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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Running title: Preoperative CPEX and surgical PVR

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Abstract:

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

Methods and Results: The outcome of PVR in adults after rTOF at a single tertiary centre was retrospectively studied. Preoperative cardiopulmonary exercise (CPEX) testing was included. Mortality was the primary outcome measure. Two-hundred-and-twenty-one PVRs were performed in 220 patients (130 male, median age 32, range 16-64 years). Homografts were used in 117, xenografts in 103 and a mechanical valve in 1 case. Early (30-day) mortality was 2%. Overall survival was 97% at one 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 to 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 $\dot{V}O_2$, VE/VCO_2 slope and heart rate reserve during CPEX testing predicted risk of early mortality when analyzed with logistic regression analysis; peak $\dot{V}O_2$ emerged as the strongest predictor amongst them on multivariable analysis (Odds ratio 0.65 per ml/kg/min,P=0.041).

Conclusions: PVR after rTOF has a low and improving mortality, with low need for re-intervention. Preoperative cardiopulmonary exercise testing predicts surgical outcome and should therefore be included in the routine assessment of these patients.

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Key words
Surgery, tetralogy of Fallot, congenital cardiac defects, homograft, pulmonary regurgitation, cardiopulmonary exercise testing, survival

INTRODUCTION

The outcome for patients with tetralogy of Fallot has dramatically improved 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), as symptoms are often volunteered late by patients and preceded by impairment in CPEX testing results. Indeed, CPEX testing has recently become part of routine medical surveillance of these patients in our centre. In other disease settings impaired cardiopulmonary exercise 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.

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

PATIENTS AND 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 records were examined. As 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 (VE/VCO_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, earlier era was defined as the period

between 1993 and 2004 (n=62), whereas 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 centre.

Results are presented as mean and standard deviation if normally distributed, or median and interquartile range (IQR) 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 earlier and later era. Differences in discrete variables were tested with Chi-squared. Comparison of these features between patients that died and those surviving was also made using 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 surgical (30 days) mortality was tested using uni- and multivariable logistic regression analyses. Cox proportional-hazards analysis was used to assess the association between variables and all-cause mortality. A two-sided *P*-value <0.05 was considered significant.

RESULTS

Patient characteristics

Patient characteristics are summarised in **Table 1**. Between 1993 and 2010, 221 surgical PVRs were performed in 220 adults with rTOF. Median age at PVR was 32 (25 – 40) years. Twelve patients (6%) had a previous pulmonary valve implant, including 2 patients who had a conduit type of rTOF. Fifty-six percent of patients were symptomatic with exertional dyspnoea and or fatigue, 21% with clinical arrhythmia, 60% were in New York Heart Association class II, III or IV, 25% were medicated with regular diuretics and 5% has signs or symptoms of heart failure (Table 1). Four (2%) operations were for acute endocarditis refractory to medical therapy, requiring urgent surgery. An additional 3 (1%) patients had endocarditis which, although medically treated, resulted in valve degeneration requiring subsequent PVR.

Pulmonary valve replacement surgical characteristics

The number of patients undergoing surgical PVR at our centre increased exponentially during the study (**Figure 1**). This increase was more pronounced from 2005 onwards. Thirty-four patients (15%) had undergone multiple (≥2) previous sternotomies at the time of index PVR. A homograft was used in 117 cases (63 pulmonary, 45 aortic, 9 unknown), stented xenograft in 103, and a mechanical prosthesis in 1 patient (**Table 2**). The rates of xenograft use increased over time (**Figure 1**). Other right ventricular (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 had complications from previous percutaneous pulmonary valve implantations (one failed deployment at initial procedure, the other developed valve failure with progressive regurgitation following 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 summarised in **Table 2**. The length of hospital stay was 7 (6-10) days.

Mortality

Thirty-day (early) mortality was 2.3%, due to severe RV failure in all 5 cases. Characteristics of patients who died are summarised in **Table 3**. Overall survival was 97% at one 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 out of 9 late deaths. Five out of 8 were due to heart failure of which one was in the context of multiorgan failure at 37 days due to unrelenting sepsis despite medical and surgical treatment for the index fulminant infective endocarditis. Three out of 8 late deaths were arrhythmic (witnessed out of hospital cardiac arrests). QRS duration from the preoperative ECG was 184±28 ms in those that died (early or late) versus 153±22 ms in survivors (P<0.001). Previous pulmonary valve implantation (n=29), whether due to conduit insertion at the time of original repair or due to previous redo surgery for pulmonary regurgitation had no influence on mortality (Hazard ratio [HR] 0.92, CI 0.21 to 4.13; P=0.92).

Preoperative cardiopulmonary exercise testing as a predictor of mortality

Preoperative cardiopulmonary exercise testing was performed in 154 patients (70% of total, 79% of those operated from 2000 when preoperative CPEX was introduced) at a median of 9 (5-16) months prior to surgery. Preoperative peak $\dot{V}O_2$ was significantly lower in those

patients that died early; furthermore 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/min. No patient died with peak $\dot{V}O_2$ > 21.5 mL/kg.min. Using a cutoff value of peak $\dot{V}O_2$ < 20mL/kg/min, gives 100% sensitivity and 56% specificity for perioperative death. Early mortality for patients with preoperative peak $\dot{V}O_2$ < 20mL/kg/min was 5.7% versus 0% in patients with preoperative peak $\dot{V}O_2 \geq$ 20mL/kg/min. **Table 4** presents the results of the uni- and multivariate logistic regression analysis 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 Cox proportional-hazard analyses were used. These confirmed a significant association between peak $\dot{V}O_2$ (HR 0.77 [95% CI 0.63-0.94]; *P*=0.012), VE/VCO_2-slope (HR 1.08 [95% CI 1.02-1.13]; *P*=0.006), and heart rate reserve and outcome (HR/10 bpm 0.73 [95% CI 0.55-0.97]; *P*=0.033). Clinical symptoms (NYHA >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 pulmonary valve replacement

Baseline characteristics and cardiopulmonary exercise testing

Earlier era patients were more commonly operated on for pulmonary stenosis or mixed pulmonary valve disease than isolated pulmonary regurgitation, (45% (28/62) versus 8% (13/159); 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 (44/56; 79% versus 79/158; 50%; *P*<0.001). There was no statistically significant difference in preoperative QRS duration between the two groups (167±26 versus 158±27 ms; *P*=0.18). Preoperative peak $\dot{V}O_2$ was higher in patients operated on more recently (ρ=0.39, *P*<0.001), (**Figure 3**). Better preoperative exercise capacity was also reflected by a lower VE/VCO_2 slope (ρ=-0.24, *P*=0.003) and a greater heart rate reserve (ρ=0.31, *P*<0.001) in more recently operated patients.

Outcome

Hospital length of stay was shorter in later era patients compared to earlier era patients (7 [6-9] days versus 9 [7-16] days; *P*<0.001). Survival following 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 when compared with the earlier era (*P*=0.019) as shown in **Figure 4.**

Clinical follow up, longevity of pulmonary valve prostheses and need for re-intervention

Functional class improved following PVR: at the latest follow up NYHA class was I/II/III/IV; 83/13/3/2 % compared to 41/48/11/1 %, preoperatively (*P*<0.001). Sixty percent of patients were in NYHA class ≥2 preoperatively compared to 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 (1.7-4.7) years from index PVR (baseline versus latest CPEX 21.6±7.5 versus 22.2±7.5 mL/kg/min; *P*=0.52), nor in VE/VCO_2 slope (36.4±11.7 versus 33.9±10.8; *P*=0.17) or in heart rate reserve (85±28 versus 81±25 bpm; *P*=0.27) whenever paired preoperative and follow-up CPEX data were available (n=53). Similarly, QRS duration did not change at a median of 3 (2.3-4.6) years (baseline 156±25 versus latest ECG 155±23ms; *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 that had pulmonary valve re-intervention after index PVR, 2 underwent further surgical PVR, and 3 percutaneous PVR. All 5 patients had received a homograft (3 aortic, 2 pulmonary) at 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 xenografts (4.3 [1.6-9.4] versus 2.4 [1.0-4.3] years). There was no difference in early mortality between patients undergoing homograft or xenograft implantation (4/121 versus 1/107; P=0.44). There was no difference in re-intervention rates between homografts and xenografts on Kaplan-Meier analysis (log-rank P=0.98).

DISCUSSION

In our single centre cohort reflecting 17 years experience of PVR in 220 adults with previous rTOF, pulmonary valve surgery is a low risk endeavour 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 cardiopulmonary exercise capacity.

A clear rise in the number of PVRs performed in our centre is evident from 2005 onwards, 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 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 TR, or increasing RV size and/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 in the decision-making. This changing clinical practice is concordant with recent reports.[7-16] Cardiopulmonary exercise testing has increasingly been employed in our centre 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] This is in spite of the fact that symptomatic patients and patients with multiple previous sternotomies were included in our report. All five patients who died early, however, died from 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*. 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%.[31] Discigil *et al*. 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 amongst children.[26] 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 cardiopulmonary exercise 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 VE/VCO_2 slope[35] are all 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 mL/min/kg reduction in preoperative peak $\dot{V}O_2$ there was an approximately 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. Though all patients that 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 has 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; patients with peak $\dot{V}O_2$<20 mL/kg/m^2 are more likely therefore to carry a higher surgical risk than the 2% risk reported herewith for allcomers.

Our data show that QRS duration was prolonged in those patients that 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 and/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 and/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 right ventricular outflow tract is present. In the current study, there was no differences in the durability of homografts compared to 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 choice of prosthesis.

Clearly, additional markers to current indices 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 $\dot{V}O_2$ following PVR unless pulmonary stenosis was the predominant lesion preoperatively.[14, 39, 40] Heart rate reserve and VE/VCO_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 reduction in RV volumes after PVR [14, 28, 43] peak $\dot{V}O_2$ has not been found to improve post intervention in our study or in other studies. [14, 39, 14, 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 due to myocardial fibrosis and 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 following 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 due to differing degrees of RV stiffness and fibrosis. Fibrosis may be due to factors present before repair such as cyanosis and pressure overload or as a result of operative technique and myocardial protection, or 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 $\dot{V}O2$ postoperatively is anticipated. Given the poor correlation between peak $\dot{V}O_2$ and RV volume increase due to 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 measured with cardiovascular magnetic resonance (CMR). 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 also reflect physical conditioning and other co-morbidity. 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.,* study of 116 rTOF patients,[17] 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 re-intervention in our series.

While we advocate earlier PVR, this approach may not be without potential problems. Younger age at pulmonary valve replacement may be associated with a higher rate of valve failure and early reoperation[44, 45] though this should be less of an issue in adult patients where somatic growth is not a concern. Operating earlier on the assumption that next valve implantation can be performed percutaneously carries an 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 pre- and post-operative CPEX data were only available in 24% (53 patients). Though 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 individualised to patients rather than adhered to a protocol. Nevertheless, we report the largest (n=221), single centre, unselected clinical series with a complete data set on early and late mortality and on the need for re-intervention.

Outcomes from our tertiary centre 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 CMR derived ventricular volumes were not routinely acquired for all patients. This is because of the relatively long period of observation without exclusions dating

back to 1993 and the lack of defined CMR cut-offs for pulmonary regurgitation at the time to guide surgery. Cut-off values suggesting RV end-diastolic volume 150-160mL/m^2 or end systolic volume >80-90mL/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 CMR for quantification of volumes, particularly so 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

Pulmonary valve replacement has a low and improving mortality, with low 10-year re-intervention rates. Patients operated more recently in our cohort were less symptomatic and had better exercise capacity at the time of referral for surgical PVR compared to those operated in the earlier part of the study, reflecting recent trends towards 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

TABLES

Table 1.

Characteristics of 220 repaired tetralogy of Fallot patients undergoing 221 pulmonary valve replacements at the Royal Brompton Hospital between 1993 and 2010

Parameter*	N=220
Male, n (%)	128 (58)
Age at PVR, years	32.0 (25.0-40.0)
Age at palliative surgery, years	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)
Number of sternotomies prior to PVR (1/2/3)†	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 in ms	156±25
Preoperative cardiopulmonary exercise testing, n=154	
- Peak $\dot{V}O_2$, mL/kg/min	23±8
- % 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, mL/m^2, n=99	156±45
-RV end systolic volume index, mL/m^2, n=99	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

Abbreviations: AT; atrial tachycardia, AF; atrial fibrillation, AV block; atrioventricular conduction block, LV; left ventricle, NYHA; New York Heart Association, PPM; permanent pacemaker, 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±standard deviation. 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.

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, minutes	113 ± 59
Cross clamp time, minutes	42 ± 45
Temperature, °C	30.9 ± 3.1
Homografts, n (%)	117 (53)
Homograft size, mm (median/ interquartile range/ range)	24 / 23-25 / 15-28
Xenografts	103 (47)
Porcine, n (%)	72 (70)
Mosaic, n (%)	49 (48)
Hancock, n (%)	20 (19)
Unspecified, n (%)	1 (1)
Matrix P xenograft, n (%)	1 (1)
Freestyle porcine aortic	1 (1)
Bovine pericardial, n (%)	31 (30)
Carpentier-Edwards Perimount, n (%)	28 (27)
Mitroflow, n (%)	3 (3)
Xenograft size, mm (median/ interquartile range/ range)	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, mm (median/ interquartile range)	32mm/ 31-33
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, days	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 following PVR (total deaths,n=14) amongst 220 adult patients with previously repaired tetralogy of Fallot undergoing 221 pulmonary valve replacements at the Royal Brompton Hospital (1993 and 2010)

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

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

* Urgent surgery involving pulmonary valve implantation was required in these 2 patients. † All patients had witnessed cardiac arrest ‡ Patient died from heart and multiorgan failure related to uncontrolled endocarditis and septicaemia

Table 4.

Association between early deaths after pulmonary valve replacement 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/kg	0.76	0.60–0.95	0.015	85
VE/VCO_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, years	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

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

FIGURES

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

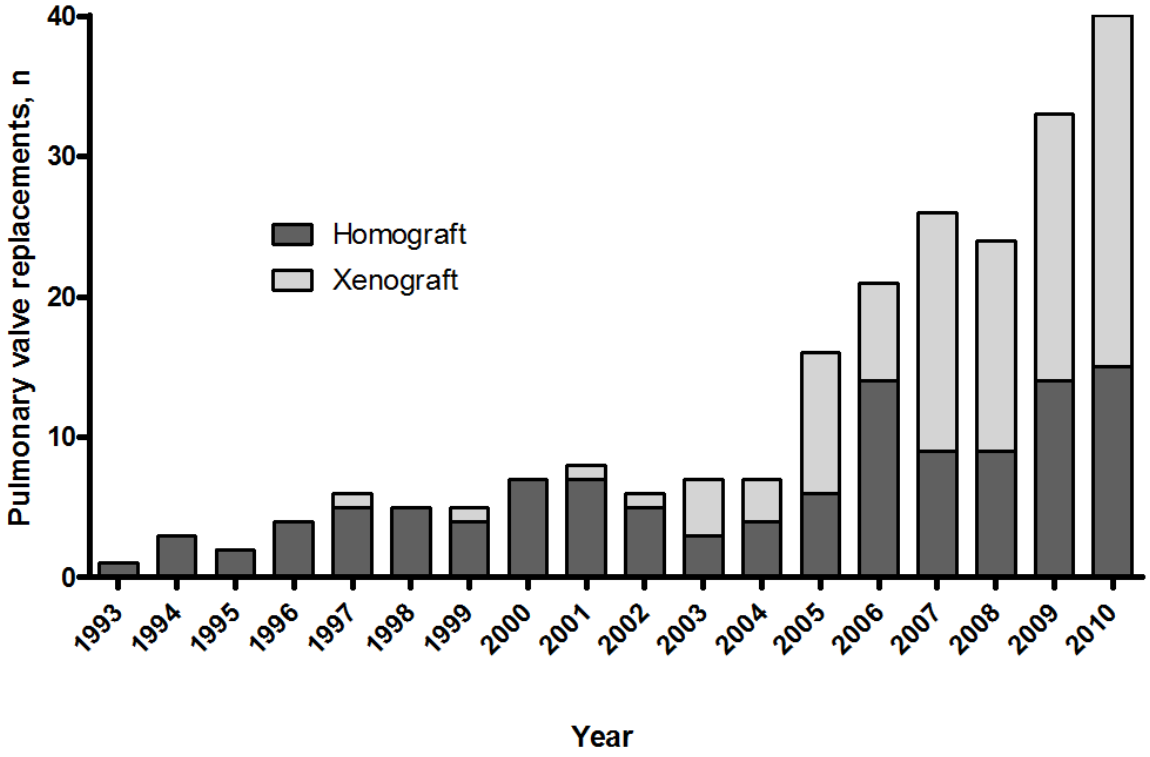


Figure 2 Baseline (preoperative) peak $\dot{V}O_2$ and survival after surgical pulmonary valve replacements in adults with repaired tetralogy of Fallot

A) Preoperative peak $\dot{V}O_2$ in those that died early versus survivors

B) Survival stratified by preoperative peak $\dot{V}O_2$

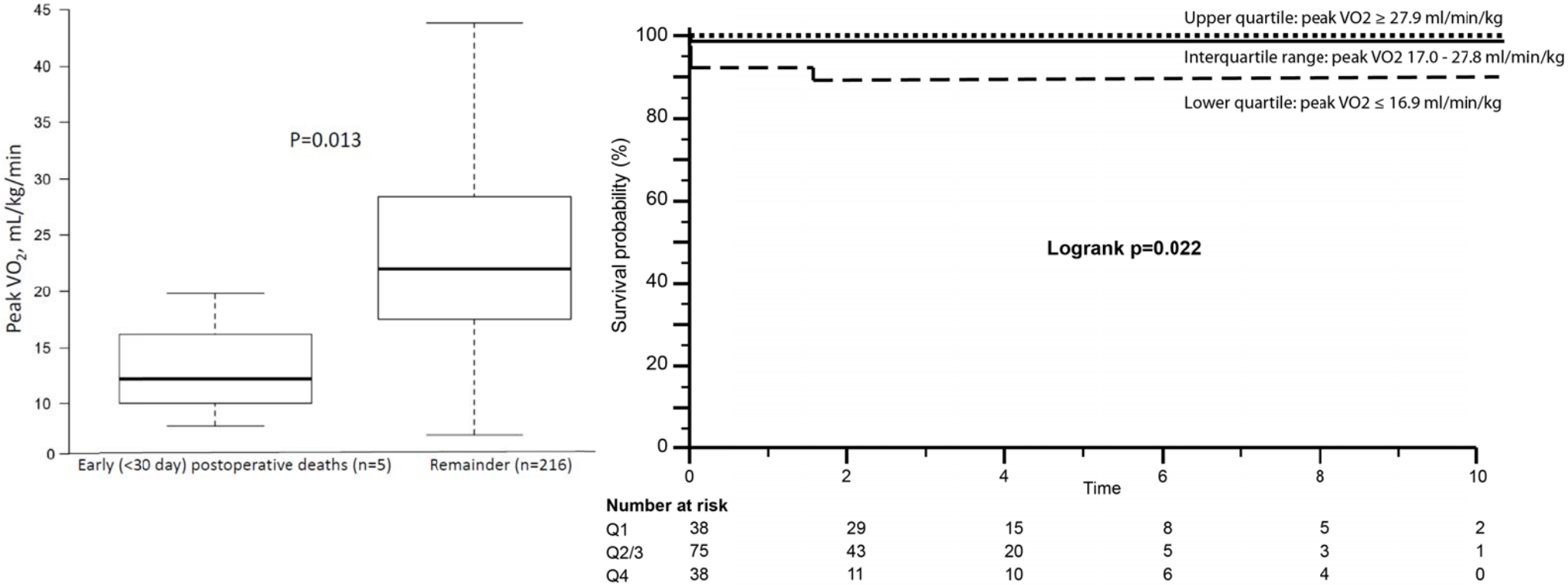


Figure 3. Change in baseline (preoperative) peak $\dot{V}O_2$ in adult patients with repaired tetralogy of Fallot referred for surgical pulmonary valve replacement over time

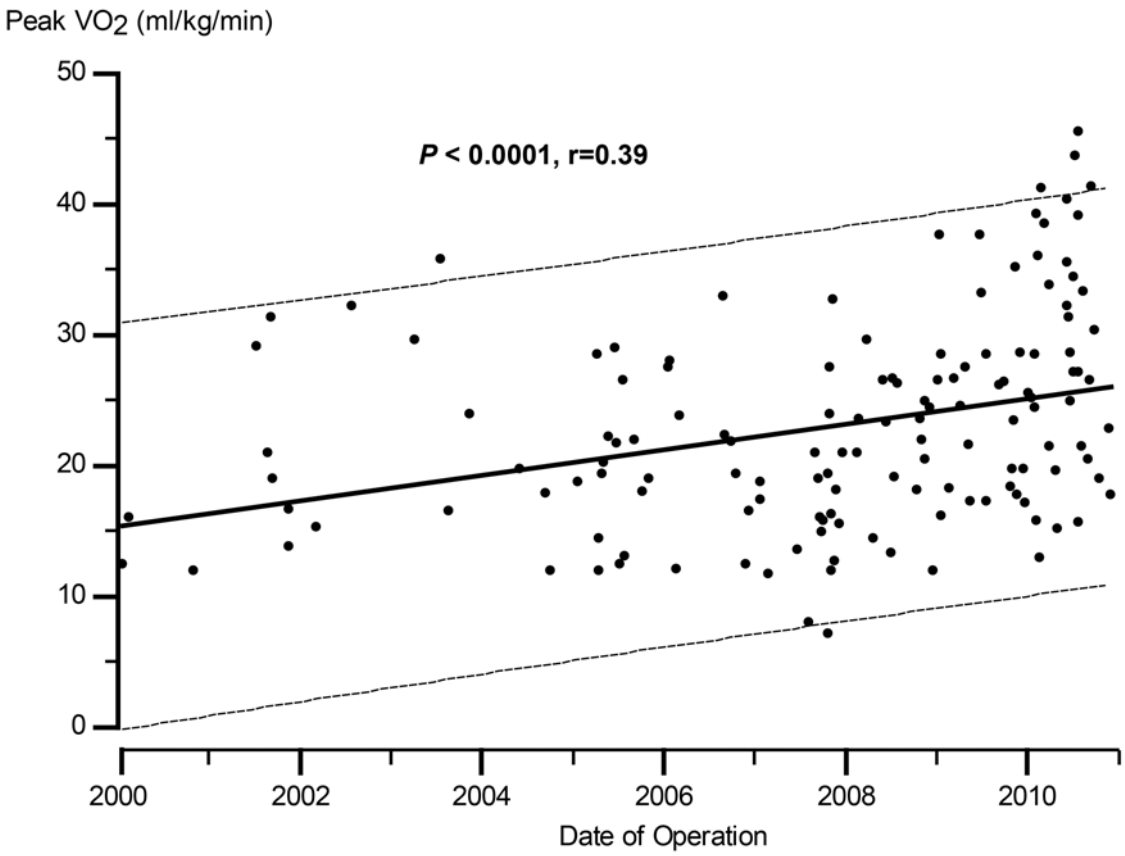


Figure 4. Survival after surgical pulmonary valve replacement in adult patients with repaired tetralogy of Fallot. A: Overall, total cohort; B: Earlier versus later surgical era.

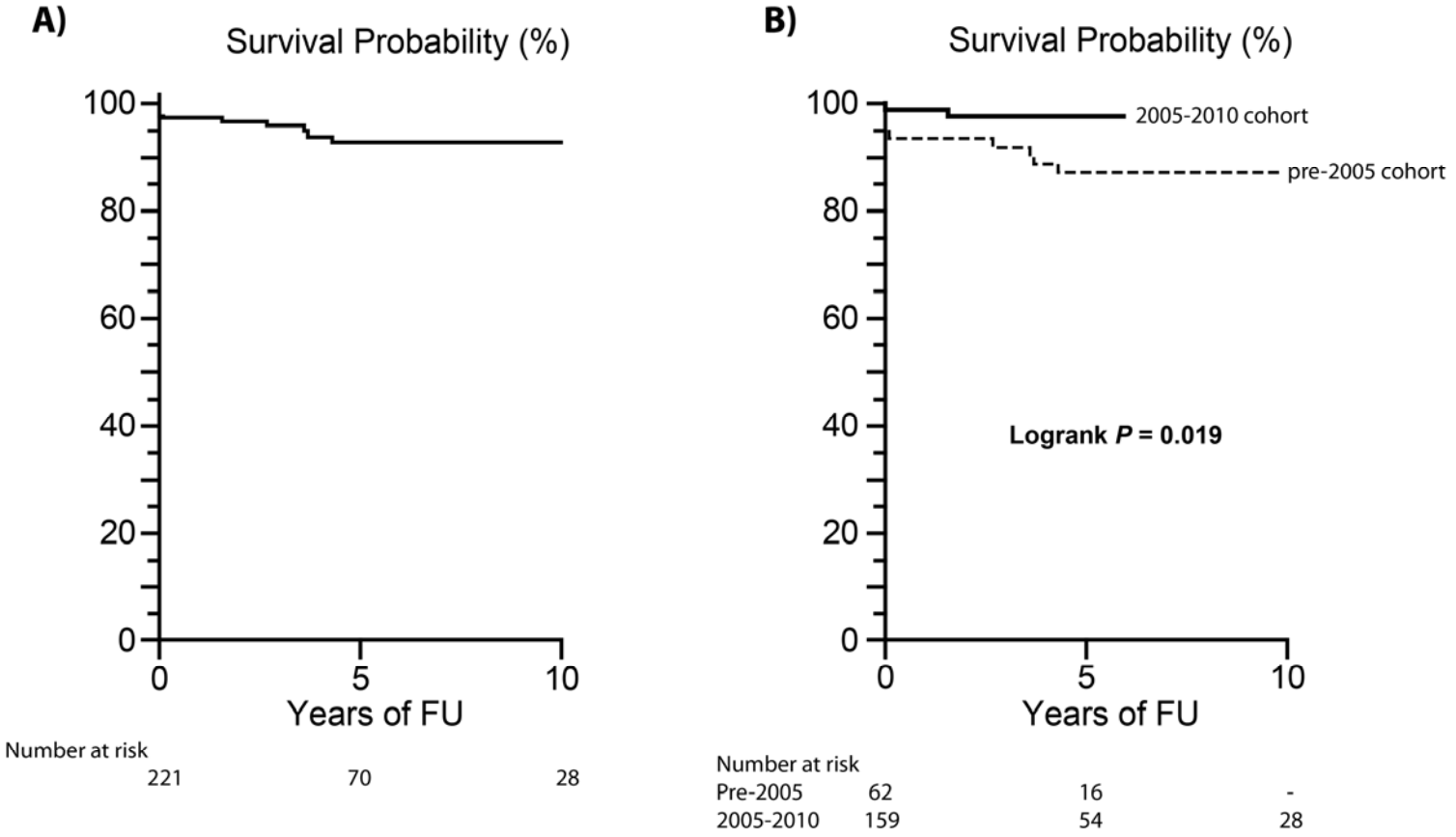
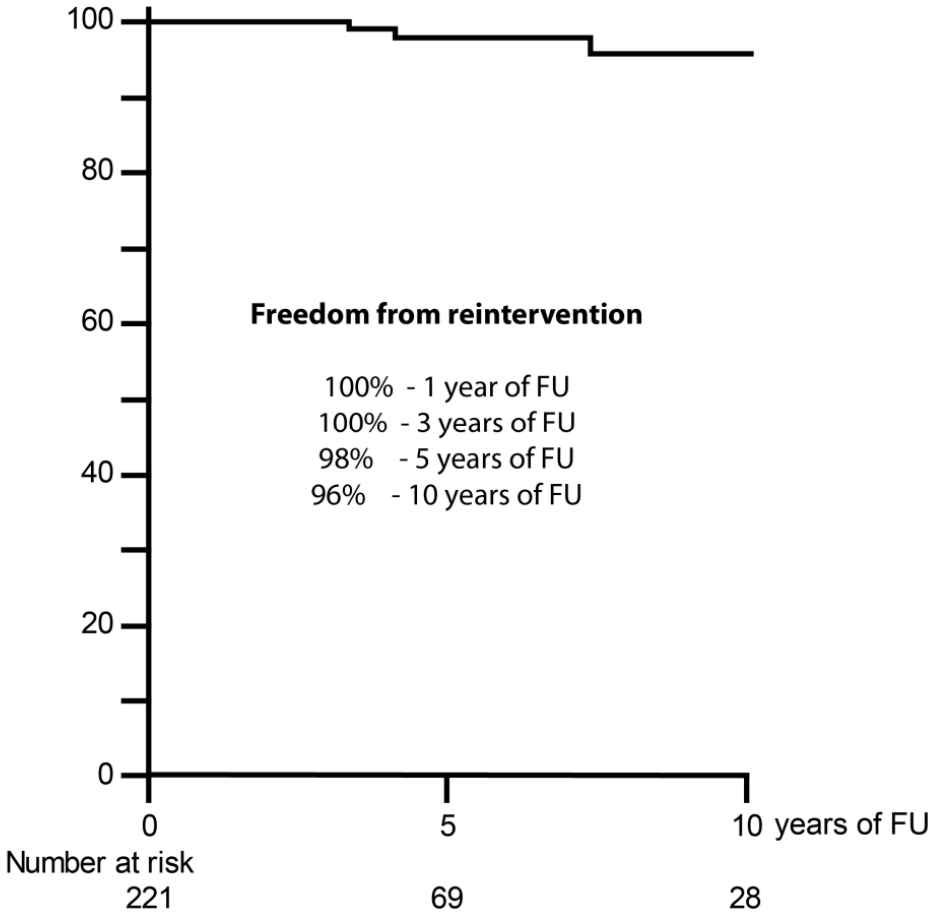


Figure 5. Freedom from surgical or transcatheter re-intervention following surgical pulmonary valve replacement in adult patients with repaired tetralogy of Fallot. FU indicates follow-up.



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Clinical commentary

Pulmonary regurgitation is common in adult patients with tetralogy of Fallot predisposing to right ventricular dilatation, ventricular dysfunction, exercise intolerance, life-threatening arrhythmia and sudden cardiac death. Implantation of a competent pulmonary valve is increasingly undertaken to mitigate such adverse clinical outcome. In this single centre surgical series of 221 consecutive pulmonary valve replacement (PVR) operations in adults spanning a 17 year period (1993-2010), we report low and improving early and late mortality rates. Cardiopulmonary exercise (CPEX) testing is increasingly employed as part of routine medical surveillance in these patients. More recently, impaired or deteriorating peak oxygen consumption during exercise (peak $\dot{V}O_2$) may be used as an indication to expedite PVR, before the onset of symptoms which are volunteered late. Our data suggest that impaired peak $\dot{V}O_2$ preceding PVR was predictive of early perioperative mortality (5.7% when peak $\dot{V}O_2$ <20mL/kg/min versus 0% when peak $\dot{V}O_2$ ≥20mL/kg/min). This cutoff value of 20mL/kg/min (100% sensitivity, 56% specificity) may therefore be used as a risk stratifier for perioperative issues. Thus, preoperative CPEX data may assist clinical decision-making regarding timing of surgical PVR. Operating earlier whilst 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.