Long-Term Follow-Up of Pulmonary Valve Replacement in Repaired Tetralogy of Fallot

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Abstract

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. Surgical repair of TOF carries excellent results with significant improvement in patient survival, however it is not curative. Residual hemodynamic lesions, most commonly pulmonary regurgitation (PR), predispose patients to chronic right ventricular overload with significant morbidity and mortality. Over a third of patients with repaired TOF will undergo pulmonary valve replacement (PVR) later in life.[1] The fate of these PVR prostheses and long-term consequences are largely unknown, inciting debate about the optimal timing of PVR and the ideal prosthesis to be used. The aim of this study is to help in understanding the long-term outcomes of PVR and whether the type of prosthesis used relates to favorable outcomes.

Methods

We conducted a retrospective cohort study of patients with repaired tetralogy of Fallot who underwent PVR from 1990 to 2015 in our institution. Patients' demographics, operative records, clinical follow-up, and imaging were reviewed. Statistical analyses compared patients who had Carpentier–Edwards, Contegra, or pulmonary homograft implanted in relation to late mortality and late adverse events (reintervention (redo-PVR or transcatheter), infective endocarditis, or arrhythmic events post-op with device implantation or ablation).

Results

A total of 69 patients were included in the study divided into three groups based on the prosthesis implanted: Carpentier-Edwards (n=14), Contegra (n=40), and pulmonary homograft (n=15). The mean age at the time of PVR was 21 ± 12 years, and the mean interval between TOF repair and PVR was 18.6 ± 9 years. Only 32 (48%) of the patients had symptoms prior to PVR. The mean pre-op RVEDVI was 210 ± 42, and the mean RVESVI was 120 ± 24. The mean follow-up was 8.5 ± 4.7 years. There were no early or late mortalities in this cohort. Twenty-three (33%) patients had late adverse events over the follow-up period of the study: 15 (22%) patients had reintervention (surgical or transcatheter), 11 (16%) patients had endocarditis, and 11 (16%) patient had post-operative arrhythmic events with device implantation or ablation. Out of the fifteen patients that underwent reintervention after PVR, only 8 patients underwent surgical redo-PVR. Overall 1, 5, and 10 years freedom from surgical redo-PVR was 98.5%, 93.6%, and 79.3%, respectively. Infective endocarditis occurred in 11 (16%) patients, 8 of which were in the Contegra group. The Contegra group had significantly higher pulmonary valve gradients post-op, and a higher risk of developing late adverse events compared to Carpentier-Edwards (p=0.046) and pulmonary homograft (p=0.055) in multivariate analysis. Contegra valved prosthesis also seem to be a risk factor for reintervention in the univariate analysis (HR of 3.4 with 95%CI 0.92 – 13; p-value 0.066).

Conclusion

Pulmonary valve replacement (PVR) in patients with repaired tetralogy of Fallot is a safe operation with acceptable short- and Intermediate-term outcomes. Contegra prosthesis had

higher risk of late adverse events (reintervention, endocarditis, and arrhythmic events post-op with device implantation or ablation) and seem to be a risk factor for reintervention with higher pulmonary valve gradients post-op compared to Carpentier-Edwards and pulmonary homograft prostheses. More studies with larger sample sizes and longer follow-up are necessary to detect differences between PVR valve types and determine long-term outcome of newer bioprosthesis.

Résumé

Introduction

La tétralogie de Fallot (TdF) est la cardiopathie congénitale cyanotique la plus courante. La réparation chirurgicale de la TOF donne d'excellents résultats avec une amélioration significative de la survie des patients, mais elle n'est pas curative. Les lésions hémodynamiques résiduelles, la régurgitation pulmonaire (RP) étant la plus commune, prédisposent les patients à une surcharge ventriculaire droite chronique avec une morbidité et une mortalité significatives. Plus d'un tiers des patients avec TdF réparé (rTdF) auront besoin d'un remplacement valvulaire pulmonaire (RVP) au cours de leur vie.[1] Le sort de ces prothèses de valve pulmonaire et leurs conséquences à long terme sont largement inconnus, ce qui suscite un débat sur le moment optimal du RVP et le type de prothèse à utiliser. Le but de cette étude est d'aider à comprendre les résultats à long terme du RVP et si le type de prothèse utilisé est lié à des résultats favorables.

Les Méthodes

Nous avons mené une étude de cohorte rétrospective de patients atteints de la tétralogie de Fallot ayant été réparée dans le passé qui ont subi une PVR de 1990 à 2015 dans notre établissement. Les données démographiques des patients, les dossiers opératoires, le suivi clinique et l'imagerie ont été examinés. Nous avons analysé et comparé les patients ayant eu une implantation de Carpentier-Edwards, Contegra ou pulmonaire en relation avec une réintervention (redo-RVP ou transcathéter) ou une endocardite infectieuse.

Résultats

Au total, 69 patients ont été inclus dans l'étude divisés en trois groupes en fonction de la prothèse implantée: Carpentier-Edwards (n = 14), Contegra (n = 40) et homogreffe pulmonaire (n = 15). L'âge moyen au moment du PVR était de 21 ± 12 ans et l'intervalle moyen entre la réparation du TOF et le PVR était de 18,5 ± 9 ans. Seuls 48% des patients présentaient des symptômes avant de subir un RVP. Le RVEDVI moyen était de 210 ± 42 et le RVESVI moyen de 120 ± 24. Le suivi moyen était de 8,5 ± 4.7 ans. Il n'y avait pas de mortalité précoce ou tardive dans cette cohorte. Vingt-trois (33%) patients ont subi une réintervention (chirurgicale ou transcathéter), ou une endocardite infectieuse au cours, ou arythmie avec implantation ou ablation du dispositif de la période de suivi de l'étude. Quinze patients ont subi une réintervention après RVP (8 patients redo-RVP chirurgical, 8 patients implantation de valve pulmonaire transcathéter). Globalement, la proportion de patient n'ayant pas nécessité de réintervention chirurgicale à 1, 5 et 10 ans sont de réintervention chirurgical ont été de 98,5%, 93,6% et 79,3% respectivement. Une endocardite infectieuse est survenue chez 11 (16%) patients. Le groupe Contegra avait des gradients de valve pulmonaire significativement plus élevés après l'opération, et une tendance à plus de réintervention et d'endocardite, et arythmie avec implantation ou ablation du dispositive en analyse multivariée (p=0.046, p=0.055).

Conclusion

Contegra a de pires résultats dans les événements indésirables tardifs (réintervention, endocardite ou arythmie avec implantation ou ablation du dispositif). Davantage d'études avec des échantillons plus grands et un suivi plus long sont nécessaires pour détecter les différences entre les types de valve de RVP et afin de déterminer les résultats à long terme d'une bioprothèse plus récente.

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Authors Contributions

AA worked on the idea of the project, collected the data, conducted statistical analyses with interpretation, and wrote the manuscript with input from CT, PB, and SM; SM contributed to design, helped in analysis and interpretation; PB supervised the project, provided data, and helped in direction and planning; CT conceived the idea of the project, supervised the project, provided data, and oversaw overall direction and planning.

List of Abbreviations

TOF: Tetralogy of Fallot

rTOF: repaired Tetralogy of Fallot

PVR: Pulmonary Valve Replacement

DORV: Double Outlet Right Ventricle

RV: Right Ventricle

PR: Pulmonary Regurgitation

PS: Pulmonary Stenosis

NYHA: New York Heart Association

MRI: Magnetic Resonance Imaging

Imaging Abbreviations:

- LVEF: Left Ventricular Ejection Fraction
- RVEF: Right Ventricular Ejection Fraction
- PV PG: Pulmonary Valve Peak Gradient, PV MG: Pulmonary Valve Mean Gradient
- LVEDV: Left Ventricular End-Diastolic Volume, LVESV: Left Ventricular End-Systolic Volume, LVEDVI: Left Ventricular End-Diastolic Volume Index, LVESVI: Left Ventricular End-Systolic Volume Index, SV: Stroke Volume, SVi: Stroke Volume index.
- RVEDV: Right Ventricular End-Diastolic Volume, RVESV: Right Ventricular End-Systolic Volume, RVEDVI: Right Ventricular End-Diastolic Volume Index, RVESVI: Right Ventricular End-Systolic Volume Index, RV CO: Right Ventricular Cardiac Output.
- %PV: Pulmonary Valve percent regurgitation

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Introduction and Literature Review

A. Tetralogy of Fallot (TOF)

Tetralogy of Fallot (TOF) is the most common congenital cyanotic heart disease (approximately 33 per 100,000 live births).[2,3] It is estimated that TOF accounts for 3–5% of all infants born with a CHD.[4] TOF develops from a conotruncal defect resulting in anterior malalignment of the infundibular septum giving rise to four main components: right ventricular outflow tract (RVOT) obstruction, ventricular septal defect (VSD), overriding aorta, and concentric right ventricular hypertrophy.

B. Tetralogy of Fallot Prognosis and Surgical Repair

Patients suffering from TOF carry a poor prognosis with 50% mortality in the first few years of life without correction. Without the TOF repair, only half of the patients reach three years of age and only few survive to 40 years of age.[5] The first successful repair of TOF was done by Dr. Lillehei in 1954.[6] Neonatal primary repair of TOF is generally avoided and primary repair is usually deferred to 3-6 months of age due to more favorable outcomes.[7,8] Since 1987, all TOF patients in our institution undergo primary repair without palliation at any age with most repairs performed at 3 months of age. The management of this anomaly evolved from palliation, to staged repair, to single-stage complete repair with operative mortality of less than 1%, an early postoperative survival exceeding 98%, and most patients survive into adulthood with approximately 90% patient survival at 30 years of age.[9-11] The surgical success of TOF repair is reflected in the increased survival of patients with repaired TOF (rTOF). In fact, adult

patients with rTOF currently outnumber children.[11,12] There is a risk of late sudden death that seems to be due to ventricular arrhythmias that may be associated with RV dilatation and decreased function. Over a third of the patients with rTOF will undergo reoperation later in life, most commonly pulmonary valve replacement (PVR) which may decrease the risk of sudden death. [1,13]

Alleviation of the right ventricular outflow tract obstruction in TOF repair sometimes requires employment of a transannular patch (TAP) with resultant pulmonary regurgitation (PR). Goals of the surgical repair of TOF include the closure of the ventricular septal defect (VSD), and the relief of the right ventricular outflow tract (RVOT) obstruction. Historically, relief of RVOT obstruction was done with generous TAP with or without pulmonary valvectomy without great concern of development of PR.[14] A small subset of patients predominantly develops residual pulmonary stenosis (PS) as opposed to PR. This depends on their underlying anomaly and the type of repair employed. TOF with pulmonary atresia, pulmonary valve-sparing techniques, and utilization of right ventricular (RV) to pulmonary artery conduits in the initial TOF correction predispose these patients to development of pulmonary stenosis, regurgitation, or both later in life.[14] The long-term hemodynamic consequences of volume overload differ from pressure overload.[15]

C. Tetralogy of Fallot Repair, Hemodynamic Consequences, and Double Outlet Right Ventricle (DORV)

Many of the patients who underwent TOF repair with TAP have residual hemodynamic lesions, of which severe pulmonary regurgitation (PR) is the most common occurring in over half of all patients.[16] Many of the patients with rTOF who develop PR remain asymptomatic for years with gradual deterioration of exercise performance, and development of symptoms that may not be readily attributed to PR.[17] The understanding of the effects of PR has evolved overtime, what was once thought to be a benign condition following TOF repair is currently a well recognized cornerstone factor affecting late outcome. Without intervention, the chronic volume overload caused by the PR leads to right ventricular dilatation and dysfunction with increased morbidity and mortality. Over the long-term, the volume overload on the RV generated by the PR results in progressive RV dilation, fibrosis, dysfunction, and may lead to left ventricular (LV) dysfunction as well.[14]

Patients with double outlet right ventricle (DORV) with subaortic VSD and pulmonary stenosis have decreased pulmonary circulation flow and are treated similarly to TOF patients. DORV patients who undergo transannular patch (TAP) repair of the RVOT also have long-term hemodynamic consequences similar to TOF patients and may develop significant pulmonary regurgitation with resultant adverse complications as mentioned previously.[18,19] DORV patients and patients with pulmonary atresia and TOF or DORV who were treated with a transannular patch were included in our cohort.

D. Pulmonary Valve Replacement (PVR) Debate

PVR in patients with rTOF is a safe operation with low operative mortality,[20] however, biological pulmonary valve prostheses are prone to structural valve degeneration, endocarditis, and dysfunction as the time passes necessitating prolonged treatment and sometimes operative reintervention. The timing of these events varies widely between patients and might be related to the type of valve implanted and other patient factors like age at PVR and number of cardiac operations prior to PVR. The timing of PVR is based on patient symptomatology, RV size, and RV function. Some advocate early PVR because of the higher likelihood of favourable remodelling of the RV size and function along with reduced risk of ventricular tachyarrhythmias compared to late PVR.[21] On the other hand, early PVR can precipitate faster degeneration of the implanted bioprosthesis and predispose to a higher prevalence of endocarditis. In a retrospective cohort comparing early PVR (patients younger than 16 years of age at the time of PVR) and late PVR (patients older than 16 years of age at the time of PVR), early PVR had better RV morphology and function preservation but a significantly earlier occurrence of the combined safety end-point (one year mortality post-PVR, endocarditis, and redo PVR) as compared to late PVR.[22] The earlier and the more aggressive PVR is performed, the higher the likelihood of bioprosthetic valvular dysfunction and prosthetic related morbidity. Postponement of PVR on the other confers higher likelihood of irreversible RV remodeling and risk of dangerous ventricular tachyarrhythmias. Therefore, the long-term consequences of different PVR strategies in patients with rTOF are largely unknown.

E. Pulmonary Valve Replacement (PVR)

Patients who had TOF repair in their early life are at risk of developing exercise intolerance, heart failure symptoms, arrhythmias, and sudden cardiac death later in their second or third decade of life.[23] The most common cause of death in this patient group is sudden cardiac death presumably related to ventricular tachyarrhythmias.[24] This has led to the emergence of pulmonary valve replacement (PVR) operations to correct the chronic severe PR and its related consequences. The number of PVR operations performed in patients older than 10 years of age has more than tripled in the period between 2004 and 2012 in an analysis of combined data of thirty-five United States centers.[25]

The benefits of PVR in patients with severe PR with previous repaired TOF reported in the literature include improvement of volume and function of the right ventricle, improvement of the function of the left ventricle, and improvement of patients' symptoms.[26] It is not clear whether PVR decreases the incidence of ventricular arrythmias or sudden death.[27] Although the current available evidence has not clearly demonstrated a survival benefit of PVR, the restoration of pulmonary valve competence and elimination of PR has been shown to confer favorable hemodynamic response on the RV and may lead to symptomatic improvement.[20,28] No significant difference has been demonstrated in death, resuscitated sudden cardiac death, or sustained ventricular tachycardia between rTOF patients who underwent PVR as compared to patients who were managed conservatively.[29] Some evidence have demonstrated improvement in terms of New York Heart Association (NYHA) classification after PVR.[30,31] PVR has also been shown to correlate with modest reductions in QRS duration (QRS prolongation is

an electrophysiologic end-point that has been linked to increased risk of ventricular tachyarrhythmias).[32,33]

Multiple studies have reported the early outcomes of late PVR in patients with rTOF, and only few published papers have reported the long-term outcomes. Surgical PVR in patients with rTOF is associated with low operative, 30-day, and 5-year mortality. Results from pooled meta-analysis data have demonstrated an operative mortality rate of PVR in rTOF from 0.87% to 2.1% and long-term mortality rates ranging from 0.5% to 2.2% per year after PVR. The pooled five-year redo PVR was 4.9%.[26,34] In a recently published meta-analysis investigating the long-term outcome of PVR in adult patients with previous rTOF, only ten papers were eligible for the study. The mean age during PVR ranged from 26 to 38 years, and the mean follow-up duration ranged from duration ranged from 2 to 22 years. Only two out of the ten papers had mean follow-up durations more than 6 years. Some reported predictors of operative mortality included older age at TOF repair, more than three previous cardiac surgeries, advanced NYHA class, and large body surface area (BSA) at the time of PVR. [20] The estimated infective endocarditis risk in surgical PVR is 0.3% per patient-year.[35]

F. Pulmonary Valve Replacement Uncertainties

Controversy still remains regarding the optimal timing of PVR in asymptomatic patients with rTOF. There is a consensus that PVR is indicated in symptomatic patients with significant PR, heart failure, or ventricular tachyarrhythmias, however, in absence of these symptoms, recommendations vary.[27] Cardiac magnetic resonance imaging (MRI) imaging is an essential

tool in evaluation and decision making for PVR. It can be used for RV functional assessment and volumetric measurements of the unique RV in TOF patients. The debate stems from which Cardiac MRI measurement and what cut-off value should be followed. Several imaging-based studies have demonstrated normalization of RV volumes after PVR if the preoperative RV end-diastolic volume index (RVEDVI) is less than 150-170 ml/m^2 or if the RV end-systolic volume index (RVESVI) is less than 82-90 ml/m^2.[27] Studies have also showed that RV remodeling and volume normalization could not be achieved once the preoperative RVEDVI exceeds 160 mL/m^2 or RVESVI exceeds 82 mL/m^2. [36] Some have advocated for a more aggressive strategy with regards to PVR in patients with rTOF recommending valve replacement when RVEDVI reaches 150 mL/m^2.[31,37] Others have suggested that preoperative RVEDVI of 168 ml/m^2 and preoperative RVESVI of less than 80 ml/m^2 were predictors for the best outcome.[38] RV ejection fraction and QRS duration were factors that have also been investigated.

G. Prosthesis Options and Transcatheter Intervention

Three types of PVR prostheses were implanted in this cohort. The choice of the bioprosthesis was based on the preference of the surgeon and influenced by the time period during which the repair was done. In the early 1990s, most repairs utilized Pulmonary Homografts (human cryopreserved pulmonary homografts). The use of Contegra (integrated valved conduit derived from a bovine jugular vein with incorporated trileaflet venous valve, Medtronic) followed and became more prevalent due to the limited availability of pulmonary homograft prosthesis and size restrictions. In the latest years of our cohort, Carpentier-Edwards (PERIMOUNT bovine pericardial bioprosthesis, Edwards Lifesciences Corporation) valves were

more commonly used and this was over increased concerns of higher rates of late infective endocarditis in bovine jugular vein valved conduits.[39] A 'surgical era' section in regression analysis was included to investigate the effect of era of implantation on different outcomes.

Currently, homograft or bioprosthetic pulmonary valves are preferred in PVR with 10-year freedom of reoperation in homograft PVR ranging from 74% to 89%.[40,41] Mechanical valve prostheses have been largely avoided despite their superior durability mainly due their inherent risk of thrombosis and embolic complications, which ranges from 25% to 80%, and the risk related to anticoagulation therapy.[42,43] Mechanical prosthesis malfunction due to thrombosis or pannus formation developed in 12.1% in a cohort of 396 patients who underwent mechanical PVR post TOF repair during a follow-up period of three years.[44] Transcatheter PVR are in development and are increasingly used in a clinical setting, but their use has limited current clinical experience in comparison to surgical PVR (the first transcatheter PVR was performed in 2000, and long-term outcomes have not yet been produced).[45] Transcatheter PVR success rate is generally good, but they are associated with a higher rate of estimated risk of infective endocarditis (2.3% per patient-year versus 0.3% in surgical PVR; at 8 years, the cumulative incidence of transcatheter PVR endocarditis was 16.2%; while at 10 years, 3.1% of surgical PVR had endocarditis (i.e. 96.9% freedom of endocarditis at 10 years)).[35,46] There is no consensus on the ideal PVR prosthesis. Homograft PVR prosthesis have been traditionally used with favorable durability but are in constant shortage. Comparisons with other PVR prosthesis types are not conclusive. Homografts as compared to Medtronic Freestyle Valve (porcine) in PVR did not show a significant difference in survival, although higher pulmonary valve gradients were

demonstrated in the Medtronic group.[47] Another paper demonstrated significantly better survival in patients with porcine or homograft valve prosthesis in PVR compared to pericardial valves.[48] A comparison of homograft, porcine, and bovine pericardial PVR prosthesis in one retrospective cohort study demonstrated similar performance of the three valve types for three years with pulmonary homograft developing PR more frequently.[49]

H. Pulmonary Valve Replacement Guidelines and Recommendations

In 2018, the American Heart Association (AHH) / American College of Cardiology (ACC) guidelines for the management of adults with congenital heart disease made a class IIa (LOE B-NR) recommendation for PVR in asymptomatic patients with rTOF if the RVEDVI is more than 160 ml/m^2 or RVESVI is more than 80 ml/m^2 among other criteria.[50] The Canadian Cardiovascular Society (CCS) 2009 consensus conference on the management of adults with congenital heart disease made a class IIa (level C) recommendation for PVR if there is: free PR associated with progressive or moderate to severe RV enlargement (RVEDVI greater than 170 mL/m^2), moderate to severe RV dysfunction, important tricuspid regurgitation, atrial or ventricular arrhythmias, or symptoms such as deteriorating exercise performance.[51] European Society of Cardiology (ESC) guidelines for the management of grown-up congenital heart disease in 2010, made a class IIa (level C) recommendation for PVR in asymptomatic rTOF patients with severe PR if there is progressive RV dilatation or systolic dysfunction.[46,52] (Class of recommendation IIa refers to a moderate strength of recommendation of the intervention of benefit outweighing the risks. Level of evidence B refers to moderate quality evidence from

randomized (R) or nonrandomized (NR) trials, while level of evidence C refers to limited data (observational or registry evidence with limited design)).

I. Aims and Objectives

With the persistent gaps of knowledge and uncertainties related to outcome of PVR in patients with pulmonary regurgitation post TOF repair, we aim to shed light into the long-term results of patients who underwent this procedure. Specifically, we look into development of adverse outcomes namely infective endocarditis and prosthesis failure requiring re-intervention. By providing this data, we will help create a more informed discussion about when and what to expect after PVR in this patient population. Secondarily, we also look into symptomatic improvement and echocardiographic progression post-op and how prosthesis choice may impact these parameters.

Methodology

A. Setting

McGill University Health Centre (MUHC) provides consultation, evaluation, surgical care, and follow-up for a wide range of pediatric and adult congenital heart defects. The center provides congenital cardiac surgical services and care in the RUIS (Réseau Universitaire Intégré de Santé) McGill, RUIS Sherbrooke, and accepts referrals from outside the province of Quebec.[53,54]

B. Study Design and Study Subjects

We conducted a retrospective cohort study at a single congenital cardiac surgery tertiary center in the province of Quebec (Canada). The study subjects included all consecutive patients with previously repaired tetralogy of Fallot (TOF) with maintained right ventricular to pulmonary artery native anatomy who underwent pulmonary valve replacement (PVR) operations at the McGill University Health Centre (MUHC) from 1990 to 2015.

Patients with TOF-type double outlet right ventricle (DORV) who underwent PVR were also included. DORV is a group of complex congenital cardiac malformations with multiple anatomic variations in which the great vessels arise from the RV. Repair of DORV with pulmonary stenosis and subaortic VSD involves alleviating the RVOTO and directing blood flow from the LV to the aorta. We included DORV-TOF type patients who underwent PVR later in life in our series because of the similarities in pathophysiology, surgical approach, and natural history between patients with DORV-TOF type and patients with TOF.

We also included patients with TOF or DORV and pulmonary atresia who were treated with a transannular patch (TAP) and preserved their native right ventricular outflow tract for the same

rationale. Patients with TOF or DORV and pulmonary atresia who had right ventricular to pulmonary artery valved conduit implanted at their primary corrective operation were excluded. The reasoning is the different behaviours of these two entities; RVOTO and RV pressure overload in patients with conduit placement in their original repair (excluded), as opposed to RV volume overload from residual pulmonary regurgitation in patients with preserved native RV outflow tract treated with a TAP. All the patients included in the study were operated by the same surgeon. Patients who were being followed at the clinic but had their PVR performed outside of our center were excluded.

C. Data Collection, Management, and Statistical Analysis

The patients' data were collected from the available electronic and physical medical records. The patients were divided into three groups based on the PVR prosthesis that was implanted. The acquired data were stored in password protected electronic files. The data was de-identified, and data cleaning and coding were done prior to the analysis. A key with the identifier and the patients' medical record number was kept in a separate file that was password protected. RStudio and Microsoft Excel software were used for the analysis. The most recent echocardiographic evaluation and cardiac magnetic resonance imaging (MRI) imaging prior to PVR were used for preoperative data collection. The categorical variables are presented in frequencies and percentages, while quantitative variables as mean ± SD. Chi-square test was used to compare the categorical variables, and independent t-test/ANOVA to compare the numerical variables. The Kaplan-Meier estimator was used to estimate the survival function, and log-rank (Mantel-Cox) test was used for survival function comparison between the interventions. Univariate and multivariate Cox regression (proportional hazards regression)

were also employed for survival analysis. The p-value was considered significant if less than 0.05.

D. Outcomes and Variables

The collected data include patients' demographics, operative data, clinical follow-up, electrocardiogram (ECG), echocardiographic, and cardiac magnetic resonance imaging (Cardiac MRI). The primary outcome is incidence of mortality, reintervention (whether a surgical redo-PVR operation or via catheter-based interventions), infective endocarditis (culture positive, treated medically or invasively), and arrhythmic events post-operatively with device implantation or ablation.

Demographics: PVR year, sex, age, concomitant anomalies, syndromes (as reported in patient's medical records).

Preoperative clinical data: New York Heart Association (NYHA) class (as documented during clinic visits in the MAUDE (McGill Adult Unit for Congenital Heart Disease) clinic), arrhythmia, symptoms.

Operative data:

- **TOF:** Other cardiac operations prior to PVR (other than the original TOF repair), age at TOF repair, height, weight, body surface area (BSA), pump time, aortic cross-clamp time, concomitant procedures.
- **PVR:** Age at PVR, height, weight, body surface area (BSA), pump time, aortic cross-clamp time, concomitant procedures, intra-operative complications, hospital stay.

ECG (at different time intervals pre- and post-PVR): QRS durations

Echocardiogram (at different time intervals pre- and post-PVR):

- **Left ventricle:** LVEF (Left Ventricular Ejection Fraction), LV %FS (Left Ventricular Fractional Shortening), LV Size, LVIDd (Left Ventricular Internal Diameter in diastole), LVIDdi (Left Ventricular Internal Diameter in diastole Index), LVEDV (Left Ventricular End-Diastolic Volume), LVEDVI (Left Ventricular End-Diastolic Volume index), LV size measurement in z-scores
- **Right ventricle:** RV function, RVEF (Right Ventricular Ejection Fraction), TAPSE (Tricuspid Annular Plane Systolic Excursion), RV Dilatation, RVIDd (Right Ventricular Internal Diameter in diastole), RV size measurements in z-scores.
- **Pulmonary valve:** PR (Pulmonary Regurgitation), PHT (Pressure Half-Time), PS (Pulmonary Stenosis), PV PG (Pulmonary Valve Peak Gradient), PV MG (Pulmonary Valve Mean Gradient).

Cardiac MRI (at different time intervals pre- and post-PVR):

- **Left ventricle:** LVEDV (Left Ventricular End-Diastolic Volume), LVESV (Left Ventricular End-Systolic Volume), LVEF (Left Ventricular Ejection Fraction), LVEDVI (Left Ventricular End-Diastolic Volume index), LVESVI (Left Ventricular End-Systolic Volume index), SV (Stroke Volume), SVi (Stroke Volume index).
- **Right ventricle:** RVEDV (Right Ventricular End-Diastolic Volume), RVESV (Right Ventricular End-Systolic Volume), RVEF (Right Ventricular Ejection Fraction), RV SV (Right Ventricular Stroke Volume), RVEDVI (Right Ventricular End-Diastolic Volume

index), RVESVI (Right Ventricular End-Systolic Volume index), RV CO (Right Ventricular Cardiac Output).

- **Pulmonary valve:** %PV (Pulmonary Valve percent regurgitation), PS (Pulmonary Stenosis).

Clinical Follow-up (at different time intervals post-PVR):

- NYHA (as documented during clinic visits in the MAUDE (McGill Adult Unit for Congenital Heart Disease) clinic), symptoms, post-op complications (within 30 days of PVR), mortality, or late adverse events (reintervention, endocarditis, or arrhythmia (as documented in the patients' chart by electrocardiogram, Holter monitor, or electrophysiologic study)). The Valve Academic Research Consortium consensus document was used as a reference for the clinical end points.[55]

E. Ethics and Legal Clearance

This study was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), as well as in respect of the requirements of the Research Institute of the McGill University Health Centre (RI-MUHC) Research Ethics Board (REB). Only data relevant to this study was collected by the research team. All the information collected during the research project remained confidential to the extent required and provided by law. Patient data were deidentified and coded. The code was kept in a password protected digital file. Confidentiality and anonymity of patients' identities was maintained, and their privacy was guarded. No reporting of patients' identifying information was carried out. Data was reported in group format. The data was stored in a secure laptop, password protected, with access limitation only to the investigators. In lieu of individual informed consent of participants, authorization to access patient charts was obtained from the Director of Professional Services (DPS) of Glen site and Montreal General Hospital, and REB approval was acquired prior to commencing the research project.

Results

A. Baseline Patient Characteristics

Between 1990 and 2015, a total of 69 patients with rTOF underwent PVR in our institution. The patients were divided into three groups based on the PVR prosthesis implanted: Carpentier-Edwards (n=14), Contegra (n=40), and Pulmonary Homograft (n=15). The mean age of the patients at the time of PVR was 21 (±12) years, and 43 (62%) of the patients were male. Symptoms were present in 32 (48%) patients preoperatively (symptoms include shortness of breath with NYHA class ≥ 2, chest pain, increased fatigue, exercise intolerance, and arrhythmias (15 patients (23%): atrial or ventricular arrhythmias treated medically, by ablation, cardioversion, or device implantation – 7 patients had atrial arrhythmias: three of which underwent ablation and one had device implantation; 7 patients had ventricular arrhythmias: one of which had device implantation and one had ablation; 1 patient had third degree AV block)). Sixteen patients (23%) were syndromic (most common syndromes being Down syndrome and DiGeorge syndrome as reported in patients' medical records). Cardiac operations prior to definitive TOF corrective surgery occurred in 23 (33%) of the patients (most commonly a palliative modified Blalock-Taussig shunt before definitive repair). Most of these patients were repaired prior to 1987 before our approach have changed to primary repair without palliation at three months of age. The most common concomitant anomaly was ASD which occurred in 33 (48%) of the patients. The mean QRS duration pre-op was 158. **Table 1** provides detailed description of patients' demographics and preoperative characteristics.

Table 1: Patient Demographic and Preoperative Characteristics

Patients' Demographics and Pre-operative Characteristics				
	CE *n=14*	**Contegra** *n=40*	**Pulmonary Homograft** *n=15*	**Overall** *n=69*
Demographics				
Sex, Male (%)	9 (64)	27 (68)	7 (47)	43 (62)
Age at PVR (mean (SD))	23.6 (10.6)	16.7 (8.5)	28.1 (16.6)	21 (12)
Anomaly (%)				
TOF	11 (79)	33 (83)	14 (93)	58 (84)
DORV - TOF type	3 (21)	7 (18)	1 (7)	11 (16)
TOF/DORV with Pulmonary Atresia	0 (0)	12 (30)	2 (13)	14 (20)
Syndromic (%)	3 (21)	9 (23)	4 (27)	16 (23)
Cardiac Operations Prior to TOF Repair	2 (14)	12 (30)	9 (60)	23 (33)
Concomitant Anomalies (%)				
PDA	2 (14)	20 (50)	1 (7)	23 (33)
ASD	7 (50)	19 (48)	7 (47)	33 (48)
Others	2 (14)	11 (28)	3 (20)	17 (25)
Age at TOF Repair in Months (mean ± SD) ; (Median)	(27 ± 57) ; (7.5)	(9 ± 16) ; (4)	(55 ± 61) ; (50)	(23 ± 43) ; (5)
Pre-op Status				
NYHA class III-IV (%)	3 (23)	2 (6)	3 (23)	8 (13)
Pre-op Symptoms (%)	6 (46)	18 (46)	8 (53)	32 (48)
Pre-op Arrhythmia (%)	2 (15)	5 (13)	8 (53)	15 (23)
Pre-op QRS Duration (mean (SD))	159 (24)	159 (15)	155 (24)	158 (20)

B. Preoperative Echocardiogram and Cardiac MRI

The right ventricular (RV) size on preoperative echocardiogram was moderately to severely dilated in 61 (91%) patients, and there was moderate to severe RV dysfunction in 20 (30%) patients. Almost all patients had severe pulmonary regurgitation (63 patients - 96%) with normal left ventricular size (98.5% of patients) and left ventricular function (95.5% of patients). Moderate or severe PS was present in 7 (10%) of patients pre-operatively. On average, preoperative echocardiogram was performed 7.9 (±7.3) months prior to PVR. On preoperative cardiac magnetic resonance imaging (MRI) imaging, the mean RVEDV (Right Ventricular End-Diastolic Volume) was 331 ± 78 ml, and the mean RVEDVI (Right Ventricular End-Diastolic Volume Index) was 210 ± 42 ml/m^2, while the mean RVESV (Right Ventricular End-Systolic Volume) was 188 ± 42 ml, and RVESVI (Right Ventricular End-Systolic Volume Index) was 120 ± 24 ml/m^2. Other measurements of Cardiac MRI along with echocardiographic data for each group are presented in **Table 2**.

Table 2: Preoperative Echocardiographic and Cardiac MRI Data

Preoperative Imaging				
	CE *n=14*	**Contegra** *n=40*	**Pulmonary Homograft** *n=15*	**Overall** *n=69*
Echocardiogram				
LV Function - Normal (%)	13 (100)	37 (93)	12 (100)	62 (95)
LV Size - Normal (%)	13 (100)	39 (98)	12 (100)	64 (99)
RV Size				
Normal or Mild Dilatation	0 (0)	2 (5)	0 (0)	2 (3)
Moderate or Severe Dilatation	13 (100)	37 (93)	11 (79)	61 (91)
RV Dysfunction Moderate or Severe (%)	5 (39)	13 (33)	2 (15)	20 (30)
PR - Severe (%)	13 (100)	38 (95)	12 (92)	63 (96)
PS Moderate or Severe (%)	0 (0)	4 (10)	3 (20)	7 (10)
TR Mild or More (%)	8 (62)	22 (58)	12 (86)	42 (65)
Cardiac MRI (mean ± SD)				
LVEDV	141 ± 35	129 ± 32	162 ± 39	137 ± 35
LVESV	68 ± 21	66 ± 20	73 ± 22	68 ± 20
LVEF	52 ± 7	50 ± 6	52 ± 5	51 ± 6
LVEDVI	86 ± 17	85 ± 14	96 ± 14	87 ± 15
LVESVI	42 ± 10	44 ± 9	45 ± 11	43 ± 9
SVi	45 ± 9	42 ± 7	51 ± 5	44 ± 8
RVEDV	329 ± 61	311 ± 69	402 ± 92	331 ± 78
RVESV	182 ± 35	183 ± 41	220 ± 51	188 ± 42
RVEF	45 ± 4	41 ± 5	42 ± 5	42 ± 5
RV SV	147 ± 31	127 ± 30	170 ± 28	139 ± 34
RVEDVI	204 ± 40	205 ± 40	242 ± 42	210 ± 42
RVESVI	117 ± 19	118 ± 26	130 ± 24	120 ± 24
RV CO	11 ± 3	9 ± 3	11 ± 3	9 ± 3
% PV Regurgitation	55 ± 10	50 ± 8	50 ± 10	51 ± 9

C. Surgical Characteristics

The most commonly implanted prosthesis type was Contegra, which was implanted in 40 (58%) of the patients. Carpentier-Edwards valve was implanted in 14 (20%) of the patients, and Pulmonary Homograft were implanted in 15 (22%) of the patients. Valve size 22 mm was most often used being implanted in 29 (42%) patients. On average, the interval between TOF repair and PVR was 19 (±9) years. A total of 28 (41%) patients had concomitant procedures during their PVR operation most commonly related to right or left pulmonary artery stenosis. Almost all patients (97%) had a transannular patch (TAP) used in the reconstruction of the right ventricular outflow during the TOF repair. **Table 3** provides more details about PVR and TOF repair operative data.

Table 3: Surgical Characteristics in PVR and TOF Repair

Surgical Characteristics	
	n=69
PVR	
PVR Prosthesis Type (%)	
CE	14 (20)
Contegra	40 (58)
Pulmonary Homograft	15 (22)
Size of PVR Prosthesis (%)	
16	1 (1)
18	4 (6)
20	10 (15)
22	29 (42)
23	3 (4)
24	2 (3)
25	9 (13)
27	9 (13)
29	2 (3)
Age (mean (SD))	21 (12)
Interval Between TOF Repair and PVR in Years (mean (SD))	19 (9)
BSA (mean (SD))	1.47 (0.35)
Weight in Kg (mean (SD))	54 (28)
CPB Time in Minutes (mean (SD))	98 (45)
X-Clamp Use in PVR	4 (6)
Operation in ≥ 2010 (%)	42 (61)
Hospital Stay in Days (mean (SD))	8 (4)
Concomitant Procedures at PVR (%)	28 (41)
RVOT Aneurysm Repair	4
Repair of LPA or RPA Stenosis	7
Repair of Infundibular PS	3
ASD Closure	3
VSD Closure	3
TV Repair	3
MVR	2
Repair of Supravalvular MS	1
CABG	2
Open Ablation of Ventricular Arrhythmias	1
Rerouting of LSVC	1
Right-sided MAZE	1
RV Tear repair	1
TOF Repair	
Age in Months (mean ± SD) ; (median)	(23 ± 43) ; (5)
TAP (%)	64 (97)
Weight in Kg (mean (SD))	6 (2.2)
BSA (mean (SD))	0.33 (0.11)
X-Clamp Time in Minutes (mean (SD))	69 (14)
Pump Time in Minutes (mean (SD))	128 (35)
Concomitant Procedures at TOF Repair (%)	48 (73)
PDA Ligation	28
ASD Closure	27
Take Down of Previous Shunt	9
Repair of LPA or RPA Stenosis	9

D. Follow-up and Outcome Data

The mean time of follow-up after PVR was 8.5 (±4.7) years, and the median was 7.5 years. The maximum follow-up was 29 years. Two patients were lost to follow-up. The follow-up for the pulmonary homograft group was longer at an average of 11.8 years due to the earlier use of this prosthesis type in our institution. Contegra conduit group had an average follow-up of 8.2 years, while CE valve group had a mean follow-up of 5.8 years. There were no early or late mortalities in our cohort. Three patients (4%) had PVR intra-operative complications, two had coronary artery injuries requiring coronary artery bypass grafting at the same setting, and one had anterior RV wall tear during sternotomy requiring repair. Nine patients (14%) had post-operative complications: 3 patients had post-operative pneumonia, 2 patients had RV or LV dysfunction, 1 patient had bleeding requiring re-exploration, 1 patient had pericardial effusion requiring drainage, 1 patient had pneumothorax requiring chest tube insertion, and 1 patient had pulmonary valve thrombosis requiring anticoagulation.

Reintervention was done in 15 (22%) patients (surgical redo-PVR in 8 patients, and Melody transcatheter pulmonary valve implantation in 8 patients), and 11 (16%) patients had infective endocarditis. Eight of the patients that had endocarditis underwent reintervention.

Arrhythmic Events Post-PVR occurred in 11 (16%) patients (8 ventricular and 5 atrial arrhythmias: one patient had syncope, inducible VF and a device was implanted; one patient had NSVT and PACs was treated medically; one had VT and a device was implanted; one had AF cardioverted and VT and a device was implanted; one had VT ablation; one had NSVT treated medically; one had VT ablation and VF and a device was implanted; one had AF and had

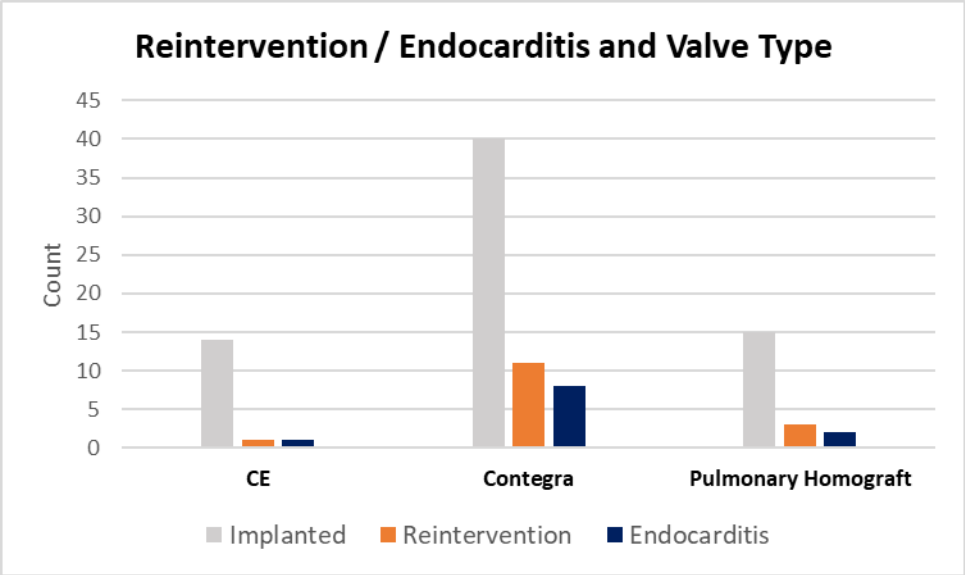
ablation and a device was implanted; one had Aflutter ablation; one had VF and a device was implanted; one had SVT medically treated. Seven of the patients that had arrhythmias underwent device implantation, and four of them underwent ablation. The mean post-op QRS duration in two and a half years was 156 (compared to an average of 158 pre-op).

Table 4 summarizes intra-operative and post-operative complications, and the late adverse events. **Figure 1** demonstrates occurrence of reintervention and endocarditis in relation to implanted PVR prosthesis valve type. Pearson's Chi-squared and Fisher's Exact tests did not show statistical significance between type of prosthesis implanted and incidence of reintervention (Chi-squared p= 0.137, Fisher's p= 0.153) or infective endocarditis (Chi-squared p= 0.483, Fisher's p= 0.609).

Table 4: Clinical Outcome in Relation to PVR Prosthesis Type

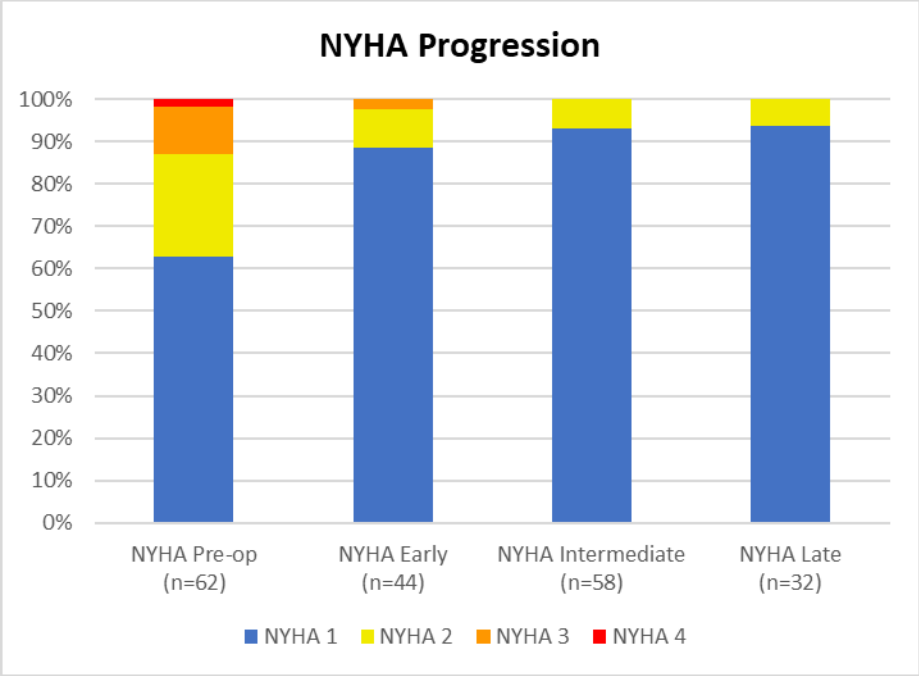
Outcomes Table				
	CE *n=14*	**Contegra** *n=40*	**Pulmonary Homograft** *n=15*	**Overall** *n=69*
Complications				
Follow-up in years (mean (SD))	**5.8 (3.7)**	**8.2 (3.3)**	**11.8 (6.7)**	**8.5 (4.7)**
PVR Intra-op Complications (%)	**1 (7)**	**0 (0)**	**2 (13)**	**3 (4)**
Coronary Artery Injury	0 (0)	0 (0)	2 (12.5)	2 (2.9)
RV Anterior Wall Tear	1 (7)	0 (0)	0 (0)	1 (1.4)
Post-op Complications (%)	**2 (15)**	**5 (13)**	**2 (14)**	**9 (14)**
Pulmonary Complications	0 (0)	2 (5)	1 (7)	3 (4)
Ventricular Dysfunction	0 (0)	2 (5)	0 (0)	2 (3)
Post-op Bleeding Requiring Re-exploration	0 (0)	0 (0)	1 (7)	1 (1.4)
Pericardial Effusion Requiring Drainage	1 (7)	0 (0)	0 (0)	1 (1.4)
Seizure	1 (7)	0 (0)	0 (0)	1 (1.4)
PV Thrombus	0 (0)	1 (2.5)	0 (0)	1 (1.4)
Early Mortality (%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Late Mortality (%)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Late Adverse Events (%)	**1 (7)**	**16 (40)**	**6 (40)**	**23 (33)**
IE (%)	1 (7)	8 (20)	2 (13)	11 (16)
Reintervention (%)	1 (7)	11 (28)	3 (20)	15 (22)
Surgical Redo-PVR only	1 (7)	6 (15)	1 (7)	8 (12)
Transcatheter Valve Implantation	0 (0)	7 (18)	1 (7)	8 (12)
Arrhythmic Events Post-PVR (%)	0 (0)	7 (18)	4 (27)	11 (16)
Underwent Device Implantation	0 (0)	5 (13)	2 (13)	7 (10)
Underwent Ablation	0 (0)	2 (5)	2 (13)	4 (6)

Figure 1: Reintervention / Endocarditis in Relation to PVR Valve Type



Approximately a third of the patients had NYHA class II or more, and only 8 (13%) of the patients were in NYHA classes III and IV prior to PVR. Pre-operatively, patients in NYHA class I composed 63% of the total, compared to 89% during the early follow-up, 93% during the intermediate follow-up, and 94% during the late follow-up (p = 0.000014). **Figure 2** demonstrates the improvement in NYHA class of the patients during clinical follow-up post-op. These improvements were maintained during the follow-up period up to 9 years post-op.

Figure 2: NYHA Pre- and Post-operative Progression*



* Early follow-up average of 1.2 (±0.67) years post-PVR, intermediate follow-up average of 4.6 (±1.2) years post-PVR, late follow-up average of 9.1 (±1.2) years post-PVR.

Kaplan-Meier curves were generated for the entire cohort (all PVR patients) for late adverse events which include: reintervention (surgical redo-PVR or transcatheter pulmonary valve implantation), endocarditis, and arrhythmic evens post-op with device implantation or ablation. (**Figures 3, 4, 5**). **Figure 3** demonstrates freedom from late adverse events (reintervention, endocarditis, or arrhythmic events with device implantation or ablation) for all PVR patients over the follow-up period. As shown in **Figure 3**, at 14 years the risk of developing late adverse events is about 40%. Risk of endocarditis at 14 years is approximately 25% as demonstrated in **Figure 5**, while risk of reintervention is higher at approximately 40% as shown in **Figure 4**. Overall freedom from reintervention (surgical redo-PVR or transcatheter pulmonary valve implantation) was 94% (CI 88.5 to 99.9), 87.6% (CI 79.9 to 96), and 70.3% (CI 56.5 to 87.4) at 1, 5, and 10 years of follow-up; while freedom from reintervention (surgical redo-PVR only) was 98.5% (CI 95.6 to 100), 93.6% (87.7 to 99.9), and 79.3% (CI 66.3 to 94.8) at 1, 5, and 10 years of follow-up (**Figure 4**).

Figure 3: Kaplan-Meier, Freedom from Late Adverse Events (Reintervention, Endocarditis, or Arrhythmic Events with Device Implantation or Ablation) for All PVR Patients

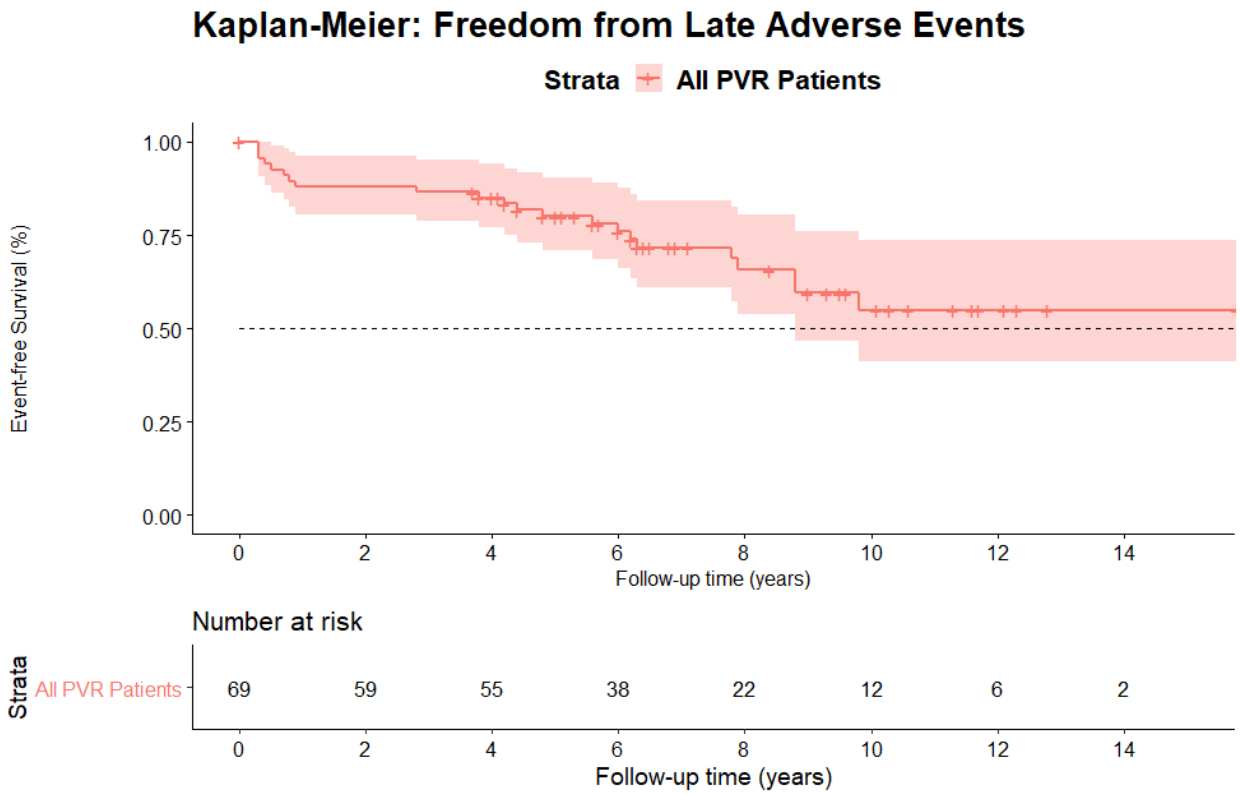


Figure 4: Kaplan-Meier, Freedom from Reintervention for All PVR Patients

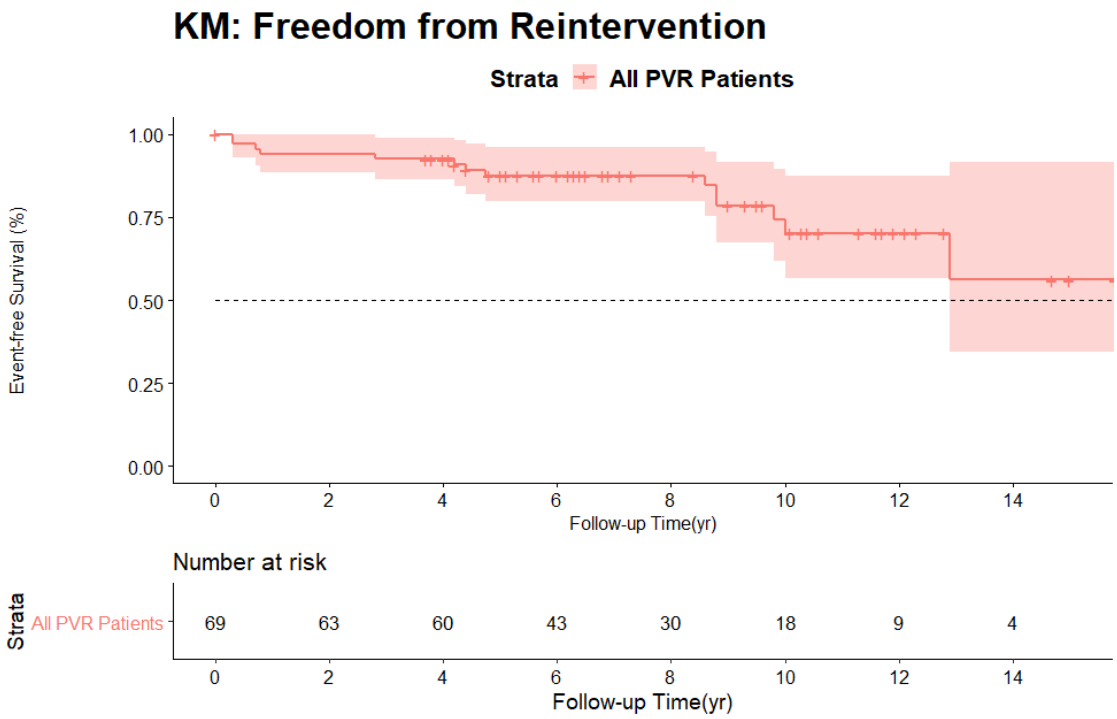
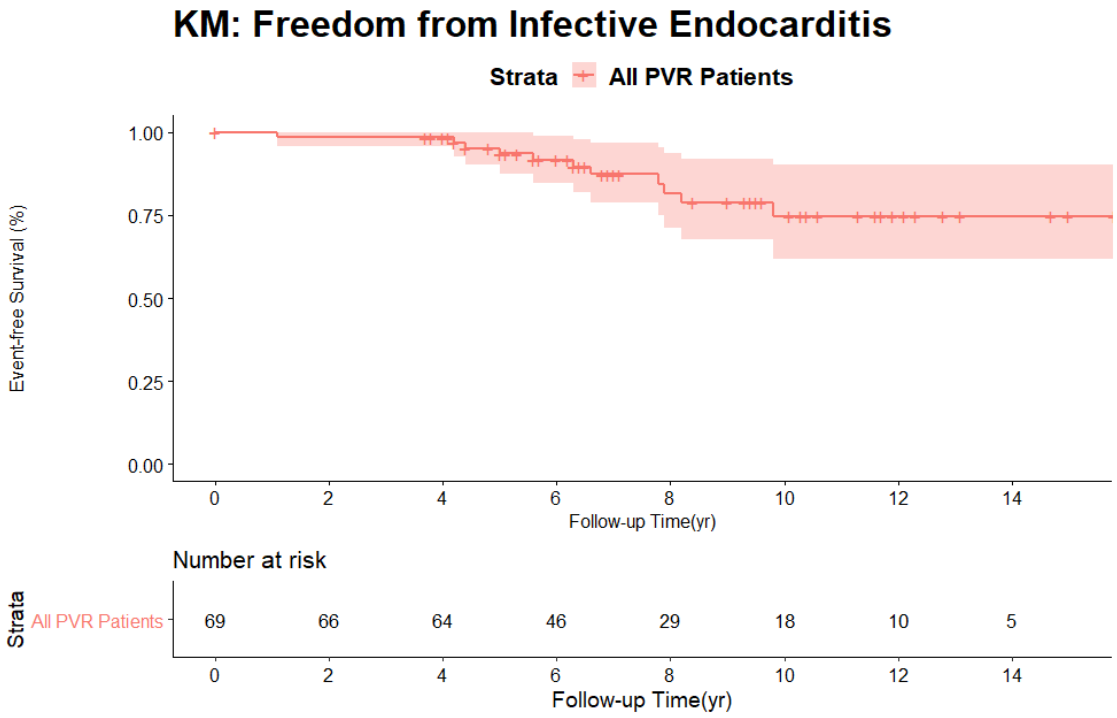


Figure 5: Kaplan-Meier, Freedom from Infective Endocarditis for All PVR Patients



Kaplan-Meier curves were also generated for late adverse events (reintervention, infective endocarditis, or arrhythmic events post-op with device implantation or ablation) for the three PVR groups (Carpentier-Edwards (CE), Contegra, and Pulmonary Homograft) (**Figures 6, 7, 8**). Differences between the groups were evaluated by log-rank testing. There were no significant differences in the event-free survival based on the PVR prosthesis in relation to reintervention or endocarditis, however, the curves show favorable trend for pulmonary homografts in comparison to Contegra grafts. Half of the patients who receive Contegra are at risk of late adverse events at 14 years, with 30% risk of endocarditis and 35% risk of re-intervention. The rate of endocarditis is 1.9% per 100 person-year of exposure.

Figure 6: Kaplan-Meier, Freedom from Late Adverse Events (Reintervention, Endocarditis, or Arrhythmic Events with Device Implantation or Ablation) for Each PVR Prosthesis Type

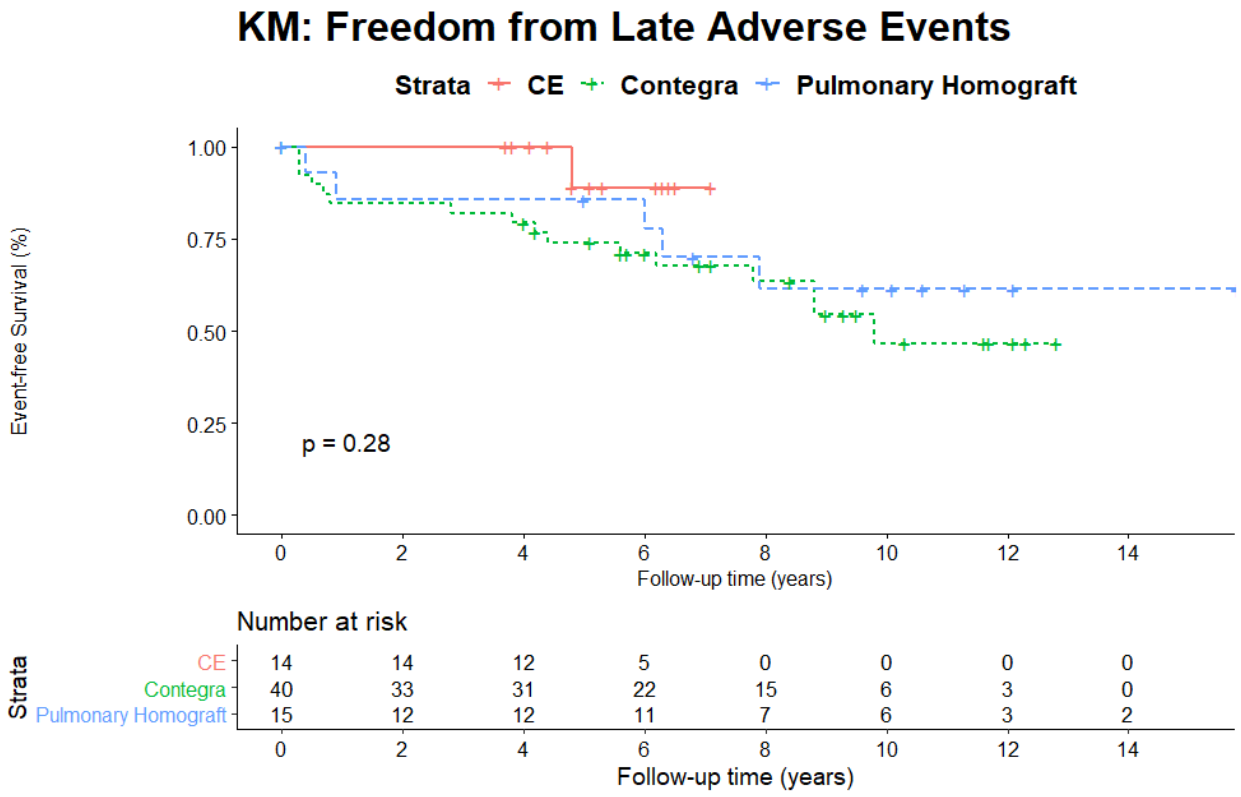


Figure 7: Kaplan-Meier, Freedom from Reintervention for Each PVR Prosthesis Type

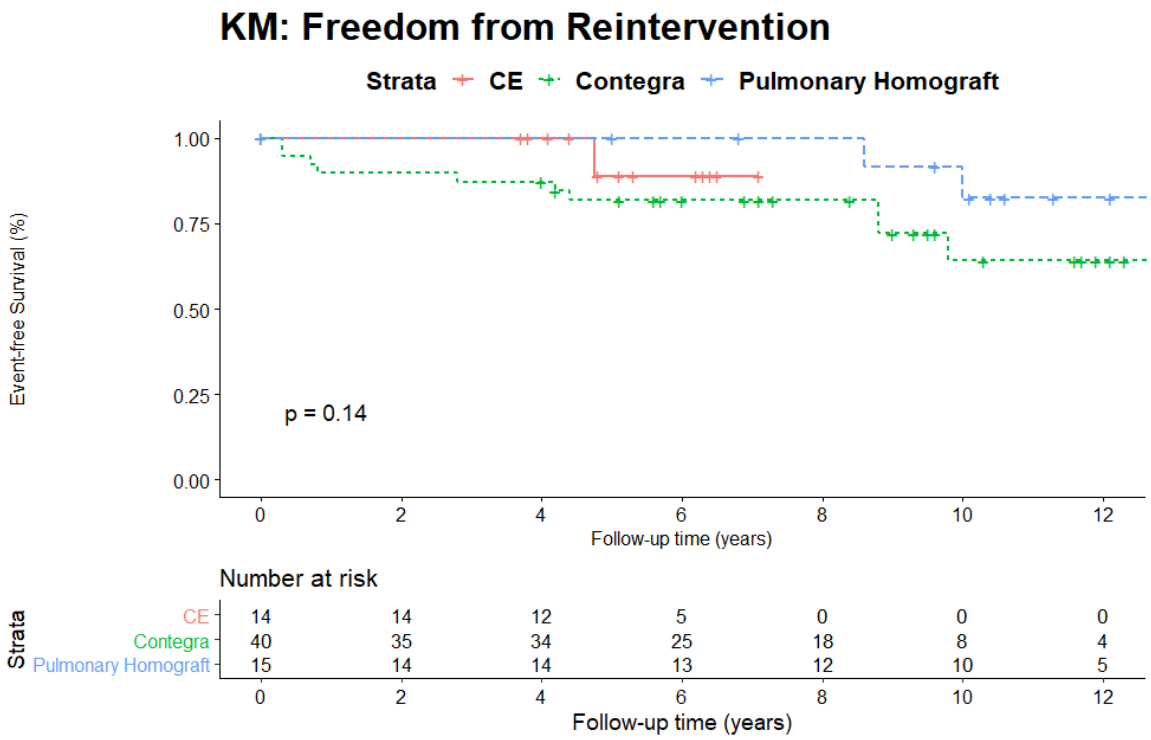
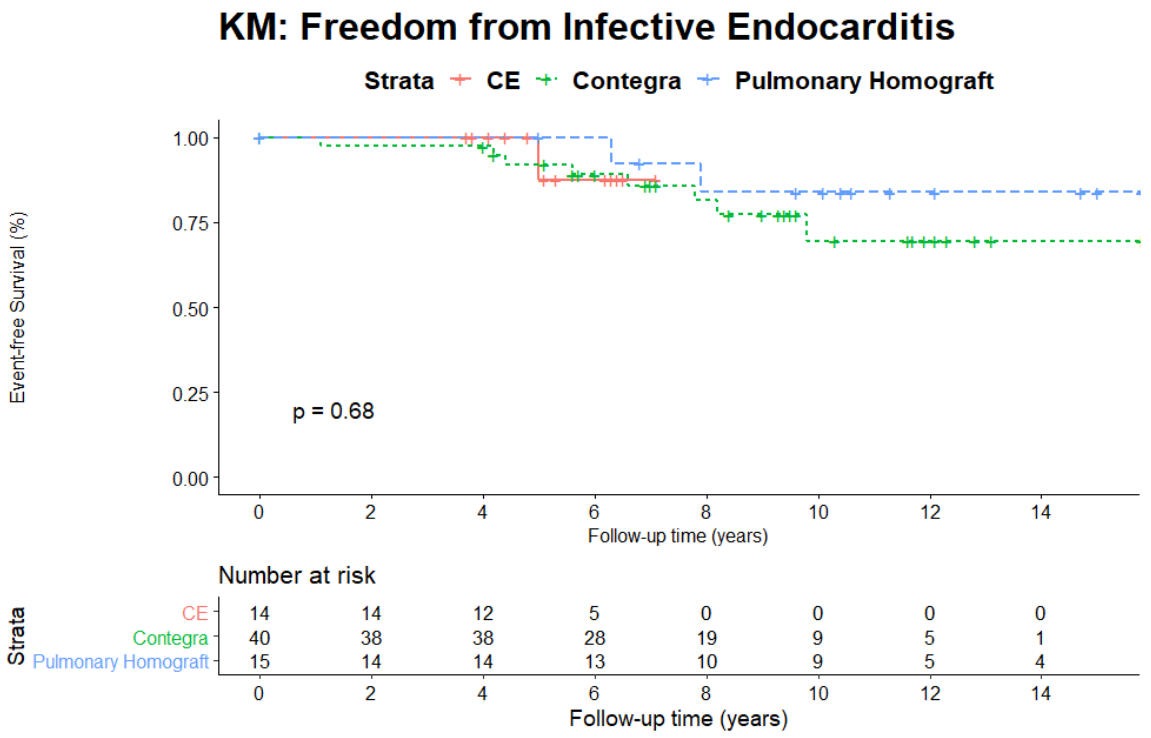


Figure 8: Kaplan-Meier, Freedom from Infective Endocarditis for Each PVR Prosthesis Type



Univariate and multivariate Cox regression analyses were conducted to determine the risk factors for late adverse events (reintervention, infective endocarditis, arrhythmic events post-op with device implantation or ablation). Contegra placement seems to be a risk factor for reintervention by univariate analysis (HR 3.4, 0.92–13 95% CI, p=0.066). DORV was a significant risk factor for endocarditis (HR 3.5, 1–12 95%CI, p=0.046). Multivariate analysis showed favorable outcomes of Carpentier–Edwards and pulmonary homograft compared to Contegra, i.e. protective effect in relation to late adverse events, statistically significant for CE: (HR 0.11, 0.01–0.96 95% CI, p=0.046); Pulmonary Homograft: (HR 0.26, 0.07–1.03 95% CI, p=0.055)). (**Table 5**).

Table 5: Univariate and Multivariate Cox Regression Analyses

Variables	Late Adverse Events				Reintervention				IE			
	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value
Univariate Analysis												
Age at PVR	1	0.99	1.1	0.24	0.96	0.91	1	0.095	0.95	0.89	1	0.16
Sex	1.6	0.62	4.1	0.33	1.8	0.56	6.1	0.32	1.6	0.42	6	0.49
Pre-op Symptoms	2.1	0.88	5	0.097	1.3	0.42	4	0.66	0.78	0.22	2.8	0.7
Syndromic	0.38	0.11	1.3	0.13	0.43	0.094	1.9	0.27	0.24	0.03	1.9	0.17
First Era (1990-2004)	2.1	0.82	5.4	0.12	1.2	0.33	4.6	0.76	1.7	0.45	6.5	0.43
Second Era (2005-2010)	0.65	0.26	1.6	0.36	0.8	0.25	2.6	0.71	0.39	0.11	1.4	0.16
Third Era (2011-2015)	0.85	0.32	2.3	0.75	1.1	0.28	4.4	0.89	2	0.47	8.3	0.35
Type of valve												
Contegra	1.9	0.74	4.8	0.18	3.4	0.92	13	0.066	1.7	0.44	6.3	0.45
CE	0.26	0.034	1.9	0.19	0.57	0.07	4.6	0.6	1.1	0.13	9.7	0.91
Pulmonary Homograft	0.82	0.3	2.2	0.7	0.26	0.053	1.3	0.095	0.5	0.11	2.4	0.39
Size of PVR Prosthesis	0.89	0.77	1	0.16	0.88	0.72	1.1	0.2	0.9	0.71	1.1	0.4
BSA at PVR	0.75	0.23	2.4	0.63	1.5	0.31	7	0.62	1.3	0.23	7.2	0.78
Concomitant Procedures at PVR	1.4	0.59	3.1	0.48	0.61	0.2	1.9	0.39	1.2	0.35	3.8	0.81
Pulmonary Atresia	0.8	0.29	2.2	0.67	0.84	0.23	3	0.78	0.26	0.033	2.1	0.2
DORV	1.6	0.58	4.3	0.38	1.4	0.38	5	0.62	3.5	1	12	0.046
Age at TOF Repair	1.1	0.96	1.2	0.24	0.86	0.67	1.1	0.24	0.89	0.69	1.2	0.39
Interval Between TOF Repair and PVR	1	0.97	1.1	0.38	0.95	0.9	1	0.076	0.95	0.88	1	0.13
Cardiac Operations Before TOF Repair	1.5	0.62	3.4	0.39	1.5	0.49	4.3	0.5	1.3	0.39	4.2	0.68
Number of Operations Before TOF Repair	1.4	0.79	2.4	0.25	1.4	0.7	2.7	0.35	1.7	0.8	3.4	0.17
RV Function Pre-op	1.4	0.51	3.9	0.51	1.3	0.37	4.5	0.7	1.6	0.31	8.4	0.58
RV EF Pre-op	0.9	0.8	1	0.066	0.96	0.84	1.1	0.56	0.94	0.79	1.1	0.43
TR Pre-op	0.89	0.34	2.3	0.82	1.4	0.47	4.4	0.52	1.1	0.27	4.1	0.94
Multivariate analysis												
Contegra	Reference											
CE	0.11	0.01	0.96	0.046								
Pulmonary Homograft	0.26	0.07	1.03	0.055								
Age at PVR	1.04	1.00	1.08	0.041								
Cardiac Operations Before TOF Repair	1.80	0.66	4.95	0.253								
Concomitant Procedures at PVR	1.90	0.73	4.95	0.188								
Sex (Male)	2.71	0.95	7.69	0.062								
Syndromic	0.34	0.10	1.24	0.103								
Pulmonary Atresia	0.53	0.17	1.67	0.280								

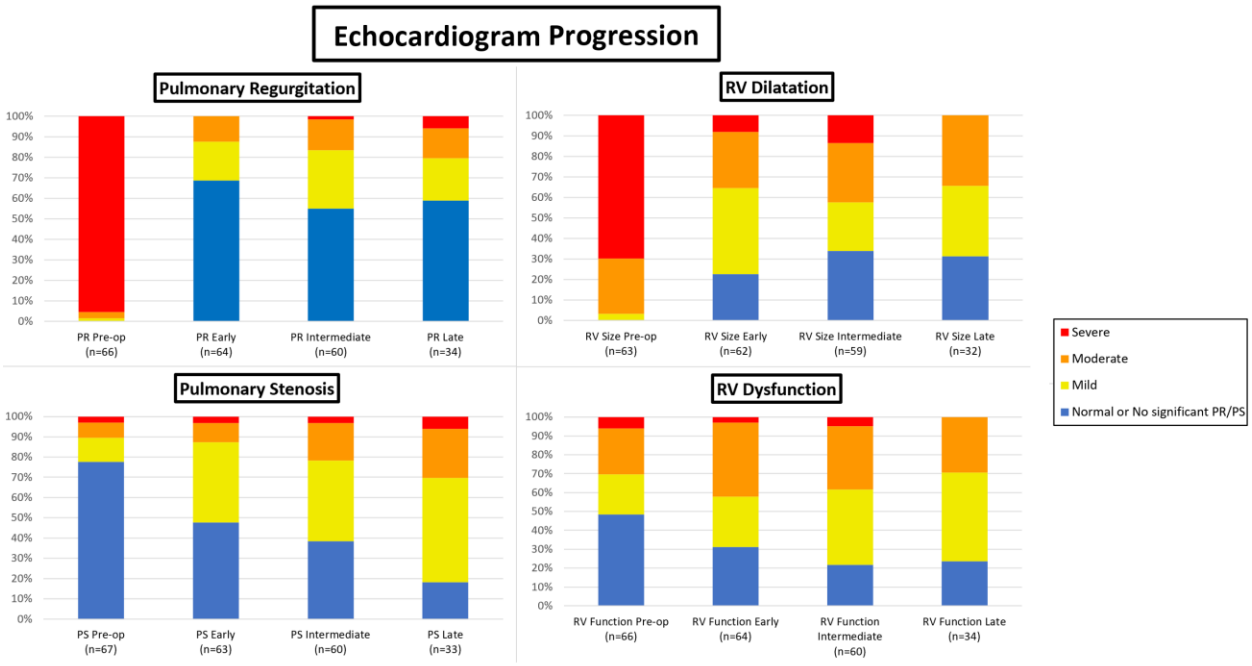
E. Changes in Hemodynamic Parameters After PVR

Echocardiographic evaluation of the patients was done pre-PVR and at certain intervals post-operatively. On average, preoperative echocardiogram was performed 7.9 (±7.3) months prior to PVR. Postoperative pulmonary valve peak gradient (PV PG) in the Contegra group was significantly higher compared to CE and pulmonary homograft groups at early echocardiogram in the first year (Contegra 33 vs. 21 in CE and 24 in Pulmonary homografts, p-value 0.023), and at the intermediate echocardiogram in the fourth year (Contegra 37 vs. 24 in CE and 22 in Pulmonary homografts, p-value 0.006).

The echocardiographic hemodynamic evolution post-PVR at three intervals (early: 1.12 (±0.72) years, intermediate: 4.2 (±1.3) years, and late 9.3 (±1.4) years) is demonstrated in **Figure 9**. As expected, pulmonary regurgitation (PR) improves immediately after prosthesis implantation. Pulmonary stenosis (PS) worsens likely due to implanted prosthesis deterioration. Right ventricular (RV) dilatation improves gradually and is evident as early as within the first year of follow-up, while RV function remained approximately similar in the cohort within the successive follow-ups.

Post-operative Cardiac MRI was performed in 15 (22%) patients only at an average of three years postoperatively. The RV the measurements are as follows (presented as mean (SD)): RVEDV 256 (72), RVESV 153 (51), RVEF 38 (9), RV SV 93 (25), RVEDVI 143 (34), RVESVI 91 (30), RV CO 5.8 (1.4).

Figure 9: Echocardiographic Progression*



* Preoperative mean of 7.9 (±7.3) months prior to PVR, early mean of 1.12 (±0.72) years post-PVR, intermediate mean of 4.2 (±1.3) years post-PVR, and late mean of 9.3 (±1.4) years post-PVR).

Discussion

We present our 25-year experience with surgical PVR in patients with repaired TOF. The study aimed to find the long-term outcome of PVR in rTOF and identify risk factors for adverse outcomes. There is still debate regarding the optimal timing of PVR in patients with rTOF, the best PVR prosthesis, and uncertainty of PVR survival benefit.

Mortality

There were no early or late mortalities in our cohort, and this is supported by published literature reporting the safety of PVR with low early mortality (1-3%) and 10-year survival of 83%.[48,56,57]

Reintervention and Endocarditis

The rate of surgical redo-PVR in our cohort (12%, 8 patients) over a follow-up period of eight and a half years is similar to previously published reports. Most of the reinterventions (other than the Contegra group) occurred four years after PVR. The rates reported in the literature range from 0 to 14%. Egbe et al. reported no reinterventions in their cohort, and Wijayarathne et al. reported a reintervention rate of 6% in their cohort.[47,58] Both of those cohorts had a follow-up of approximately five years (5.75 years in the former, and 4.25 years in the latter). Series with follow-ups more than five years had higher rates of reintervention. Dobbels et al. followed 273 patients with PVR post TOF repair for an average of 24 years (median 21 years), and they reported a reintervention rate of 14% (36 patients). [22]

The rate of endocarditis in our series was higher than reported papers (16%, 11 patients). In the same series of Dobbels et al. with a median follow-up of 21 years, only 17 patients (6%) developed endocarditis.[22] Egbe et al, reported only 1 patient (1.1%) with endocarditis in their series of 88 patients. Their PVR prostheses implanted included three types: porcine, pericardial, and homograft. There are reports in the literature indicating increased rate of late infective endocarditis in bovine jugular vein valved conduits (Contegra and Melody). A systematic review of fifty studies looking into infective endocarditis reported that the cumulative incidence of endocarditis in bovine jugular vein valves was 5.4% compared to 1.2% in other valve types during a median follow-up of 24 and 35 months, respectively (p = 0.03).[39] Albanesi et al. reported incidence of Contegra graft infection in 12 (11.3%) of 106 patients at a median follow-up time of 4.4 years. [59] Beckerman et al. published similar results reporting development of endocarditis in 25 bovine jugular vein valved conduits (10%) during a median follow-up of 6 years.[60]

The higher rate of endocarditis in our series (11 patients – 16% with a mean follow-up of 8.6 years) could be attributed to the increased utilization of bovine conduits in the cohort and the longer follow-up period. Forty patients (58%) in our cohort underwent Contegra graft implantation, and 8 patients underwent Melody transcatheter pulmonary valve implantation. Three of the patients who received Melody valves, also developed endocarditis. The overall risk of endocarditis in our cohort is 1.9% per 100 person-year of follow-up.

The Kaplan-Meier graphs generated show a high risk of endocarditis (30% in 14 years) and reintervention (35% in 14 years) in the Contegra groups. This could be attributed to the prosthesis itself, but other factors could be contributing to the increased risk. The patients in the Contegra group were on average younger, included more pulmonary atresia and DORV-TOF type anomalies, and underwent more Melody transcatheter pulmonary valve implantation. However, univariate analysis of these three factors only demonstrated DORV-TOF type to be significantly associated with risk of endocarditis (HR 3.5, 1–12 95%CI, p=0.046) (**Table 5**). The patients in the Contegra group seem to have an increased risk of reintervention in the univariate analysis (HR 3.4, 0.92–13 95% CI, p=0.066). Although the p-value was not statistically significant in the univariate analysis, the HR was more than one. To confirm these results, we would need a higher sample size. A similar comment could be made regarding Contegra and risk of endocarditis in the univariate analysis (HR 1.7, 0.44–6.3 95% CI, p = 0.45).

In the multivariate analysis, we used a combined late adverse events endpoint which included: endocarditis, reintervention, or post-op arrhythmic events with device implantation or ablation. The Carpentier–Edwards and pulmonary homograft groups were associated with lower rates of the late adverse events endpoint as compared to Contegra group with a p-value of 0.046 and 0.055, respectively.

Rotes et al. demonstrated that the total number of cardiac operations and preoperative NYHA classification were important prognostic factors associated with increased mortality.[48] Our

study did not demonstrate these factors to be significantly associated with reintervention or endocarditis possibly due to the lower sample size in our cohort.

Quality of Life

In agreement with previous literature, NYHA improvement post PVR was observed and maintained during the follow-up (63% of patients in NYHA class I pre-op, compared to 94% of patients in NYHA class I in their last follow-up at an average of 9 years, **Figure 2**).[47,61] No significant differences were found between the PVR valve prosthesis type in relation to NYHA classification.

Cardiac Size and Function (Echocardiography and Cardiac MRI)

The pulmonary valve peak gradient was significantly elevated in early (p-value 0.023) and intermediate (p-value 0.006) echocardiogram in the Contegra group. The consequences of this observed difference might be more evident with increased cohort size and longer follow-up. Multiple studies have reported different Cardiac MRI measurements of the preoperative RV size as cut-off values. Performing PVR replacement beyond these values resulted in lower likelihood of RV volume normalization. Oosterhof et al. reported RV volume normalization when preoperative RVEDVI was less than 160 mL/m^2 or RVESVI less than 82 mL/m^2.[36] Bokma et al. reported no RV volume normalization when RVESVI is more than 95 mL/m^2, and the best preoperative threshold for normalizing RV volume was RVESVI less than 80 mL/m^2.[21] Moderate to severe RV dilatation was evident in preoperative echocardiogram in 91.2% of our patients, and the mean preoperative Cardiac MRI measurement of RVEDVI and RVESVI were 210 ± 42

and 120 ± 24, respectively. Most of our patients did not have postoperative Cardiac MRI. Only fifteen patients (24%) had Cardiac MRI measurements post-operatively in our cohort as routine postoperative Cardiac MRI was not performed in our institution. In those patients, the mean postoperative RVEDVI was 143 ± 34 mL/m^2, and the mean postoperative RVESVI was 91 ± 30 mL/m^2. RV size reduction was also noted on follow-up echocardiogram. Severe RV dilatation was noted in 69% of the patients preoperatively, while severe RV dilatation was demonstrated in only 8% of the patients during the first year of echocardiogram follow up (**Figure 9**). It is evident that the RV size improved after PVR despite the mean right ventricular size being considerably greater (RVEDVI 210) than the previously quoted values for the likelihood of RV size normalization.

In regard to RV function, the mean pre-operative RVEF is 42%, while the mean post-operative RVEF is 38% (by MRI). Keeping in mind the limitations addressed previously about post-operative MRI in our institution. **Figure 9** presents an interesting paradox; after conduit placement the RV size improves, but the function remains impaired. This could be a result of the larger pre-operative RV size in our patient cohort (RVEDVI 210 ± 42 ml/m^2). Previous studies have demonstrated favorable RV remodeling and improvement of size and function post PVR in patients with TOF. Gune et al. followed a small cohort of patients for three years and compared pre-operative size and function by MRI and demonstrated significant reduction of RVEDVI in one year (from 161 ± 33 ml/m^2 to 120 ± 23 ml/m^2). In the same series, the RVEF improved as well, but it was not statistically significant (from 46% to 42%, p=0.34).[62] The notion of RV size improvement with no significant improvement in function is also demonstrated in a recently

published meta-analysis which reported a mean significant reduction of 61 mL/m^2 in indexed RVEDV after PVR but did not reveal any significant improvement in RVEF after PVR.[20]

Strengths and Limitations of the Study

The study is limited by its retrospective design. The long-term follow-up, high follow-up rates, and the consistency in terms of recruitment of patients operated on by a single surgeon are in favor of the study. The smaller sample size may be underpowered to detect a difference in endocarditis or reintervention rate. Longer follow-up duration is needed for newer valve prostheses. An important limitation is era effect; different conduit types placed at different times.

Conclusion

PVR following TOF repair is a safe operation with acceptable short- and intermediate-term outcomes. Contegra valved conduits are associated with higher risks of reintervention, endocarditis, and post-op arrhythmia with device implantation or ablation compared to Carpentier–Edwards or pulmonary homografts. Contegra group also had significantly higher postoperative pulmonary valve pressure gradients and worse outcome trend. More studies with larger sample sizes and longer follow-up are necessary to further delineate the differences between PVR valve types and determine long-term outcome of newer bioprosthesis. The results of our study show higher rates of endocarditis likely related to the increased used of bovine jugular vein grafts in this cohort (Contegra and Melody) and add to the growing body of knowledge about long term outcomes of PVR in patients with repaired TOF. Bridging the knowledge gap in late outcomes of PVR can help in determining the optimal timing of the operation, the impact of the different pulmonary prostheses used, and aid in development of better management guidelines with stronger evidence.

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