distributed. Rank correlation analyses were used to investigate the association between year of surgery and baseline CPEX parameters. Log-rank statistic was calculated to assess the difference in survival between the earlier and later eras. Differences in discrete variables were tested with χ^2 tests. Comparison of these features between patients who died and those who survived was also made by unpaired *t* tests or Wilcoxon tests, depending on data distribution. Kaplan-Meier curves were constructed to illustrate survival and freedom from events, and log-rank *P* values are provided. The correlation between preoperative parameters of CPEX and early (30-day) surgical mortality was tested with univariable and multivariable logistic regression analyses. Cox proportional hazards analysis was used to assess the association between variables and all-cause mortality. A 2-sided value of $P<0.05$ was considered significant.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. Between 1993 and 2010, 221 surgical PVRs were performed in 220 adults with rTOF. Median age at PVR was 32 years (25–40

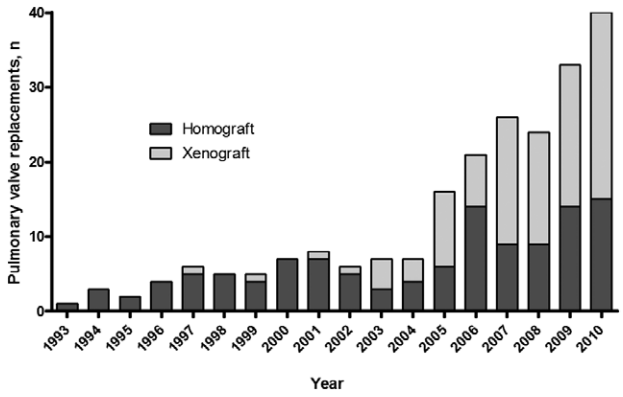

Figure 1. Royal Brompton Hospital surgical pulmonary valve replacements in adult patients with repaired tetralogy of Fallot between 1993 and 2010.

years). Twelve patients (6%) had a previous pulmonary valve implantation, including 2 patients who had a conduit type of rTOF. Fifty-six percent of patients were symptomatic with exertional dyspnea or fatigue; 21% had clinical arrhythmia; 60% were in NYHA class II, III, or IV; 25% were medicated with regular diuretics; and 5% had signs or symptoms of heart failure (Table 1). Four operations (2%) were for acute endocarditis refractory to medical therapy, requiring urgent surgery. An additional 3 patients (1%) had endocarditis that, although medically treated, resulted in valve degeneration requiring subsequent PVR.

PVR Surgical Characteristics

The number of patients undergoing surgical PVR at our center increased exponentially during the study (Figure 1). This increase was more pronounced beginning in 2005. Thirty-four patients (15%) had undergone multiple (≥2) previous sternotomies at the time of index PVR. A homograft was used in 117 patients (63 pulmonary, 45 aortic, 9 unknown), stented xenograft in 103 patients, and a mechanical prosthesis in 1 patient (Table 2). The rates of xenograft use increased over time (Figure 1). Other RV interventions at the time of PVR included revision of RV outflow tract, including patching (40%), pulmonary artery patching (29%), RV muscle resection (11%), and RV plication (19%). Two patients had complications from previous percutaneous pulmonary valve implantations (1 failed deployment at initial procedure, 1 developed valve failure with progressive regurgitation after incomplete medical treatment of fungal endocarditis); both underwent surgical percutaneous pulmonary valve explantation combined with surgical PVR. Thirty-six percent of cases involved additional surgery, including tricuspid valve repair (13%), branch pulmonary artery augmentation (12%), and residual ventricular septal defect closure (9%). Surgical details, including choice of prosthesis and concomitant lesions requiring treatment, are summarized in Table 2. The length of hospital stay was 7 days (6–10 days).

Mortality

Thirty-day (early) mortality was 2.3% (5 patients) as a result of severe RV failure in all 5 patients. Characteristics of patients who died are summarized in Table 3. Overall survival was 97% at 1 year (95% confidence interval [CI], 95–99), 96% at 3 years (95% CI, 93–99), and 92% at 10 years (95% CI, 89–97). Cardiac causes accounted for 8 of 9 late deaths. Five of the 8 deaths were to the result of heart failure, of which 1 death was in the context of multiorgan failure at 37 days resulting from unrelenting sepsis despite medical and surgical treatment for the index fulminant infective endocarditis. Three of 8 late deaths were arrhythmic (witnessed out-of-hospital cardiac arrests). QRS duration from the

Table 2. Pulmonary Valve Surgical Characteristics of 220 Repaired Tetralogy of Fallot Patients Undergoing 221 Pulmonary Valve Replacements at the Royal Brompton Hospital Between 1993 and 2010

Parameter	
Beating heart procedures, n (%)	99 (45)
Bypass time, min	113±59
Cross-clamp time, min	42±45
Temperature, °C	30.9±3.1
Homografts, n (%)	117 (53)
Homograft size (median/ interquartile range/ range), mm	24/23–25/15–28
Xenografts, (%)	103 (47)
Porcine	72 (70)
Mosaic	49 (48)
Hancock	20 (19)
Unspecified	1 (1)
Matrix P xenograft	1 (1)
Freestyle porcine aortic	1 (1)
Bovine pericardial	31 (30)
Carpentier-Edwards Perimount	28 (27)
Mitroflow	3 (3)
Xenograft size (median/ interquartile range/ range), mm	25/25–27/23–29
Additional surgical procedures, n (%)*	76 (36)
Branch pulmonary artery augmentation, n (%)	26 (12)
Pulmonary artery patch, n (%)	61 (29)
Right ventricular outflow tract patch, n (%)	84 (40)
Right ventricular outflow tract muscle resection, n (%)	24 (11)
Right ventricular outflow tract plication, n (%)	40 (19)
Residual ventricular septal defect closure, n (%)	18 (9)
Tricuspid valve surgery	
Tricuspid ring annuloplasty, n	10
Tricuspid annuloplasty ring size (median/interquartile range, range), mm	32/31–33/30-36
Atrial septal defect or patent foramen ovale closure, n (%)	6 (3)
Aortic root intervention, n (%)	1 (1)
Aortic valve replacement, n (%)	1 (1)
Coronary surgery, n (%)	4 (2)
Surgical ablation procedures, n (%)	5 (2)
Other surgical procedures, n (%)†	12 (5)
Length of hospital stay, d	7 (6–10)

*The subsets listed are not mutually exclusive.

†Additional procedures, including right coronary artery fistula repair, right coronary artery repair, removal of thrombus from branch pulmonary artery, suture of aortic cusp perforation from previous endocarditis, pericardectomy, fenestration of ventricular septal defect, right atrial plication, and left atrioventricular valve repair.

Table 3. Details of Early and Late Mortality After PVR (Total Deaths=14) Among 220 Adult Patients With Previously Repaired Tetralogy of Fallot Undergoing 221 PVRs at the Royal Brompton Hospital (1993 and 2010)

Death	Year of Surgery	Age at Surgery, y	Additional Surgical Procedures	Timing of Death in Relation to Index PVR	Cause of Death	Documented Arrhythmia	QRSd, ms
Early (<30 d)							
	2000	54.8	TV annuloplasty	2 d	Heart failure	A Flutter/AF	179
	2004	34.9		5 d	Heart failure	No	Paced
	2004	30.9	Repair aortic root rupture and false aneurysm	4 d	Heart failure*	No	111
	2006	36.5		3 d	Heart failure	No	157
	2007	42.9	RA plication	3 d	Heart failure	Established AF	150
Late (>30 d)							
	1993	21.5		12.6 y	Arrhythmia†	Syncope	165
	1995	42.0	TV valve repair	10.3 y	Arrhythmia†	AF/A flutter	184
	1996	26.8	Previous conduit	3.7 y	Heart failure	AF	
	1997	40.8	Previous conduit	4.3 y	Heart failure	AF	200
	1997	24.1	Previous conduit, IE	0.1 y	Heart failure*‡	No	
	1998	23.8	Previous conduit	2.7 y	Heart failure	AF	178
	1999	46.1	CABG SVGs to LAD and RCA	13.4 y	Heart failure	VT with ICD in situ	180
	1999	39.3		3.6 y	Perforated gallbladder	AF	200
	2007	34.1		1.6 y	Arrhythmia†	No	206

A Flutter indicates atrial flutter; AF; atrial fibrillation; ASD, atrial septal defect; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; LAD, left anterior diagonal; PA, pulmonary artery; PVR, pulmonary valve replacement; RA, right atrium; RCA, right coronary artery; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect; and VT, ventricular tachycardia.

*Urgent surgery involving pulmonary valve implantation was required in these 2 patients.

†All patients had witnessed cardiac arrest.

‡Patient died of heart and multiorgan failure related to uncontrolled endocarditis and septicaemia.

preoperative ECG was 184±28 milliseconds in those who died (early or late) compared with 153±22 milliseconds in survivors (P<0.001). Previous pulmonary valve implantation (n=29), whether as a result of conduit insertion at the time of original repair or previous redo surgery for pulmonary regurgitation, had no influence on mortality (hazard ratio [HR], 0.92; 95% CI, 0.21–4.13; P=0.92).

Preoperative CPEX Testing as a Predictor of Mortality

Preoperative CPEX testing was performed in 154 patients (70% of total, 79% of those operated on beginning in 2000 when preoperative CPEX was introduced) at a median of 9 months (5–16 months) before surgery. Preoperative peak $\dot{V}O_2$ was significantly lower in those patients who died early; furthermore,

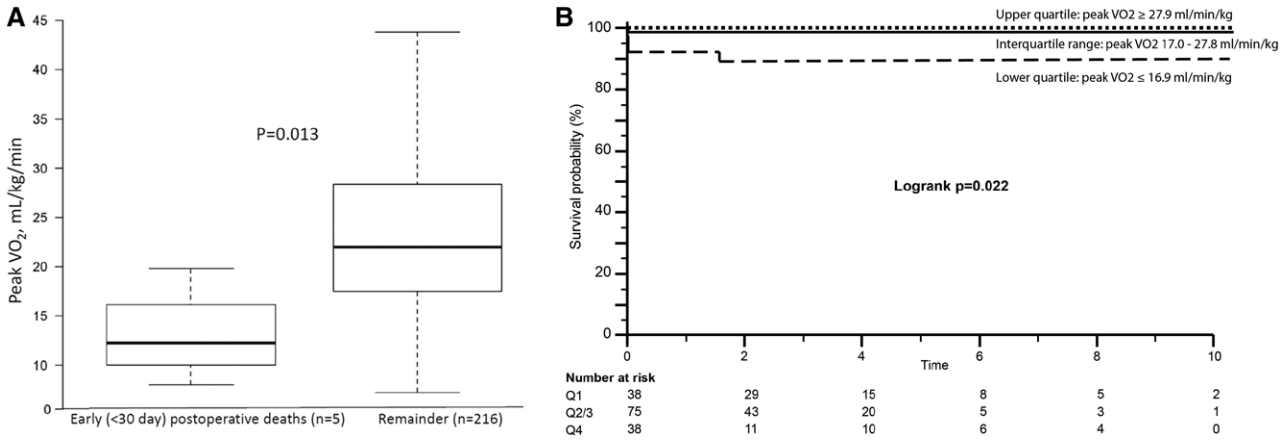

Figure 2. Baseline (preoperative) peak oxygen consumption ($\dot{V}O_2$) and survival after surgical pulmonary valve replacements in adults with repaired tetralogy of Fallot. **A**, Preoperative peak $\dot{V}O_2$ in those patients who died early. **B**, Survival stratified by preoperative peak $\dot{V}O_2$.

Table 4. Association Between Early Deaths After PVR and Parameters of Cardiopulmonary Exercise Testing on Logistic Regression Analysis

Variable	Odds Ratio	95% Confidence Interval	*P* Value	C Statistic, %
Univariate				
Peak $\dot{V}O_2$, mL·min^{-1}·kg^{-1}	0.76	0.60–0.95	0.015	85
$\dot{V}E/\dot{V}CO_2$ slope	1.09	1.02–1.17	0.009	89
Heart rate reserve, bpm	0.97	0.94–1.00	0.041	68
Age at index PVR, y	1.06	0.98–1.16	0.15	69
Multivariate*				
Peak $\dot{V}O_2$, mL·min^{-1}·kg^{-1}	0.65	0.58–0.93	0.041	86

PVR indicates pulmonary valve replacement.

*The 3 significant univariate predictors including peak $\dot{V}O_2$ were used in the multivariate model.

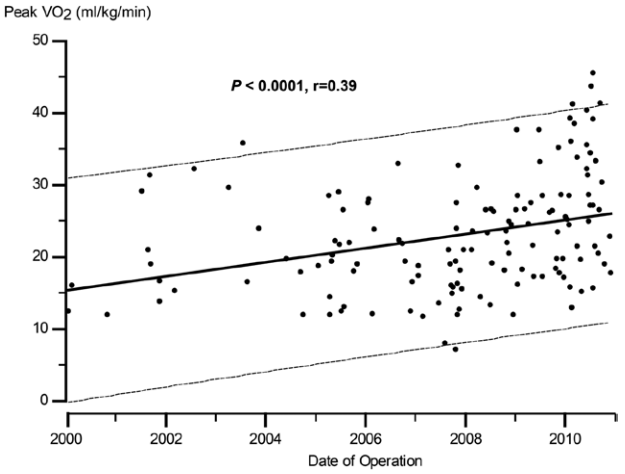

Figure 3. Change in baseline (preoperative) peak oxygen consumption ($\dot{V}O_2$) in adult patients with repaired tetralogy of Fallot referred for surgical pulmonary valve replacement over time.

patients with a lower quartile peak $\dot{V}O_2$ had markedly increased mortality (Figure 2).

The median preoperative peak $\dot{V}O_2$ was 21.5 mL·kg^{-1}·min^{-1}. No patient died with peak $\dot{V}O_2$ >21.5 mL·kg^{-1}·min^{-1}. Using a cutoff value of peak $\dot{V}O_2$ <20 mL·kg^{-1}·min^{-1} gives 100% sensitivity and 56% specificity for perioperative death. Early mortality for patients with preoperative peak $\dot{V}O_2$ <20 mL·kg^{-1}·min^{-1} was 5.7% versus 0% in patients with preoperative peak $\dot{V}O_2$ ≥20 mL·kg^{-1}·min^{-1}. Table 4 presents the results of the univariate and multivariate logistic regression analyses exploring the association between peak $\dot{V}O_2$ and early mortality. In a stepwise multivariate logistic regression, peak $\dot{V}O_2$ achieved was the only independent predictor of early mortality (Table 4).

To investigate the association between these variables and early or late mortality, we used Cox proportional hazard analyses. They confirmed a significant association between peak $\dot{V}O_2$ (HR, 0.77; 95% CI, 0.63–0.94; *P*=0.012), $\dot{V}E/\dot{V}CO_2$ slope (HR, 1.08; 95% CI, 1.02–1.13; *P*=0.006), and heart rate reserve (HR per 10 bpm, 0.73; 95% CI, 0.55–0.97; *P*=0.033) and outcome. Clinical symptoms (NYHA class >1) did not predict early mortality (HR, 2.21; 95% CI, 0.22–21.80; *P*=0.47). RV function on echocardiography (RV score ≥1; at least mild RV impairment) did not predict early mortality (HR, 1.26; 95% CI, 0.11–14.15; *P*=0.8).

Earlier Versus Later Era PVR

Baseline Characteristics and CPEX Testing

Earlier era patients were more commonly operated on for pulmonary stenosis or mixed pulmonary valve disease than for isolated pulmonary regurgitation (45% [28 of 62] versus 8% [13 of 159]; *P*=0.01). Earlier era patients had a worse functional class compared with later era patients (NYHA class I/II/III/IV, 31%/47%/19%/3% versus 43%/48%/9%/0%, respectively; *P*=0.008). Earlier era patients were more likely to volunteer symptoms of shortness of breath and fatigue than later era patients (44 of 56 [79%] versus 79 of 158 [50%]; *P*<0.001). There was no statistically significant difference in preoperative QRS duration between the 2 groups (167±26 versus 158±27 milliseconds; *P*=0.18). Preoperative peak $\dot{V}O_2$ was higher in patients operated on more recently (*r*=0.39, *P*<0.001; Figure 3). Better preoperative exercise capacity was also reflected by a lower $\dot{V}E/\dot{V}CO_2$ slope (*r*=–0.24, *P*=0.003) and a greater heart rate reserve (*r*=0.31, *P*<0.001) in patients operated on more recently.

Outcome

Hospital length of stay was shorter in later era patients compared with earlier era patients (7 days [6–9 days] versus 9 days [7–16 days]; *P*<0.001). Survival after PVR in the earlier era was 94% (95% CI, 88–100) at 1 year, 92% (95% CI, 85–99) at 3 years, and 87% (95% CI, 79–96) at 10 years. Survival in the later era was 99% (95% CI, 97–100) at 1 year and 98% (95% CI, 95–100) at 3 years, which was significantly better compared with the earlier era (*P*=0.019), as shown in Figure 4.

Clinical Follow-Up, Longevity of Pulmonary Valve Prostheses, and Need for Reintervention

Functional class improved after PVR; at the latest follow-up, NYHA class I/II/III/IV was 83%/13%/3%/2% compared with 41%/48%/11%/1% preoperatively (*P*<0.001). Sixty percent of patients were in NYHA class 2 or greater preoperatively compared with 18% at the latest follow-up. In contrast to improvement in NYHA class, there was no significant change in peak $\dot{V}O_2$ at a median follow-up of 3.0 years (1.7–4.7 years) from the index PVR (baseline versus latest CPEX, 21.6±7.5 versus 22.2±7.5 mL·kg^{-1}·min^{-1}; *P*=0.52) or in $\dot{V}E/\dot{V}CO_2$ slope (36.4±11.7 versus 33.9±10.8; *P*=0.17) or heart rate reserve (85±28 versus 81±25 bpm; *P*=0.27) when paired preoperative and follow-up CPEX data were available (n=53). Similarly, QRS duration did not change at a median of 3 years (2.3–4.6 years; baseline, 156±25 milliseconds versus latest ECG, 155±23 milliseconds; *P*=0.35).

Freedom from moderate or severe pulmonary stenosis at transthoracic echocardiography was 93% (95% CI, 88–98) at 5 years, whereas freedom from moderate or severe pulmonary regurgitation was 95% (95% CI, 91–99) at 5 years (number at risk, 48 for both). Of the 5 patients who had pulmonary valve

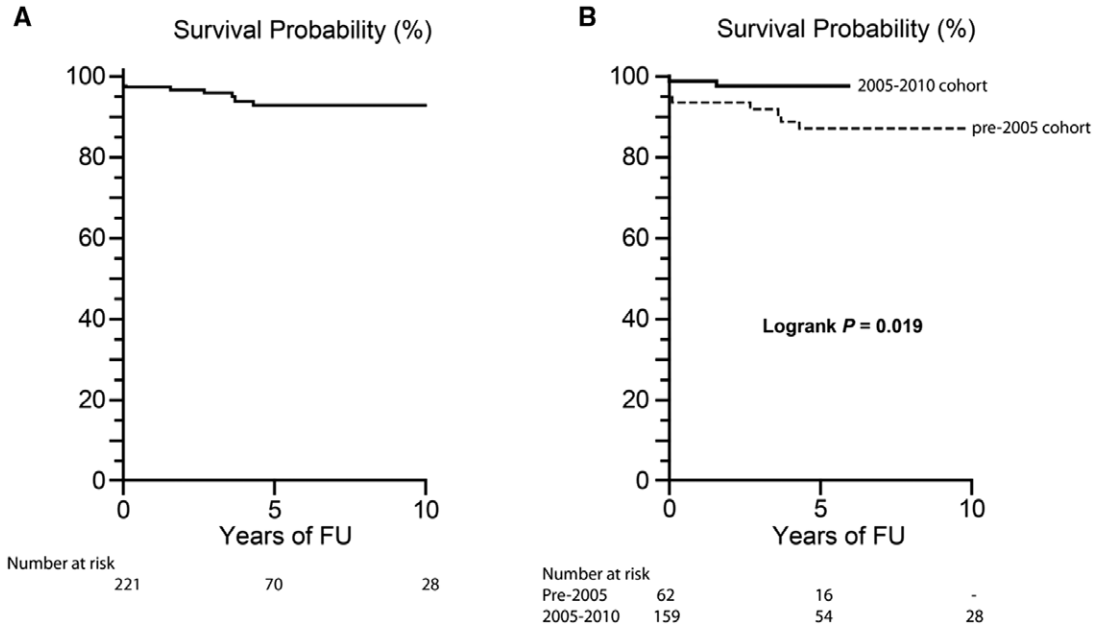

Figure 4. Survival after surgical pulmonary valve replacement in adult patients with repaired tetralogy of Fallot. **A**, Overall, total cohort. **B**, Earlier vs later surgical era. FU indicates follow-up.

reintervention after the index PVR, 2 underwent further surgical PVR, and 3 underwent percutaneous PVR. All 5 patients had received a homograft (3 aortic, 2 pulmonary) at the index PVR. Freedom from redo surgical or transcatheter PVR was 100% at 1 year, 98% at 5 years (95% CI, 95–100), and 96% at 10 years (95% CI, 91–100; Figure 5). Median follow-up for homografts was longer than for xenografts (4.3 years [1.6–9.4 years] versus 2.4 years [1.0–4.3 years]). There was no difference in early mortality between patients undergoing homograft and those undergoing xenograft implantation (4 of 121 versus 1 of 107; P=0.44). There was no difference in reintervention rates between homografts and xenografts on Kaplan-Meier analysis (log-rank P=0.98).

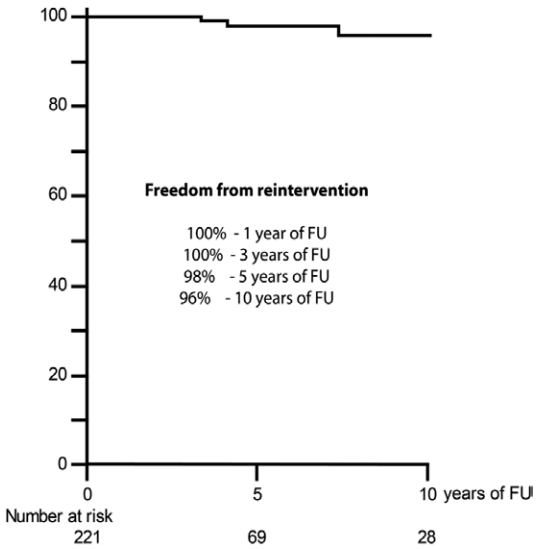

Figure 5. Freedom from surgical or transcatheter reintervention after surgical pulmonary valve replacement in adult patients with repaired tetralogy of Fallot. FU indicates follow-up.

Discussion

In our single-center cohort reflecting 17 years of experience of PVR in 220 adults with previous rTOF, pulmonary valve surgery is a low risk endeavor with low early and late mortality. Preoperative peak oxygen consumption was predictive of early mortality. Furthermore, patients undergoing PVR in the later era had a better early and mid-term outcome compared with those operated on in the earlier era, the former being referred for surgery while in better functional class and with better objective CPEX capacity.

A clear rise in the number of PVRs performed in our center is evident beginning in 2005, in keeping with evolving and broadening indications for PVR in this group of patients. The detrimental effects of pulmonary regurgitation are now widely accepted, which, in turn, has led to earlier PVR, in most instances before overt symptoms and cardiovascular decompensation develop. In the past, in keeping with the practice at the time, patients were considered for PVR only for significant RV outflow tract obstruction (RV pressure 2/3 systemic) or for severe pulmonary regurgitation in conjunction with arrhythmia, exercise intolerance, and heart failure. With time, milder symptoms, new-onset tricuspid regurgitation, or increasing RV size or deteriorating function became selective indications. When the deleterious effects of pulmonary regurgitation were more fully appreciated circa 2000, asymptomatic patients with pulmonary regurgitation were considered for PVR, including patients with lower or declining peak $\dot{V}O_2$, usually but not necessarily in conjunction with other clinical features. From circa 2005, quantified RV volumes measured with cardiovascular magnetic resonance were also incorporated into the decision-making process. This changing clinical practice is concordant with recent reports.[7–16] CPEX testing has increasingly been used in our center since 2000 in assessing patients and assisting the timing of surgical or transcatheter intervention rather than relying solely on symptoms.

Our data confirm that surgical PVR is a low-risk operation,[10,14,17–30] despite the fact that symptomatic patients and patients with multiple previous sternotomies were included in our report. All 5 patients who died early, however, died of right heart failure, suggesting that despite our modified, proactive approach for PVR, we still operate too late in some cases. Our series, confined to adult patients, had an overall survival of 97% at 1 year, 96 % at 3 years, and 92% at 10 years. Therrien et al[31] reported 92% survival at 5 years and 86% at 10 years in 70 adult rTOF patients after pulmonary valve surgery and early mortality of 4%. Discigil et al[26] reported 95% survival at 5 years and 76% at 10 years in 42 adults undergoing PVR; the same group reported a 2% early and 14% late mortality among children. Our data suggest a drop in mortality in contemporary surgical PVR. This may be associated with higher-volume adult congenital heart surgery, improved experience with redo sternotomy, improved surgical myocardial protection, and perhaps above all evolving and better selection criteria, leading to earlier PVR. Conversely, PVR in the earlier era was performed later in symptomatic patients who may have had a more advanced myocardial impairment, accounting for the higher NYHA class and objectively worse impairment of CPEX capacity. It is reasonable to presume that patients referred for PVR in the earlier era were at a later stage of disease progression. Their reduced peak oxygen uptake[32,33] or blunted heart rate reserve[34] and increased $\dot{V}E/\dot{V}CO_2$ slope[35] are established risk factors for adverse outcome in adult congenital heart disease irrespective of surgery.

Importantly, peak $\dot{V}O_2$ was predictive of early mortality in our study. For every 2- $mL \cdot min^{-1} \cdot kg^{-1}$ reduction in preoperative peak $\dot{V}O_2$, there was an ≈30% increased risk of early mortality. This novel finding of a relationship between CPEX results and perioperative mortality is of interest and merits further, prospective validation not only in patients undergoing PVR but also in other adult congenital heart disease subjects considered for redo surgery.

Peak $\dot{V}O_2$ was highly sensitive to high operative risk, but its limitation is lack of specificity. Although all patients who died had peak $\dot{V}O_2$ <20 $mL/kg/m^2$, a lower range result for peak $\dot{V}O_2$ was also recorded in 55% of survivors which in turn did not preclude a good outcome. Clinically, our data have taught us that a low peak $\dot{V}O_2$ may be judiciously used, in conjunction with other clinical data and context, as an indicator of potentially increased surgical risk; therefore, patients with peak $\dot{V}O_2$ <20 $mL \cdot kg^{-1} \cdot m^{-2}$ are more likely to carry a higher surgical risk than the 2% risk reported here for all-comers.

Our data show that QRS duration was prolonged in those patients who died. QRS prolongation is a predictor of sustained ventricular tachycardia and sudden cardiac death in rTOF.[3] QRS duration remains a risk factor if prolonged after restoration of pulmonary competence.[36] Mean QRS duration did not shorten significantly 3 years after PVR in our study. Late cardiac death was arrhythmic in 3 cases despite successful PVR (all 3 patients from the earlier era). This reinforces the point that hemodynamic intervention with PVR alone does not necessarily abort the risk of sudden cardiac death. High-risk patients, for example, with extensive fibrosis at cardiovascular magnetic resonance imaging,[37,38] may need and benefit from additional arrhythmia-targeting intervention or implantation of an automated internal cardiac defibrillator.

There was an increase in the proportion of xenografts used in the course of our study. This may reflect limited availability of suitably sized valves or a change in surgical preference. A potential advantage of homografts over stented valves (xenografts) is better hemodynamics. Homografts may also provide a more suitable substrate for later percutaneous pulmonary valve implantation. A perceived disadvantage of homografts is the greater risk for early regurgitation if the geometry of the valve is jeopardized during implantation. This may be true when a markedly enlarged and distorted RV outflow tract is present. In the present study, there were no differences in the durability of homografts compared with xenografts. Longer follow-up data may be necessary to elucidate the potential advantages of the superior hemodynamics associated with homografts. There was no difference in early mortality associated with the choice of prosthesis.

Clearly, additional markers to current indexes are required for optimal timing of PVR. CPEX testing may be one of them. Surgical PVR may be lower risk when cardiovascular fitness is maintained, justifying earlier intervention. Indeed, our data show that a better peak $\dot{V}O_2$ at baseline is associated with lower early mortality after PVR. Patients who had follow-up CPEX seem to have stable rather than improving exercise capacity in the medium term. This may be a reflection that isolated pulmonary regurgitation was the most common culprit lesion for PVR in our series. Others have demonstrated similar lack of improvement in peak $\dot{V}O_2$ after PVR unless pulmonary stenosis was the predominant lesion preoperatively.[14,39,40] Heart rate reserve and $\dot{V}E/\dot{V}CO_2$ slope also remained unchanged in our study. Thus far, RV volumes do not correlate well with peak $\dot{V}O_2$ in pulmonary regurgitation.[41,42] Despite improvement in LV filling and cardiac output and a reduction in RV volumes after PVR,[14,28,43] peak $\dot{V}O_2$ has not been found to improve after intervention in our study or in other studies.[14,39,40] Pulmonary regurgitation may significantly limit cardiac output during exercise, although other factors such as reduced diastolic time with increased heart rate, abnormal RV diastolic and pressure response to exercise caused by myocardial fibrosis or hypertrophy, and reduced pulmonary vascular resistance may also play a role in effective forward pulmonary blood flow. For these reasons, peak $\dot{V}O_2$ may be insensitive to change after restoration of pulmonary valve competence. Additionally, once peak $\dot{V}O_2$ becomes impaired, irreversible RV dysfunction may already play a role. It may be that different responses to surgery are attributable to differing degrees of RV stiffness and fibrosis. Fibrosis may be attributable to factors present before repair such as cyanosis and pressure overload, to operative technique and myocardial protection, or to progressive changes with age and prolonged and increasing volume overloading. Further studies could explore the possibility that there are cutoff values of preoperative peak $\dot{V}O_2$ above which an improvement in peak $\dot{V}O_2$ postoperatively is anticipated. Given the poor correlation between peak $\dot{V}O_2$ and RV volume increase resulting from pulmonary regurgitation,[41,42] such cutoff values in a future larger study may

or may not relate to those so far suggested for RV recovery as measured by reduction in RV volumes assessed with cardiovascular magnetic resonance. We propose therefore that PVR may still be considered too late even with our current proactive approach to generate significant improvement in exercise capacity. Earlier intervention, in the presence of a more compliant RV with preserved RV function, may lead to improved exercise performance, but this clearly needs to be validated in future studies. Peak $\dot{V}O_2$ is a composite measure of integrated cardiovascular and respiratory function and may reflect physical conditioning and other comorbidity. Not all these aspects will necessarily be improved with hemodynamic intervention alone but nevertheless contribute to surgical risk.

Freedom from surgical or transcatheter pulmonary valve reimplantation in our adult series was reassuring at 100% at 1 year, 98% at 5 years, and 96% at 10 years. Freedom from redo homograft replacement was 91% at 5 years and 84% at 10 years in the Oosterhof et al[17] study of 116 rTOF patients, and freedom from redo PVR 75% at 10 years in the study of 170 adults and children by Lee et al,[16] suggesting an improving trend of lesser need for reintervention in our series.

Although we advocate earlier PVR, this approach may not be without potential problems. Younger age at PVR may be associated with a higher rate of valve failure and early reoperation,[44,45] although this should be less of an issue in adult patients in whom somatic growth is not a concern. Operating earlier on the assumption that the next valve implantation can be performed percutaneously has additional appeal, but some patients may not be suitable for this evolving technique in future. Hence, longevity of pulmonary valve prostheses remains a concern with respect to timing of surgical pulmonary valve implantation.

Limitations

Our data are limited by the retrospective study design. Although 70% of patients had preoperative CPEX testing, paired preoperative and postoperative CPEX data were available in only 24% (53 patients). Although there was clear value in preoperative peak $\dot{V}O_2$ in evaluating mortality risk, low peak $\dot{V}O_2$ was highly sensitive but not specific, and causality cannot be assumed. Furthermore, the indications for PVR evolved with time during the study period and were individualized to patients rather than adhering to a protocol. Nevertheless, we report the largest (n=221) single-center, unselected clinical series with a complete data set on early and late mortality and on the need for reintervention.

Outcomes from our tertiary center with high-volume care of congenital heart disease cannot necessarily be extrapolated to other settings. We believe, however, our group of patients to be representative of contemporary tertiary practice.

Imaging data with cardiovascular magnetic resonance-derived ventricular volumes were not routinely acquired for all patients. This reasons are the relatively long period of observation without exclusions dating back to 1993 and the lack of defined cardiovascular magnetic resonance cutoffs for pulmonary regurgitation at the time to guide surgery. Cutoff values suggesting RV end-diastolic volume 150 to 160 mL/m^2 or end systolic volume >80 to 90mL/m^2 were not proposed until 2005[11] to 2008,[13,14] and they continue to evolve.[15,16] Furthermore, many patients herewith did not undergo clinical cardiovascular magnetic resonance for quantification of volumes, particularly in the earlier surgical era (n=8, only). Further data, including the degree of postoperative RV volume change, however, are the subject of ongoing prospective studies.

Conclusions

PVR has a low and improving mortality, with low 10-year reintervention rates. Patients operated on more recently in our cohort were less symptomatic and had better exercise capacity at the time of referral for surgical PVR compared with those operated on in the earlier part of the study, reflecting recent trends toward earlier PVR. This trend of earlier PVR was associated with lower mortality. Furthermore, preoperative peak oxygen uptake was predictive of early postoperative mortality, reinforcing the value of CPEX in this patient group.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Pulmonary regurgitation is common in adult patients with tetralogy of Fallot predisposing to right ventricular dilatation, ventricular dysfunction, exercise intolerance, and eventually life-threatening arrhythmia and sudden cardiac death. Implantation of a competent pulmonary valve is increasingly undertaken to mitigate such adverse clinical outcomes. In this single-center surgical series of 221 consecutive pulmonary valve replacement operations in adults spanning a 17-year period (1993–2010), we report low and improving early and late mortality rates. Cardiopulmonary exercise testing is increasingly used as part of routine medical surveillance in these patients. More recently, impaired or deteriorating peak oxygen consumption during exercise (peak $\dot{V}O_2$) has been used as an indication to expedite pulmonary valve replacement, before the onset of symptoms that are volunteered late. Our data suggest that impaired peak $\dot{V}O_2$ preceding pulmonary valve replacement was predictive of early perioperative mortality (5.7% when peak $\dot{V}O_2$ was <20 mL·kg^{-1}·min^{-1} versus 0% when peak $\dot{V}O_2$ was ≥ 20 mL·kg^{-1}·min^{-1}). This cutoff value of 20 mL·kg^{-1}·min^{-1} (100% sensitivity, 56% specificity) may therefore be used as a risk stratifier for perioperative issues. These preoperative peak $\dot{V}O_2$ data may assist clinical decision making on the optimal timing of pulmonary valve replacement and support the notion for early pulmonary valve replacement. Operating earlier while preoperative peak $\dot{V}O_2$ remains relatively preserved enables patients to undergo surgery with lower perioperative surgical risk, an advantage to be balanced with the finite longevity of currently available interventions.

Clinical Outcomes of Surgical Pulmonary Valve Replacement After Repair of Tetralogy of Fallot and Potential Prognostic Value of Preoperative Cardiopulmonary Exercise Testing

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