

# Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot

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## KEYWORDS

Tetralogy of Fallot;  
Pulmonary valve  
replacement;  
Pulmonary homograft;  
Pulmonary stenosis;  
Pulmonary regurgitation

**Aims** To analyse the long-term outcomes after pulmonary valve replacement (PVR) in patients with a previous correction for tetralogy of Fallot.

**Methods and results** In a retrospective study, 158 adult patients with a diagnosis of tetralogy of Fallot, who had undergone a PVR after initial total correction in childhood, were identified from the CONCOR (CONgenital CORvitia) registry. All patients underwent 175 PVRs between June 1986 and June 2005. To analyse the predictors for homograft dysfunction and adverse events (death, reoperations, balloon angioplasty), Cox-regression analysis was performed. Overall freedom from significant homograft dysfunction was 66% after 5 years and 47% after 10 years. We could not identify predictors for combined homograft dysfunction. Event-free survival was 78% at 10 years and 68% at 15 years after PVR. Both early significant pulmonary regurgitation (PR) (HR 6.8,  $P = 0.017$ ) and pulmonary stenosis (PS) (HR 4.0,  $P = 0.037$ ) after surgery were associated with adverse events. When analysing direct post-operative PR or PS, we observed that in patients with severe, pre-operative PR, right ventricular aneurysm/patch resection resulted in a lower post-operative PR (mean difference grade  $0.38 \pm 0.14$ ,  $P = 0.01$ ). Less significant post-operative PS was associated with a higher diameter of the homograft (HR 0.37,  $P = 0.006$ ).

**Conclusion** While 47% of the patients in our study were free from homograft dysfunction at 10 years after PVR, event-free survival after PVR remained fairly good (78%). Significant residual lesions directly after surgery influenced event-free survival. A smaller diameter of the pulmonary homograft and severe pre-surgical PR were related to early homograft dysfunction after surgery.

## Introduction

In adult patients with tetralogy of Fallot, controversy remains on the optimal timing of pulmonary valve replacement (PVR).<sup>1</sup> When an 'early' PVR is advocated, an important issue is the need for future reoperations for a failing homograft. Freedom from homograft failure [in right ventricular outflow tract (RVOT) allograft recipients] varies between 60 and 91% at 5 years after implantation, implying careful follow-up of homograft function after initial implantation.<sup>2,3</sup> However, homograft failure is known to depend on the presence of various predictors, including younger age at repair, complex congenital heart disease, use of aortic homografts, and heterotopic position of homograft implantation.<sup>4–6</sup>

In tetralogy of Fallot, some of these predictors are not present. Therefore, it is not certain how current results on

homograft function can be translated to adult patients with tetralogy of Fallot. Furthermore, it is unknown how typical features of tetralogy of Fallot [RV dilatation, peripheral pulmonary stenosis (PS)] reflect on outcomes after valve replacement. Therefore, the aim of this study was to identify predictors for homograft dysfunction and for adverse events after PVR in patients with corrected tetralogy of Fallot.

## Methods

### Study population

In a retrospective study, 158 adult patients with a diagnosis of tetralogy of Fallot, who had undergone a PVR after initial total correction, were identified from the CONCOR (CONgenital CORvitia) registry in the Netherlands.<sup>7</sup> Patients with a homograft used for initial correction were excluded from the analysis. All patients identified in the CONCOR registry could enter the study. Patient

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**Table 1** Patient characteristics

	All patients (n = 158)
Male/female	94/64
Previous shunt procedure	76 (48%)
Waterston	32 (20%)
Pott's	9 (6%)
(Modified) Blalock Taussig	32 (20%)
Other	3 (2%)
Median age at previous shunt procedure (years)	1.7 (0–4.4)
Type of RVOT reconstruction at initial correction	
Myectomy/valvulotomy	9/93 (10%)
RVOT patch	13/93 (14%)
Transannular patch	65/93 (70%)
Valved conduit	6/93 (7%)
Median age at initial correction (years)	6.3 (1.5–11.2)

Data are described as number with frequency or median with interquartile range.

characteristics are listed in *Table 1*. The medical records for all patients were reviewed. Data collected included patient demographics, anatomical diagnoses, cardiac catheterizations, operations and concomitant procedures, echocardiographies, and follow-up of the clinical status. To analyse the effect of pregnancy on homograft durability and function, data on pregnancies from 33 patients could be obtained from the ZAHARA trial.<sup>8</sup> In the remaining 31 patients, no data on pregnancies could be obtained.

### Pulmonary valve replacement

All patients underwent 175 PVRs between June 1986 and June 2005 and characteristics of surgery are listed in *Table 2*. Guidelines for replacing PV in patients with severe pulmonary regurgitation (PR) included progressive RV enlargement, progressive tricuspid regurgitation, arrhythmias, or symptoms such as deteriorating exercise performance.<sup>9</sup> After PVR, median follow-up was 4.2 years (1 month–16 years, available in 100% of the procedures). All homografts were allocated by Bio Implant Services, Leiden, The Netherlands, from whom the data on homograft and donor characteristics were obtained.

### Haemodynamic data

Data on the last echocardiographic assessment before PVR and all available echocardiographic assessments after PVRs were acquired (n = 756). Before surgery, data on 133 echocardiograms were obtained and in the first year after surgery, 128 echocardiograms were obtained. In the remaining surgeries, data on echocardiographies were missing from patient records. Peak systolic pressure gradient across the RVOT was estimated by continuous wave Doppler echocardiography, using the modified Bernoulli equation. Pressure gradient >40 mmHg was considered significant. Colour flow mapping of the RVOT and branch pulmonary arteries was used to grade the PR. This was graded into five categories: 0, absent; 1, trivial; 2, mild; 3, moderate; and 4, severe. Any regurgitation more than grade 2 was defined as significant. Data on pre-operative cardiovascular magnetic resonance (CMR) could be obtained before 74 surgeries. CMR was performed following local MR protocols.<sup>10</sup> In the remaining cases, CMR was missing because MR equipment/techniques were not available to the participating centres at the time of surgery.

### Definition of endpoints

Homograft dysfunction was defined as significant PS (at any level >40 mmHg) or significant PR (grades 3 and 4). Clinical events

**Table 2** Characteristics of PVR (n = 175)

Haemodynamic parameters prior to PVR (MRI in n = 74)	
RVEDVI (mL/m <sup>2</sup> )	173 ± 42
RVESVI (mL/m <sup>2</sup> )	103 ± 36
RVEF (%)	42 ± 10
LVEDVI (mL/m <sup>2</sup> )	88 ± 22
LVEF (%)	52 ± 10
PR (%)	45 ± 13
Age at MRI assessment (years)	29 (13–45)
Valvular PS (>40 mmHg)	19/105 (15%)
Severe PR (grade 4/4)	56/116 (48%)
Surgical parameters	
Time after initial correction (years)	22 (10–34)
Concomitant RV aneurysm/patch resection	67 (38%)
Concomitant APD/APS angioplasty	34 (20%)
Proximal extension of the homograft with patch	17 (10%)
Concomitant tricuspid valve annuloplasty/De Vega/ring	26 (15%)
Concomitant VSD closure	11 (6%)
Concomitant RV myotomy/myectomy	10 (6%)
Anatomic position of the homograft	175 (100%)
Homograft and donor characteristics	
Aortic/Pulmonary homograft	8/167
Homograft quality (grade 1–10)	2 (1–3)
Diameter homograft (mm)	25 ± 2.1
Homograft bifurcation present	84/147 (57%)
Distal main pulmonary artery diameter (mm)	25 ± 3.0
APD diameter (mm)	21 ± 2.7
APS diameter (mm)	21 ± 2.7
Donor sex (male/female)	99/51
Donor age (years)	50 (38–62)
Time to explantation (hours)	7.4 (0–16.9)

Data are described as number with frequency, mean with standard deviation or median with interquartile range.

APD, arteria pulmonalis dextra; APS, arteria pulmonalis sinistra; EF, ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; VSD, ventricular septal defect.

were defined as: death (all causes), need for surgical homograft replacement for any reason, or catheter balloon dilatation/stent implantation.

### Data analysis

Data are described as number with frequency, median with range and mean with standard deviation. Differences in peak systolic gradients and PR before and the first measurement after PVR were analysed with a linear mixed effects model, assuming compound symmetry covariance structure for patients with more than one PVR.

Univariate Cox-regression analysis was used to identify the predictors for homograft dysfunction and adverse events after surgery. As some patients underwent two operations, it is not correct to assume that all observations are independent. Therefore, a Cox model with the patient as a gamma-frailty coefficient was fitted to investigate the different predictors. Multivariable analysis was not attempted because of the low number of events. The fit of the Cox-regression model was checked by assessing martingale residuals. Predictors for significant PS or PR in the first year after surgery were evaluated with univariate Cox-regression analysis.

A mixed linear regression model was used to analyse the course of transvalvular peak gradient and PR after surgery and were assumed to increase linearly after surgery. Peak transvalvular

gradient and PR were entered as dependent variables, patient as random effect, and time at echocardiography after surgery as fixed effect, in two separate models. Significant independent variables (patient and surgical parameters) and their interaction with time were analysed as fixed effects. To evaluate whether the peak transvalvular gradient or PR was different between the first and later follow-up years,<sup>11</sup> a dichotomous variable was entered, indicating whether echocardiography took place in the first year or thereafter.

Analyses were performed with SPSS 12.0.1 or S-Plus 6.2. A *P*-value <0.05 was considered statistically significant.

## Results

### Haemodynamic changes after surgery

Haemodynamic changes after surgery are listed in *Table 3*. In patients with a significant pre-operative PS (>40 mmHg), a mean reduction of 51 mmHg (SE 3.4, *P* < 0.001) in the transvalvular peak gradient was observed.

### Freedom from homograft dysfunction

Overall freedom from homograft dysfunction (significant PS at any level or significant PR) was 66% after 5 years and 47% after 10 years (*Table 3*). No predictors could be identified for (combined) homograft dysfunction. In 14/52 (27%) patients with homograft dysfunction, homograft explantation was performed at a median of 1.1 (0–3.7) years after identification of homograft dysfunction. The remaining 38/52 (73%) patients were followed for a median of 3.1 (0–8.4) years without homograft replacement at latest follow-up.

**Table 3** Clinical characteristics after PVR

<i>Haemodynamic changes after surgery</i>			
Decrease in peak transvalvular gradient (mmHg)	7.9 <sup>a</sup>	(SE 2.3)	
Decrease in PR (grades 0–4)	2.3 <sup>a</sup>	(SE 0.11)	
Decrease in peak gradient across branch pulmonary artery (mmHg)	11 <sup>a</sup>	(SE 4.1)	
<i>Homograft function after surgery</i>			
	<i>5 years</i>	<i>10 years</i>	
Freedom from homograft dysfunction	66% (SE 5)	47% (SE 7)	
Freedom from significant PV stenosis	79% (SE 4)	70% (SE 6)	
Freedom from significant PR	88% (SE 3)	75% (SE 6)	
PR grade (grades 0–4)	1.3 (SE 0.07)	1.7 (SE 0.07)	
Peak systolic gradient PV (mmHg)	26 (SE 1.5)	35 (SE 1.5)	
<i>Clinical events after surgery</i>			
Event-free survival <sup>b</sup>	88% (SE 3)	78% (SE 5)	
Deaths	2% (SE 1)	2% (SE 1)	
Freedom from repeat homograft replacement	91% (SE 3)	84% (SE 5)	
Freedom from balloon angioplasty	97% (SE 2)	91% (SE 4)	

<sup>a</sup>Indicates statistical-significant difference between pre-operative and first post-operative measurement.

<sup>b</sup>Events were defined as: death, homograft explantation, or balloon angioplasty.

### Event-free survival and homograft explantation

The management and survival of the patients are illustrated in *Figure 1*. Two patients died after PVR. One patient died from excessive ventricular arrhythmias while admitted for terminal heart failure. The other patient died suddenly, without symptoms of RV failure at latest follow-up. Actuarial survival at 5 and 10 years after PVR was 98%. Event-free survival at 15 years was 68% (*Figure 2*). Freedom from homograft explantation was 84% at 10 years and 73% at 15 years after PVR (*Table 3*). Reasons for homograft explantation and balloon angioplasty are listed in *Table 4*. All subvalvular (2/2), 50% (2/4) of the valvular, and none (0/4) of the supra-valvular balloon angioplasties were followed by homograft explantation.

### Predictors for event-free survival

In the first year after PVR, significant PR was present in 6% (7/125) and significant PS in 14% (17/124) of the patients. Early PR and PS were associated with adverse events (*Table 5*; *Figure 3*). No significant difference was observed in homograft failure between the first and second homograft (*P* = 0.46; *Table 5*). In a patient without significant PR or PS in the first year after surgery, event-free survival was 95% at 5 and 84% at 10 years (*Figure 3*).

### Valvular PS after surgery

Freedom from significant valvular homograft stenosis was 79% at 5 years and 70% at 10 years after PVR. In statistical analysis, there appeared to be a substantial difference in the increase of peak transvalvular between the first year (7.6 mmHg/year, SE 2.3) compared with the following years (1.2 mmHg/year, SE 0.3; *P* = 0.005). Furthermore, men showed a higher increase in transvalvular pulmonary gradient per year compared with women (mean difference 1.3 mmHg/year, SE 0.64; *P* = 0.049; *Figure 4*). Patients with a greater diameter of the homograft (indexed for body surface area) had a lower risk of significant PS in the first year after surgery [HR 0.37 (0.18–0.75), *P* = 0.006].

### PR after surgery

Freedom from significant PR was 88% at 5 years and 75% at 10 years. Mean increase in PR per year was 0.08 grade (SE 0.02; *P* < 0.001). No gender differences were observed in the progression of PR over time. Increase in PR per year was not significantly greater in the first year compared with the following years [mean difference 0.26 (SE 0.03) grades PR per year; *P* = 0.09]. Patients with severe pre-operative PR (grade 4/4), had a higher post-operative PR [mean difference 0.41 (SE 0.08) grade, *P* < 0.001] compared with those with lower pre-operative PR (grade 0–3/4). In those patients with severe pre-operative PR, a beneficial effect of a concomitant RV aneurysm/patch resection was observed [mean difference 0.38 (SE 0.14) grade, *P* = 0.01].

### Distal homograft/pulmonary branch stenosis

Freedom from significant distal homograft/pulmonary branch stenosis was 93% at 5 years and 91% at 10 years after PVR. Of the patients receiving a concomitant pulmonary artery angioplasty during surgery, 3/34 (9%) patients developed a distal homograft/pulmonary branch stenosis.

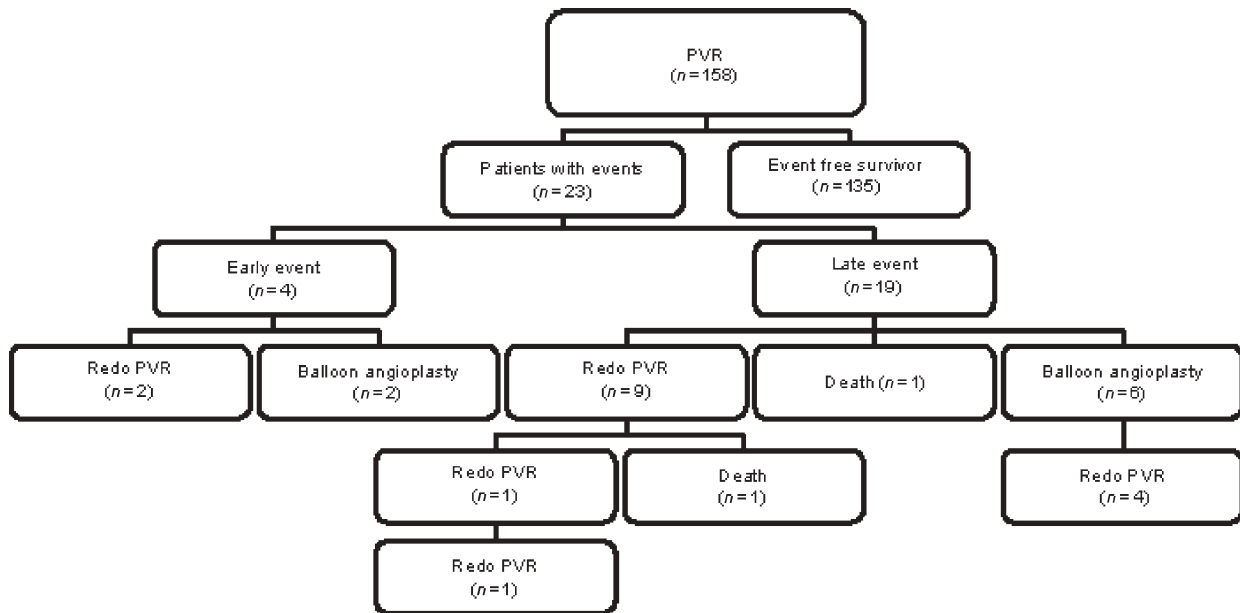


Figure 1 Management and outcomes after PVR.

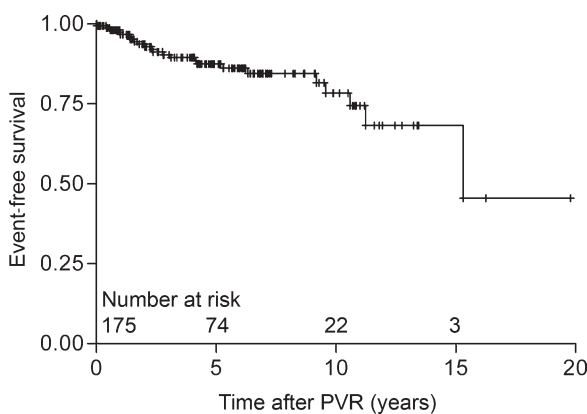


Figure 2 Event-free survival after PVR. Patient numbers are given.

In total, 10/175 (6%) patients developed significant distal homograft/pulmonary branch stenosis after surgery. In 8/10 (80%) patients, the stenosis occurred within the first year after PVR and in 3/10 (30%) patients, a subsequent balloon dilatation was performed at a median of 0.6 (0–2.7) years after detection of the stenosis.

**Pregnancy**

Data on pregnancies were obtained in 33/64 (52%) females. Of these patients, seven (23%) were pregnant before PVR and four (13%) became pregnant after surgery. These patients were not at increased risk for homograft failure or homograft dysfunction (Table 3). One patient required a second PVR 10 years after initial valve replacement. None of the patients had significant PR or PS at latest follow-up.

**Discussion**

In our study, we observed that 10 years after PVR in tetralogy of Fallot patients, homograft dysfunction occurred in

53% of the patients, whereas homograft explantation occurred in 16%. No risk factors for combined homograft dysfunction could be identified. Homograft dysfunction in the first year after surgery did influence event-free survival greatly. When analysing the predictors for homograft dysfunction separately, a smaller diameter of the pulmonary homograft and severe pre-surgical PR were related to early homograft stenosis and regurgitation, respectively. An RV aneurysm/patch resection appeared to reduce the amount of PR after surgery.

**Timing of PVR**

Optimal timing of PVR is still a subject of debate, where the decrease in RV volumes following PVR has to be weighed against the risk of subsequent reoperation for homograft failure.<sup>12,13</sup> In our population, event-free survival at 5, 10, and 15 years were 88, 78, and 68%, respectively. As event-free survival did not vary greatly from freedom from homograft explantation (68 vs. 73%, respectively at 15 years), a 20-year-old patient will require 4–5 homografts during his/her life, assuming 3rd or 4th homografts perform as well as the previous ones. In contrast, postponing PVR might negatively affect the post-operative recovery of RV function.<sup>14</sup> In our study, factors associated with postponing surgery (high RVEDVI, long time interval between initial correction and valve replacement) at least did not influence homograft dysfunction and/or event-free survival. The long-term results of percutaneous insertion of the PV are eagerly awaited.<sup>15,16</sup>

**Management of homograft dysfunction**

Although event-free survival was good in our population, 53% had a significant homograft dysfunction within 10 years after surgery. Close clinical follow-up is warranted in these patients. Indication for PVR includes: progressive RV enlargement, progressive tricuspid regurgitation, arrhythmias, or symptoms such as deteriorating exercise

**Table 4** Events after PVR (*n* = 17)

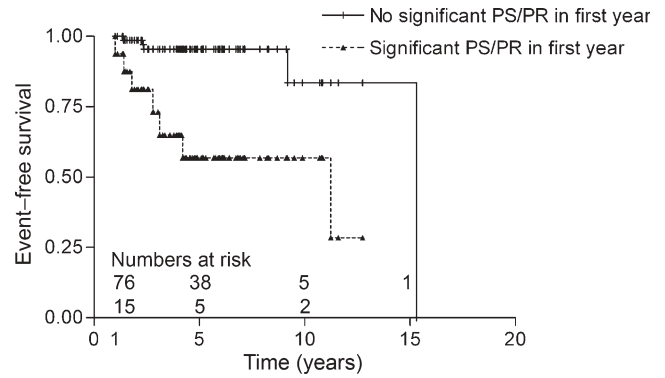
Indication for homograft explantation ( <i>n</i> = 17)	
PR	6 (35%)
Valvular PS	4 (24%)
Subvalvular stenosis	4 (24%)
Supravalvular stenosis	2 (12%)
Endocarditis	1 (1%)
Indication for Balloon angioplasty ( <i>n</i> = 8)	
Supravalvular stenosis	4 (50%)
Valvular PS	2 (25%)
Subvalvular stenosis	2 (25%)

**Table 5** Predictors for adverse events during median follow-up period of 4.1 years

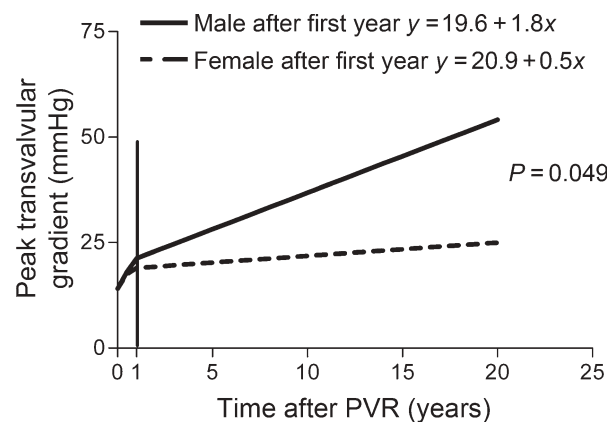
Parameter	Hazard ratio (95% CI)	<i>P</i> -value
<i>Parameter in first year after PVR</i>		
Significant PR in first year (yes, no)	6.8 (1.4–33)	0.017
Significant PS in first year (yes, no)	4.0 (1.1–15)	0.027
<i>Patient characteristics</i>		
Age < 18 at PVR (yes, no)	1.3 (0.5–3.1)	0.25
Time after total correction (years)	1.0 (0.94–1.1)	0.88
Recipient sex (male, female)	0.77 (0.3–1.9)	0.57
> 1 PVRs (yes, no)	1.5 (0.3–6.3)	0.46
RVEDVI (mL/m <sup>2</sup> )	1.0 (0.99–1.0)	0.72
RVESVI (mL/m <sup>2</sup> )	1.0 (0.99–1.0)	0.31
RVEF (%)	0.95 (0.88–1.0)	0.22
LVEF (%)	1.0 (0.95–1.1)	0.78
Pregnancy (yes, no)	1.0 (0.1–11)	0.99
<i>Procedural, homograft, and donor characteristics</i>		
Use of aortic homograft (yes, no)	2.4 (0.7–9.1)	0.19
Concomitant De Vega plastiek (yes, no)	2.4 (0.7–8.4)	0.18
Concomitant RVOT reduction (yes, no)	1.3 (0.5–3.1)	0.56
Concomitant APD/APS angioplasty	1.3 (0.51–3.3)	0.59
Homograft diameter (in mm/m <sup>2</sup> )	1.0 (0.8–1.3)	0.75

CI, Confidence interval; EDV, end-diastolic volume index; ESV, end-systolic volume index; VSD, ventricular septal defect.

performance. Many patients with homograft dysfunction did not undergo a second PVR during a mean follow-up period of 3.6 years. Possibly, these patients did not meet the guidelines yet for valve replacement. Furthermore, the will of adult patients to be operated once again and the general reluctance for reoperations even by surgeons play an important role in postponing redo PVR. Catheter interventions targeted against valvular or subvalvular stenosis did not appear very successful, with 4/6 patients requiring a further surgical intervention after the procedure.



**Figure 3** Event-free survival after PVR in patients who did or did not have significant PS and/or PR in the first year after PVR. Early homograft dysfunction resulted in increased adverse events until 5 years after PVR.



**Figure 4** Prediction lines of the peak systolic pulmonary valvular gradient with echocardiography after surgery. Note the higher increase of the peak gradient in the first year after PVR. Closed line represents the mean increase of the peak gradient for men, dashed line represents the mean increase for women. *P*-value for the difference in peak gradient increase between men and women per year is given.

When identifying risk factors for homograft dysfunction, we observed a beneficial effect of a concomitant RV aneurysm/patch resection on post-operative PR. In a report by van Straten *et al.*,<sup>17</sup> the recurrence of PR reduced the recovery of cardiac volumes after PVR. Possibly, reducing the size of the enlarged RVOT may protect the severely enlarged RV against residual PR after surgery.<sup>18</sup> More reports are needed to verify these findings. A second observation was that a smaller homograft (corrected for body surface area) increased the risk for significant PS in the first year after surgery. However, a smaller homograft was not a predictor for adverse events, likely due to the small number of patients requiring redo surgery for PS (*n* = 4).

We observed a higher increase in pressure gradient across the PV in the first year, compared with the following years.<sup>11</sup> Koolbergen *et al.* clearly indicated that cryopreserved homografts lose their cellular components within the first year after implantation.<sup>19</sup> Interestingly, we observed a difference in increase between males and females. Koolbergen *et al.*<sup>19</sup> stated that some important features of atherosclerotic changes can be observed in homograft explants. Possibly, the higher increase in pressure gradient of males compared with females, who are mostly

pre-menopausal in our study and protected by oestrogens, is a reflection of this atherosclerotic process, although we do not have direct evidence. At least these findings and possible pharmacotherapeutic options (statins) should be further investigated.

### Event-free survival

In comparison to event-free survival in this report, higher survival rates have been observed for Ross patients (97% after 5 years).<sup>20</sup> Lower event-free survival rates have been reported (between the 42 and 71% after 5 years) in other patient groups with more predictors for homograft failure (younger age at repair, use of smaller homografts, and extra-anatomic position).<sup>3-5,21,22</sup> Important differences of PVR in Fallot compared with the Ross procedure are the high incidence of RV dysfunction (severe PR and low RVEF, Table 2) and concomitant surgical procedures targeted at reducing the size of the RVOT (patch/aneurysm resection) or at increasing the size of the distal homograft connection (pulmonary angioplasty).

### Predictors for adverse events

Event-free survival was very good in patients without significant PR/PS in the first year after PVR. Although, this finding is not very surprising, it may help in risk stratification of patients directly after surgery. In correspondence with a recent report by Meyns *et al.*,<sup>6</sup> other factors [aortic homograft, a second homograft (or more)] did not show a significant risk on outcomes after PVR. In some reports, a donor specific immune response has been shown to influence the life span of pulmonary homografts.<sup>23</sup> The question as to whether an immunological response influences homograft longevity, probably, is still not settled.<sup>24</sup>

### Pregnancy

Pregnancies did not appear to be a risk factor on adverse outcomes after PVR in our population. In a recent report, it was observed that severe PR might be a risk for complications during pregnancy.<sup>8</sup> Therefore, our study supports the idea that PVR can be considered in female patients with severe PR and a pregnancy wish. However, more prospective studies are needed to verify these findings.

### Limitations

The results of this study are limited by the retrospective nature of the data collection, and the reliance on the medical record over a relatively long period of time. Furthermore, the gold standard for determining RV function in these patients (CMR) was not available in most of the patients.

### Conclusion

In patients with corrected tetralogy of Fallot, event-free survival (78% after 10 years) is fairly good, although 53% of the patients had a significant homograft stenosis or regurgitation within 10 years after PVR. Residual lesions, in the first year after PVR, had a serious impact on event-free survival. A second homograft had no additional risk. A smaller diameter of the homograft and severe PR before surgery were related to homograft dysfunction directly after surgery.

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**Conflict of interest:** none.

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