

Alma Mater Studiorum - Università di Bologna

DOTTORATO DI RICERCA IN
SCIENZE CARDIO NEFRO TORACICHE

Ciclo 36

Settore Concorsuale: 06/E1 - CHIRURGIA CARDIO - TORACO - VASCOLARE

Settore Scientifico Disciplinare: MED/23 - CHIRURGIA CARDIACA

PERFORMANCE AND FAILURE OF SURGICALLY IMPLANTED RIGHT
VENTRICLE TO PULMONARY ARTERY (RV-PA) CONDUIT IN CONGENITAL
HEART DISEASE

Presentata da: Emanuela Concetta D'Angelo

Coordinatore Dottorato

Niccolò Daddi

Supervisore

Gaetano Domenico Gargiulo

Co-supervisore

Gabriele Egidy Assenza

Esame finale anno 2024

INDEX

| | |
|---|----------|
| ABSTRACT | 1 |
| <i>INTRODUCTION</i> | 1 |
| <i>METHODS</i> | 1 |
| <i>RESULTS</i> | 1 |
| <i>CONCLUSIONS</i> | 2 |
| STATE OF ART | 4 |
| RIGHT VENTRICLE TO PULMONARY ARTERY RECONSTRUCTION | 4 |
| TYPE OF CONDUITS | 4 |
| CONDUIT FAILURE | 5 |
| DIAGNOSIS OF CONDUIT DISFUNCTION | 6 |
| RECOMMENDATIONS FOR RE-INTERVENTION | 7 |
| SURGERY VERSUS PERCUTANEOUS TREATMENT OF CONDUIT FAILURE | 8 |
| CLINICAL STUDY | 9 |
| BACKGROUND | 9 |
| METHODS | 11 |
| <i>Study population</i> | 11 |
| <i>Outcome</i> | 11 |
| <i>Pulmonary homografts and surgery</i> | 12 |
| <i>Statistical analysis</i> | 13 |
| <i>Ethics</i> | 14 |
| RESULTS | 15 |
| <i>Longterm follow-up</i> | 15 |
| <i>Early failure</i> | 16 |
| <i>Longitudinal change of peak gradient across surgically implanted RV-PA conduit</i> | 16 |
| DISCUSSION | 18 |
| LIMITATIONS | 21 |
| CONCLUSIONS | 21 |
| FIGURES | 22 |
| TABLES | 28 |
| REFERENCES | 32 |

ABSTRACT

Introduction

Surgical implantation of right ventricle to pulmonary artery (RV-PA) conduit is an important component of congenital heart disease (CHD) surgery but with limited durability and need for re-intervention. Current single center, retrospective, cohort study is reporting longterm performance of surgically implanted RV-PA conduit in a consecutive series of children and adults with CHD.

Methods

Patients with CHD referred for RV-PA conduit surgical implantation (October 1997 and January 2022) have been included. Primary outcome was conduit failure defined as peak gradient above 64mmHg/severe regurgitation/ need for conduit-related interventions. Secondary outcome was longitudinal change (increase) of continuous wave Doppler-derived peak gradient across conduit in postoperative echocardiographic studies. Longitudinal echocardiographic studies were available for mixed-effect linear regression analysis.

Results

Two-hundred and fifty-two patients were initially included. One-hundred and fifty-one patients were available and eligible for follow-up data collection. After a median follow-up time of 49 months the primary study endpoint occurred in 44 (29%) patients. Multivariable Cox regression model identified adult age (>18 years) at implantation and pulmonary homograft as protective factors (HR 0.11, 95% CI 0.02-0.47, p-value 0.003 and HR 0.34, 95% CI 0.16-0.74, p-value 0.006, respectively). Fever within 7 days of surgical conduit implantation was a strong, independent risk factor for early (within 24 months) failure (HR 4.29, 95% CI 1.41-13.01, p-value 0.01). Longterm use of oral anticoagulant was independently associated with slower progression of peak echocardiographic gradient across conduits (p-value 0.027).

Conclusions

In patients with CHD, surgically implanted RV-PA conduit failure is faster in children and after non-homograft conduit implantation. Early fever after surgery is a strong risk factor for early failure. Longterm anticoagulation seems to exert a protective effect.

LIST OF ABBREVIATIONS:

AC, Anti-Coagulation

ACHD, Adult Congenital Heart Disease

AV, Aortic Valve

BSA, Body Surface Area

CHD, Congenital Heart Disease

DORV, Doublet Outlet Right Ventricle

EF, Ejection Fraction

FAC, Fractional Area Contraction

HR, Hazard Ratio

MV, Mitral Valve

OR, Odds Ratio

PA, Pulmonary Artery

PA-IVS, Pulmonary Atresia with Intact Ventricular Septum

PR, Pulmonary Regurgitation

PV, Pulmonary Valve

PVR, Pulmonary Valve Replacement

RA, Right Atrium

RV, Right Ventricle

RV-PA, Right Ventricle to Pulmonary Artery

RVOT, Right Ventricular Outflow Tract

RVOTO, Right Ventricular Outflow Tract Obstruction

TAPSE, Tricuspid Annulus Plane Systolic Excursion

TGA, Transposition of the Great Arteries

TR, Tricuspid Regurgitation

STATE OF ART

Right ventricle to pulmonary artery reconstruction

Five decades ago, the first artificial conduit connecting the right ventricle (RV) with the pulmonary artery (PA) was surgically implanted in a 6-year-old child with pulmonary atresia¹. Nowadays, right ventricle-to-pulmonary artery (RV-PA) conduits are essential components of contemporary pediatric and adult congenital heart disease (ACHD) cardiac surgical practice for many complex congenital cardiac anomalies: they are used to establish a continuity between the RV and PA, when the native tract is not amenable for reconstruction. Most common indications for use of RV-PA conduits include tetralogy of Fallot (TOF) with or without pulmonary atresia, truncus arteriosus (TA), some forms of transposition of the great arteries (TGA) with ventricular septal defect, and pulmonary stenosis; RV-PA conduit is also required for the Ross operation for aortic valve disease, where the native pulmonary valve is moved to the aortic position and a RV-PA conduit is used to replace the resulting deficit². In addition to the primary procedure, replacement of the conduit is usually required 1 to 2 times during childhood or in adult age, often conditioned by the lack of the conduit growth compared to the growth of the patient's vascular structures or by conduit dysfunction^{3,4}. Moreover, the use of artificial RV-PA conduits is limited by the durability and inevitable degeneration which lead to need for reintervention. Beyond surgical reintervention also, balloon angioplasty/stenting and percutaneous transcatheter placement of pulmonary valve within an existing RV-PA conduit are options in larger pediatric and adult patients (>20 kg).^{5,6}

Type of conduits

Types of conduits include allograft, xenografts and hybrid xeno-synthetic grafts. The first RV-PA conduit allograft was described in 1966 and was made of cadaveric human tissue ('homograft')¹. Homografts continued to be the mainstone of RV-PA connection for many years, but their work is limited by the smaller sizes suitable for infant procedures. Xenografts (animal products usually from

cows or pigs) and hybrid xeno-synthetic grafts become after available as alternatives to homografts. The bovine jugular vein (BJV) graft was introduced as an alternative option in 1999 and contained a trileaflet venous valve. The BJV maintains good valve competence but has been associated with distal anastomotic stenosis and a higher rate of endocarditis when compared to homografts^{7,8}. Porcine stented valves with Dacron tube (Hancock conduits), were also utilized. However, in the pediatric setting, the early developing of pseudointimal formations and calcifications as well as inferior tissue handling properties, make the Hancock conduit a less common choice^{7,9}. To date, different types of conduits made of different materials, exist but each of these present limitations. Moreover, the selection between the available options represents a major challenge for the treatment of the patients¹⁰.

Conduit Failure

All current homograft and xenograft conduits, lack of any capacity for additional growth. As a child grows, the conduit has a fixed size: this means that there is a progressive size mismatch between the patient and the conduit that necessitates future replacement surgery. Typically, conduit replacement is required around 4–5 years after initial placement in an infant or young child³. Multiple medical issues can contribute to conduit failure in addition to somatic outgrowth, even in adult patients. These include stenosis of the distal anastomosis, aneurysm formation at the site of proximal anastomosis, valvular stenosis or regurgitation. Previous studies showed that in pediatric population shorter time to reintervention was associated to younger age at first surgery, higher right ventricle outflow tract (RVOT) pressure gradient, conduit type, underlying anatomy and multiple surgeries^{8,11,12,13,14}. Data on conduit-related adverse outcomes in ACHD patients are more limited. As shown by Buber et al and Thuraiasingam et al^{15,16}, smaller conduit diameter, active smoking and higher BMI were significantly associated with shorter freedom from dysfunction while Ross procedure conversely showed a reverse association with this outcome.

Some of these factors reflect the outcomes of surgical work required to customize the donor valve to the host but probably donor specific and non-specific immune responses could be the cause of conduit dysfunction. Interestingly, in one recent study, cases of both homograft and xenograft were shown to trigger the recipient's immune response resulting in calcification with thick intima or pannus formation and/or stenosis with deterioration of valve function ¹⁷.

Diagnosis of conduit dysfunction

Echocardiography is the first line imaging technique used to follow-up patients with RV-PA conduits. Echocardiography may evaluate the presence of conduit regurgitation (PR), conduit stenosis (PS), and gives information about the shape of the conduit, the associated lesions and about the function of both ventricles. Sometimes, the gradient across the conduit may be difficult to measure and unreliable, this is often related to a vertical location of the conduit within the chest with a parallel course to the chest wall that makes Doppler interrogation cumbersome; RV pressure derived from tricuspid regurgitation (TR) velocity should be always used to assess and confirm indirectly the conduit stenosis.

CMR is a second level imaging technique used to study the conduit's shape and quantify regurgitation and RV volumes. CMR is very useful in case of poor acoustic window; it is used also to give indication to surgery or to plan surgery.

CT scan is another imaging technique used to study conduit, pulmonary anatomy, anatomy of the surrounding structures and relation with coronary arteries. CT scan is used to plan surgery or percutaneous treatment.

CT and CMR imaging allow 3D multiplanar reconstruction and provides accurate delineation of anatomy, size, and geometry of the RVOT and pulmonary arteries useful to surgical or percutaneous plan. Catheterization with hemodynamic assessment is always required if intervention is considered.

Angiography provides information about conduit stenosis, peripheral PA stenoses and coronary anatomy (anomalies/abnormal course)^{18,19}.

Recommendations for re-intervention

In pediatric patients, recommendation to perform catheterization and treat RV-PA conduit dysfunction are not very updated and date back to the 2011 American Guidelines²⁰.

In adult patients with CHD, recommendations for intervention are updated in American and European Guidelines¹⁹.

In the American Guidelines²¹:

- Right ventricle-to-PA conduit intervention is reasonable for adults with right ventricle-to-PA conduit and moderate or greater PR or moderate or greater stenosis with reduced functional capacity or arrhythmia (Class IIa B)
- Right ventricle-to-PA conduit intervention may be reasonable for asymptomatic adults with right ventricle-to-PA conduit and severe stenosis or severe regurgitation with reduced RV ejection fraction or RV dilation (Class IIb B)

Latest recommendation for treatment of RV-PA dysfunction are provided from European guidelines²²:

- Symptomatic patients with RVSP >60 mmHg (may be lower in case of reduced flow) and/or severe PR should undergo intervention with preference for catheter intervention (TPVI) if anatomically feasible. (Class I C)
- Asymptomatic patients with severe RVOTO and/ or severe PR should be considered for intervention, preferably catheter intervention (TPVI) if anatomically feasible, when at least one of the following criteria is present:
 - Decrease in objective exercise capacity (CPET);

- Progressive RV dilation to RVESVi > 80 mL/m², and/or RVEDVi > 160 mL/m², and/ or progression of TR to at least moderate;
- Progressive RV systolic dysfunction;
- RVSP >80 mmHg. (Class IIa C)

Surgery versus percutaneous treatment of conduit failure

In children, surgical re-intervention is often a preferred modality due to anatomical constraints, limited patient weight, higher transcatheter procedural risk and relatively low surgical risk.

However, the percutaneous intervention may decompress the right ventricle in case of conduit stenosis and delay cardiac surgery. The treatment of failure in terms of pulmonary insufficiency is debated and it depends on children age, weight and size^{6,20}.

In adult patients, balloon dilation/stent implantation have been reported to be safe and to prolong the lifespan of failing conduits. Percutaneous pulmonary valve implantation has now become the treatment of choice for dysfunction if technically feasible. Current exclusions for percutaneous valve replacement include occluded systemic veins, active infection, unsuitable outflow tract morphology, and unfavourable coronary anatomy (compression by the expanded implant). Surgery is preferred when additional interventions are considered (ex. tricuspid annuloplasty) or the anatomy is not suitable for percutaneous intervention^{21,22,23}.

CLINICAL STUDY

BACKGROUND

Surgical implantation of right ventricle to pulmonary artery (RV-PA) conduit is an important component of congenital heart disease (CHD) surgery either at the time of primary repair/palliation or later in life due to right ventricular outflow tract (RVOT) (or previous conduit) dysfunction. In the rapidly growing population of adults with congenital heart disease (ACHD) is estimated that ~20% of patients have had RVOT revision at the time of the initial intracardiac repair and at least a subset of these received an RV-PA conduit implantation along the therapeutic road²³. In addition, primary surgical repair of many (usually complex) CHD require RV-PA conduit placement during infancy (such as in many cono-truncal abnormalities, aortic valve disease treated with Ross procedure, complex form of transposition of the great arteries and others)².

A wide array of conduit typologies has been used in the last decades, including aortic or pulmonary homograft, composite grafts, decellularized bioprosthetic conduits. Limited durability, increased risk of endocarditis and need for surgical re-intervention have been reported in this patient population^{8,11,12,13,14,15,16}. More recently, transcatheter “pulmonary” valve implantation (PVR) proved to be a reliable technology to treat RV-PA conduit dysfunction and unfolded itself as an effective methodology to prolong conduit lifespan reducing the need for repeated surgical interventions^{5,6}.

Multiple investigations have reported on the longterm results after RV-PA conduit implantation in patients with CHD^{8,17,24}. Collectively these data suggest that risk factors for early failure include smaller conduit diameter, complex congenital heart disease with non-anatomical conduit placement, specific conduit types, younger age at conduit implantation, smoking, higher body mass index^{8,11,12,13,14,15,16}. However significant uncertainties do exist regarding the pathogenic mechanisms overarching conduit deterioration over time, the competitive effectiveness of different types of conduits (bovine jugular vein, homograft, decellularized xenografts and others) across different age groups and it is unproven if there are protective factors that may prolong conduit survival. In addition,

many of the risk factors reported in the literature are largely unmodifiable and are strongly influenced by individual- and lesion-specific constraints.

Current single center, retrospective, cohort study is reporting longterm performance after surgical implantation of RV-PA conduit in a consecutive series of patients with CHD treated by uniform and standardized approach with different conduit typologies, coupled with longitudinal echocardiographic serial assessment along with collection of data on pre-specified, potentially modifiable and patient-specific conduit failure risk factors/attenuator (type of conduit, early fever in the post-operative period and longterm anticoagulation).

In patients with CHD, surgically implanted RV-PA conduit failure is increased in children and after non-homograft conduit implantation. Early fever after surgery seems to be associated with higher incidence rate of conduit failure. Longterm anticoagulation seems to exert a protective effect with slower progression of echocardiographic-based peak wave velocity across RV-PA conduit during follow-up.

METHODS

Study population

Patients with CHD referred to our institution for RV-PA conduit surgical implantation between October 1997 and January 2022 have been included. A standardized, retrospective chart review was used to collect data regarding demographics, primary congenital anomaly, surgical history, comorbidities, imaging data, index surgical intervention procedural data, periprocedural variables (including early post-operative fever, longterm anticoagulation, periprocedural mortality), longitudinal clinical and imaging pertinent variables. In our institution surgical patients are routinely followed-up on average two weeks after surgery, ~ every 9-12 months for the first two years and every 2 years thereafter.

Outcome

Primary study outcome was conduit failure defined as the early occurrence of post-implantation peak gradient above 64mmHg (4 meter/second of jet velocity measured using continuous wave Doppler echocardiography), and/or severe “pulmonary/conduit” regurgitation defined as the concomitant presence of at least two among: a) jet width in relation to conduit diameter >40%, b) flow reversal in the branch pulmonary arteries, c) pressure half-time <100msec, d) dense wave form velocity profile with early termination and/or need for conduit-related surgical or transcatheter interventions^{19,18}.

Review of imaging studies was performed by a single investigator, blinded to patient identifiers.

Secondary outcome was longitudinal change (increase) of continuous wave Doppler-derived peak gradient across conduit in postoperative echocardiographic studies.

Exploratory outcomes included overall procedural mortality and periprocedural adverse events.

Pulmonary homografts and surgery

All pulmonary homografts were collected, processed (including treatment with antibiotics), cryopreserved, and stored in the institutional tissue bank. Sizing was accomplished at the time of retrieval using Hegar dilators. All other non-homograft conduits were obtained by nationally approved vendors and used as per company/producer recommendations. All surgical interventions were performed in our institutions. Anatomic versus non-anatomic choice of conduit placement was decided at the time of surgery, and standard intraoperative protocols were followed with respect to preparation of either cryopreserved pulmonary homografts or non-homograft conduits. Indication for conduit implantation were either primary surgical repair of CHD or right ventricular outflow tract function restoring, each indication was assessed, reviewed and formalized in a dedicated congenital heart team meeting following current evidence and guidelines¹⁹. The operative technique varied according to primary CHD diagnosis and individual anatomy. However, the RV-to-PA conduit reconstruction was consistently performed with either single- or double-venous cannulation, aortic arterial cannulation, under cardioplegic arrest. An adequate runoff was ensured to the pulmonary circulation, and the distal anastomosis was fashioned first. The conduit was trimmed so that the conduit valve was placed as near as possible to the pulmonary bifurcation to avoid compression and deformation by the sternum. The operation was then completed with the proximal anastomosis between the conduit and right ventricle. All pulmonary homografts were trimmed of excess musculature to avoid calcification and stenosis. Ascending aorta extension was used in selected cases to ensure proper space for the distal anastomosis and to reduce branch pulmonary artery stenosis. When proximal extension was needed this was usually carried with treated bovine pericardial patch. Patients received routine perioperative antibiotics and prophylactic low dose aspirin for one month post-operatively.

Statistical analysis

Between-group comparisons for clinical and outcome variables were performed using independent samples t-test, Wilcoxon rank sum test, chi-square analysis, or Fisher's exact test using appropriate variable-specific denominators.

The primary study endpoint was conduit failure as previously defined. Pre-specified candidate predictors of conduit failure were selected using available evidences and were: 1) pulmonary homograft; 2) adult versus children (dichotomizing category) at the time of surgical implantation; conduit size treated as continuous variable and as binary variable (>22mm versus <22mm); indication for conduit implantation. Two additional new variables were pre-specified in the analytic plan as candidates for accelerated conduit failure risk factors/attenuators: 1) fever in the first 7 days after conduit implantation and 2) longterm use of anticoagulation.

The time-to-primary outcome was computed using Kaplan-Meier estimates and log-rank test was used to compare equality of survival across pre-specified binary group comparison. Cox modeling was used to compute hazard ratio (with 95% confidence interval) of the primary end point. A univariable Cox regression analysis was carried-out using the pre-specified predictors in the primary analysis and additional predictors in an exploratory analysis. Predictors achieving marginal significance (p value < 0.15) were entered in a multivariable Cox regression model. The final model retained (parsimonious approach) only variables with strong significance using stepwise backward selection. Modeling diagnostics were run using visual inspection of log-log plot and Schoenfeld residuals test and model robustness was assessed using bootstrapping resampling of the dataset (500 replications).

Logistic regression was used to model early conduit failure (defined as conduit failure occurring before 24 months from the date of surgical implantation), and model robustness was assessed using bootstrapping resampling of the dataset (500 replications).

Finally, to test if longterm use of anticoagulation was associated with slower, longitudinal increase of conduit peak gradient (measured using continuous wave Doppler echocardiography) a mixed-effect

linear regression model was run testing longitudinal peak gradient change (across multiple exams) as dependent outcome and time from conduit implantation/longterm anticoagulation use interaction variable as predictors, retaining the patient as the clustering variable and adjusting the analysis for major confounders. For this analysis an unstructured covariance matrix was defined, allowing a high degree of flexibility to account for the inherently unbalanced profile of longitudinal examination within and among patients.

Data are reported as mean±standard deviation, median (first and third quartile) or frequency (%). All tests were two-sided. A p-value <0.05 was considered significant. Analysis was performed using STATA® 17th Release data analysis software (StataCorp LP, College Station, TX).

Ethics

Institutional Review Board approved the study and granted a waiver for patient consent given the retrospective nature of the study, with minimal patient interaction.

RESULTS

Between October 18th 1997 and January 10th 2022, 252 patients with CHD underwent surgical implantation of RV-PA conduit in our Center. **Figure 1** summarizes the structure of this observational cohort as per Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) approach. Data lock was on December 31st 2022. **Table 1** summarizes pertinent demographic, clinical and procedural data for the entire cohort and by age at the time surgical procedure (**Table 1**). As expected, the two groups of patients diverged for a number of important clinical and procedural variables including body size, age, type of primary congenital heart disease (CHD), type of conduit, conduit diameter, procedural data. Conotruncal abnormalities were the primary CHD for the majority of patients. In 145 cases (out of 252, ~58%) a previous surgical procedure occurred before the index procedure and 71 patients (28%) have a RV-PA conduit already implanted (that was replaced at the time of the index procedure). The three most common indications for conduit placement were “pulmonary regurgitation” (that was the most common indication in the adult subgroup), primary CHD repair (that was the most common indication in the children subgroup) and right ventricular outflow tract obstruction. In 81 patients (32%) an additional surgical component was needed beyond conduit implantation. Pulmonary homograft was the most common type of conduit implanted both in children and adult subgroup, no aortic homograft was used in this study.

Acute hemodynamic effect of conduit implantation is presented in **Figure 2**, that summarizes pre- and post-procedural distribution of differential grading of tricuspid regurgitation, “pulmonary” regurgitation and peak gradient across RVOT by echocardiography.

Longterm follow-up

Follow-up data were available for 151 patients (**Figure 1**). **Table 2** reports pertinent comparison between patients excluded and included in the follow-up analysis. After a median follow-up time of 49 months (interquartile range 9-132 months) the primary study endpoint occurred in 44 (29%)

patients. The most common component of the primary study endpoint was peak echocardiographic gradient $> 64\text{mmHg}$ ($n=44$). Forty-one (27%) patients underwent conduit-related transcatheter intervention due to conduit failure (conduit stenting in 22 patients and transcatheter pulmonary valve implantation in 25 patients, non-mutually-exclusive events) and surgical re-intervention was required in ten patients (7%). Freedom from conduit failure is presented in **Figure 3**. The 1- 5- and 10-year freedom rate from conduit failure was 91%, 83% and 66%. Results of univariable and multivariable Cox regression model are presented in **Table 3**. Pulmonary homograft and adult age at the time of intervention were independently associated to longer freedom from conduit failure. **Figure 4** is reporting survival estimates from conduit failure in homograft versus non-homograft subgroup (A) and adult versus children subgroup (B). The 10-year freedom rate from conduit failure was 46% in the non-homograft group compared to 85% in the homograft group. Similarly, the 10-year freedom rate from conduit failure was 47% in patients implanted before age of 18 years compared to 86% in patients implanted after age of 18years. The interaction between these two factors was particularly striking because the 10-year freedom rate from conduit failure in adults implanted with homograft was 96%.

Early failure

In 15 patients (~10%, 11 children and 4 adults) early failure (defined as failure occurring before 24 months) did occur. The univariable logistic regression analysis is reported in **Table 4**. The multivariable logistic regression analysis (**Table 4**) shows that fever within 7-days of implantation, was independently associated with early failure, while homograft was associated with trend toward reduced risk of early failure.

Longitudinal change of peak gradient across surgically implanted RV-PA conduit

In the entire study group a total of 441 echocardiographic evaluations have been performed during follow-up. Longitudinal change of peak gradient across surgically implanted RV-PA conduit has been

measured. Specifically, 142 patients (94%) had one measurement, 105 (70%) had two longitudinal echocardiographic measurements, 95 patients (63%) had three measurements and 109 patients (72%) had four measurements during follow-up. A pre-specified analysis comparing the longitudinal change of peak gradient across surgically implanted conduits in patients with and without longterm anticoagulation was carried out. **Figure 5** shows box-plot summary of peak conduit gradient over four clustering time points in both subgroups. A mixed-effect linear regression analysis was set so to retain the patient as clustering variable and an interaction between time from surgery and anticoagulation as primary predictor for peak gradient longitudinal change over time, adjusting this analysis for age at implantation and type of conduit. Compared to patients without anticoagulation, in a small group of patients with longterm anticoagulation (n=33, 8 children and 25 adults) there is evidence of a slower progression of peak gradient across surgically implanted conduit over time (**Figure 5**).

DISCUSSION

The quest for the perfect RV-PA conduit in congenital cardiac surgery is still an active field of investigation. RV-PA conduits remain a pivotal element of surgical repair in a variety of complex CHD, but the clinical burden related to conduit dysfunction is significant and includes endocarditis, symptomatic conduit stenosis and/or regurgitation leading to heart failure and the need for surgical or transcatheter intervention^{8,16,25,26}.

Our report provides additive data to current evidences regarding longterm future of patients undergone surgical RV-PA conduit implantation in the setting of (complex) congenital heart disease. Main study findings are: 1) longterm performance of RV-PA conduit is still plagued by sub-optimal durability with less than 70% of patients free from conduit failure 10 years after surgical implantation; 2) in adults, pulmonary homografts present excellent performance with more than 90% of patients free from conduit failure 10 years after placement; 3) early (within 7 days of surgery) fever seems to be associated with higher propensity to early conduit failure; 4) longterm anticoagulation may exert a protective role with slower progression of peak echocardiophic gradient across surgically implanted RV-PA conduit.

It must be reinforced that RV-PA conduits are usually implanted in young patients, already undergone surgical intervention and both these elements make RV-PA conduit failure a major source of disease burden, especially in the ACHD population.

A complex interplay is likely affecting longterm durability of RV-PA conduits in congenital heart patients. Available evidences suggest that three main clusters of risk factors can be identified: 1) patient-related factors (age at implantation, body size, susceptibility to infection and/or previous endocarditis); 2) conduit-related factors (type of conduit, conduit diameter); 3) anatomical factors (primary CHD, quality and residual turbulence of landing branch pulmonary arteries, surrounding structures such as aorta or sternum, anatomical conduit location versus non anatomical).^{2, 8,14 ,15, 16,27}

Navigating the evidences regarding risk factors for conduit failure is challenging due to a number of relevant methodological aspects affecting published studies: 1) patient heterogeneity across studies; 2) institutional preferences regarding conduit choice and pulmonary homograft availability; 3) unmeasurable surgical factors; 4) outcome definition and ascertainment; 5) lack of granular patient-level data that usually affects large multicenter cohort studies in this field.

Our data contrast in part previous evidences, suggesting that pulmonary homograft conduit, especially in adult patients, may present a very favorable durability profile even when adjusted for other conventional risk factors for early conduit failure. Pulmonary homografts have been shown to sub-perform compared to bovine jugular vein conduit in small children⁸. Potential mechanisms of better performance of bovine jugular vein conduits in small children may include: limited availability in pulmonary homograft small sizes (forcing sub-optimal choices), better antigen masking with bovine jugular vein preservation, better geometry of bovine jugular vein conduit that allows the valve to be placed nearly the distal anastomosis with the pulmonary artery reducing the risk of valve compression by the sternum. It is possible that these mechanisms are not in place or less pronounced in adult patients. In addition, it is possible that standardized and institutional harvesting of pulmonary homografts increased conduit quality and preservation.

If our data will be confirmed in other series, pulmonary homograft should be considered an important modifiable protective factor against early conduit failure, especially for adult patients where body size and tissue availability allow more flexible choice of conduit type compared to neonatal period and infancy. This should support collaborating efforts to promote pulmonary homograft availability and preservation (multicenter collaborating tissue banks).

Preliminary evidences and expert opinion suggested that thrombosis and inflammation may play a role in longitudinal RV-PA conduit deterioration^{28,29}. Extensive conduit calcification has been observed after RV-PA conduit implantation especially in specific type of conduits (such as aortic homograft)³⁰. Unexplained fever after conduit placement, including homograft, has been reported³¹. Current

investigation, using a pre-specified analysis, hypothesizes that fever within seven days from surgical operation is an independent risk factor for early (two years) deterioration. In our Center post-surgical fever is mandatory reported, accordingly our variable ascertainment should be reliable. We believe that if confirmed in other independent cohorts, this may indicate how inappropriate inflammation after conduit placement may trigger accelerated deterioration. The relatively low number of observations precluded us to further dissect the interaction between differential propensity of post-surgery early fever with conduit type and/or age at implantation. This observation triggers a discussion about potential benefit of host response modulation after conduit placement to mitigate detrimental effects of inflammation.

Low-grade thrombosis and peeling have been questioned as potential mechanisms of RV-PA conduit dysfunction³². It is of interest that in a small group of our patients on longterm anticoagulation (the great majority of them were adults taking anticoagulation due to paroxysmal or permanent atrial arrhythmias) the longitudinal change of peak gradient across surgically implanted RV-PA conduit was significantly slower than what was observed in the non-anticoagulated patients. We took the opportunity of extensive longitudinal and repeated echocardiographic evaluations to investigate this differential behavior using mixed-effect linear regression model. Such model allowed us to account for the clustered and imbalanced nature of data structure, providing a robust statistical to adjust the analysis for other important confounders.

Taken together, these last two observations carry some clinical interest because inflammatory-mediated fever and anticoagulation may be considered potential modifiable targets, testable in prospective interventional clinical investigations.

LIMITATIONS

Our study is not without meaningful limitations. This is a retrospective study prone to the usual biases of such study approach. Standardized institutional practice and homogeneous surgical approach tend to limit unmeasured confounders, although these cannot be completely excluded. Patients lost to follow-up may be inherently different from patients in follow-up.

Missing data are significant in our study. Multiple attempts were used to reduce data missingness including telephone and mail tracking of patients lost to follow-up and use of available alive/status public indicator. In addition, over the years institutional informatic infrastructure relocation affected data preservation, along with massive data lost due to local earthquake leading to unforeseeable data storage collapse. Accordingly, results must be generalized with caution to the entire patient cohort.

Fever and longterm anticoagulation have been analyzed in a small subset of patients and these analysis must be considered hypothesis generating rather than definitive proof of causation.

CONCLUSIONS

In patients with CHD, surgically implanted RV-PA conduit failure is increased in children and after non-homograft conduit implantation. Early fever after surgery seems to be associated with higher incidence rate of conduit failure. Longterm anticoagulation seems to exert a protective effect with slower progression of echocardiographic-based peak wave velocity across RV-PA conduit during follow-up. If confirmed in other series, these data may trigger interventional clinical investigation aiming at prolonging conduit survival in this patient population.

FIGURES

Figure 1. Study patient flow chart as per Strengthening the Reporting of Observational studies in Epidemiology (STROBE) approach.

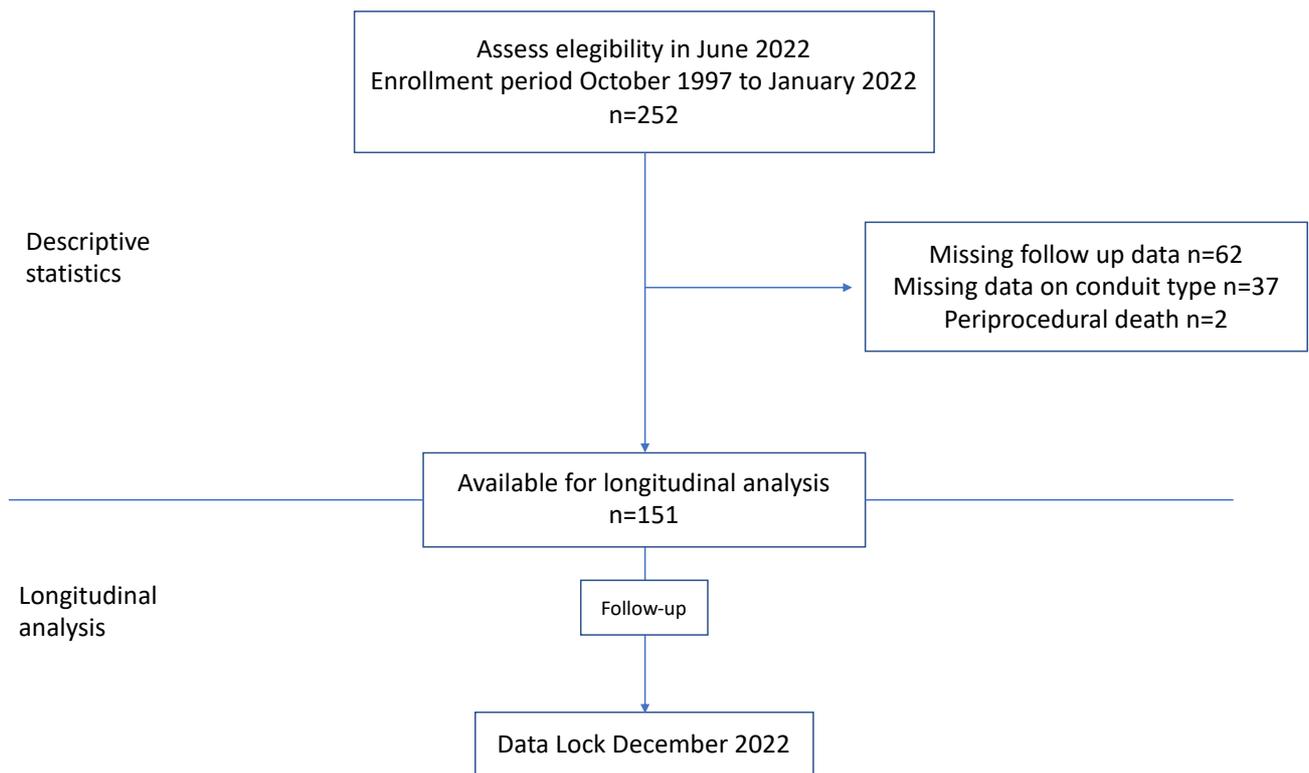
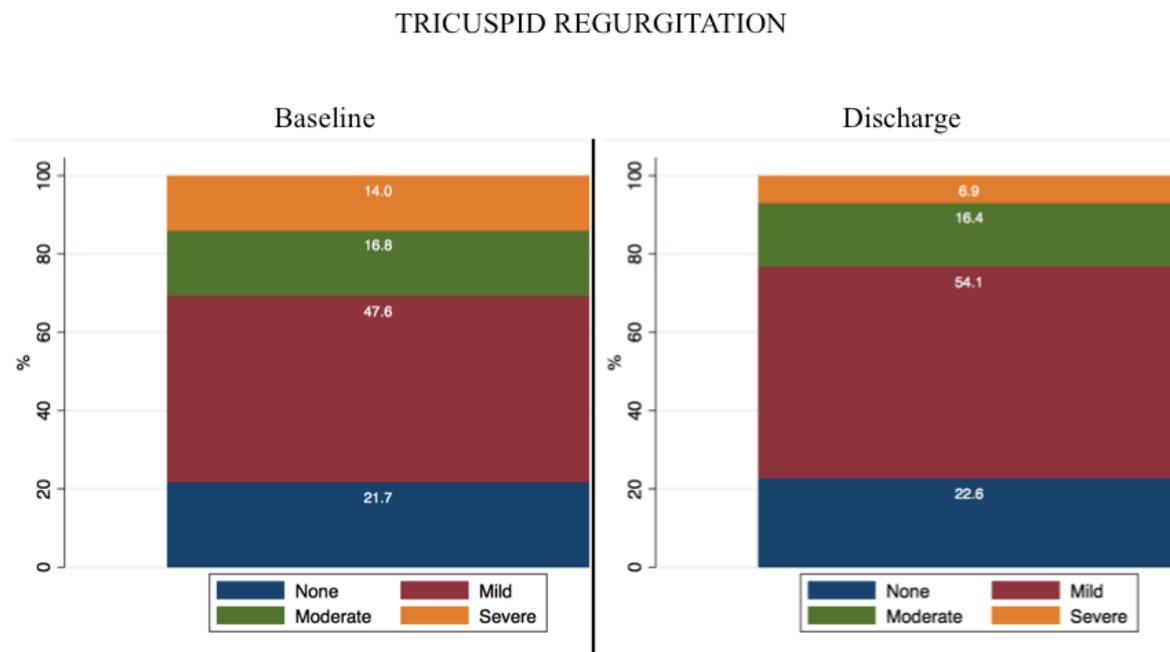


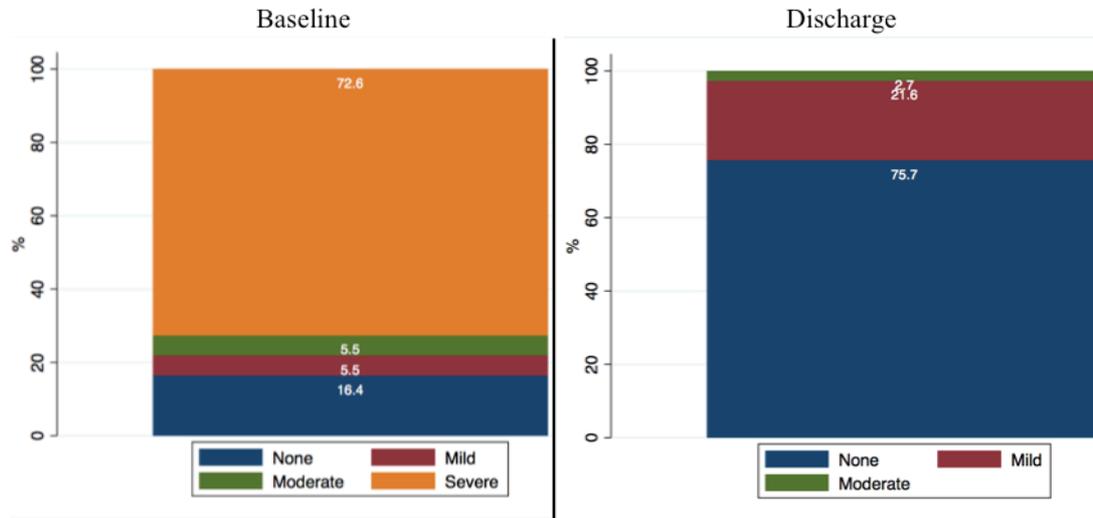
Figure 2. Comparison of basal and pre-discharge of tricuspid regurgitation (A), “pulmonary” regurgitation (B) percent distribution of differential grading in the study population. Figure 2C reports comparison of basal and pre-discharge peak echocardiographic gradient across RVOT in the study population.

2A.



2B.

“PULMONARY” REGURGITATION



2C.

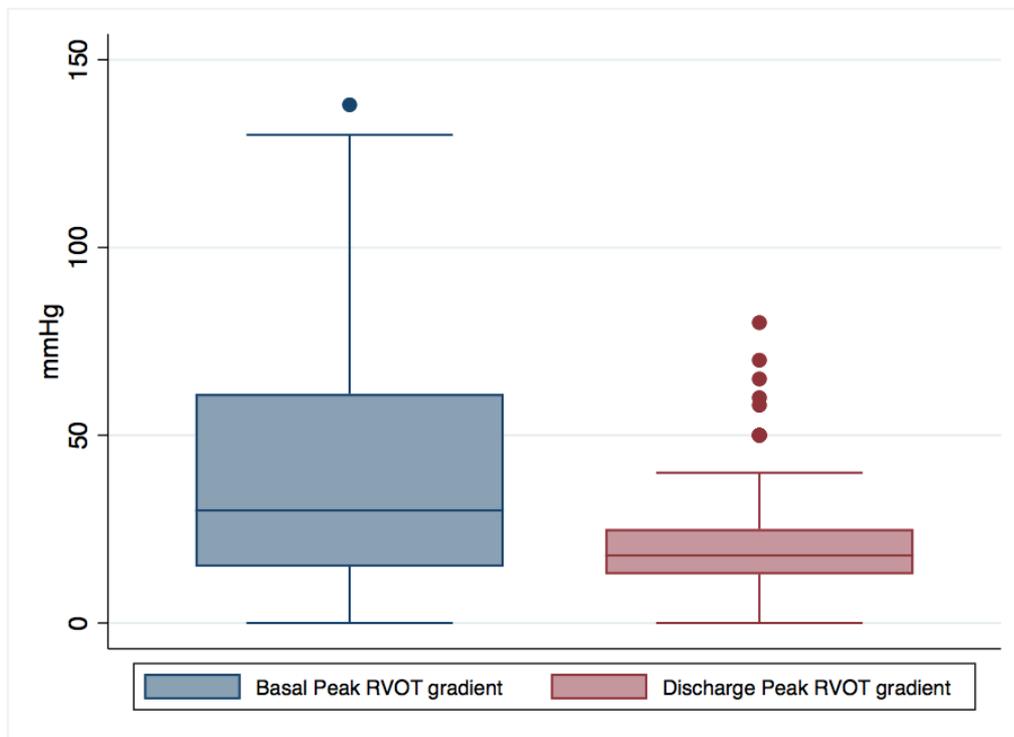


Figure 3. Kaplan-Meier estimates of survival from conduit failure in the entire study population.

Multivariable Cox regression model results are provided in the table.

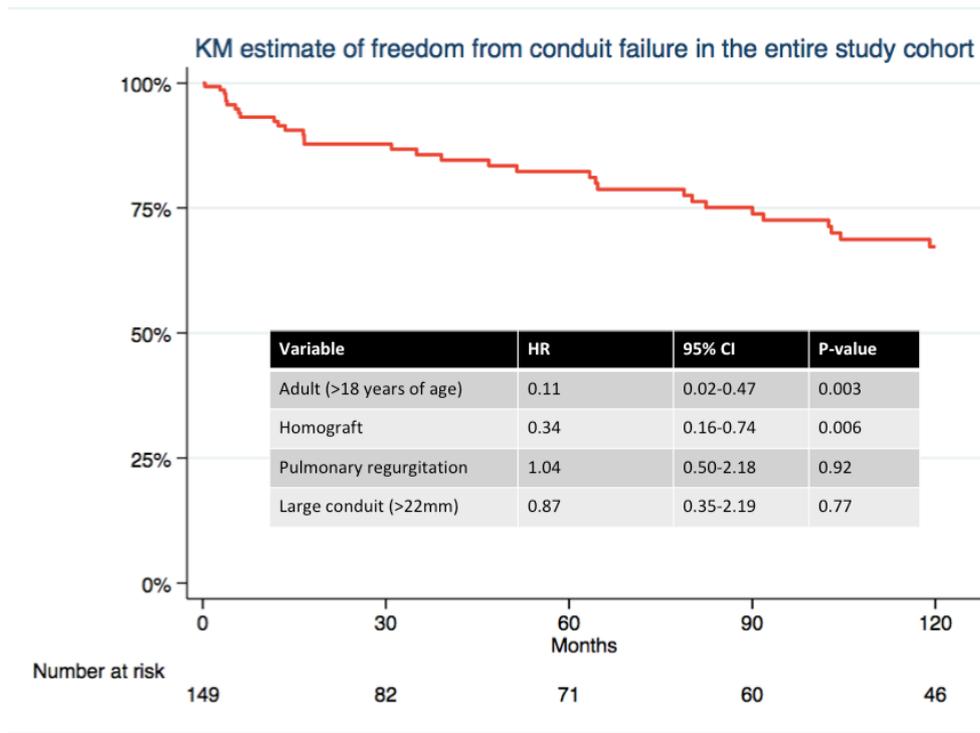
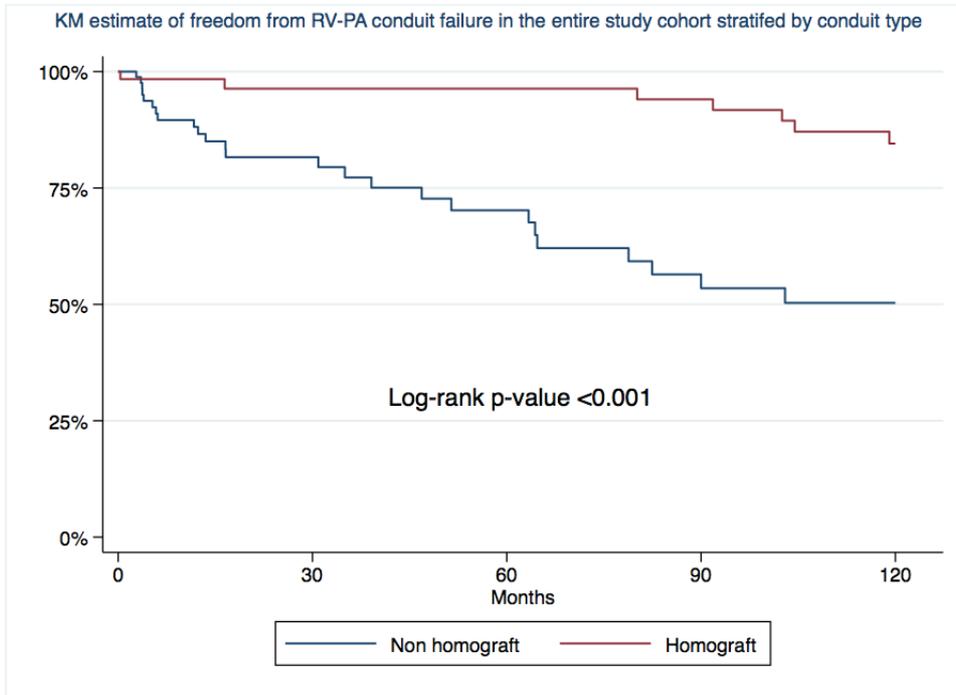


Figure 4. Kaplan-Meier estimates comparing survival from conduit failure in the study population by age group (A) and type of conduit (B). Log-rank equality survival test is provided.

4A.



4B.

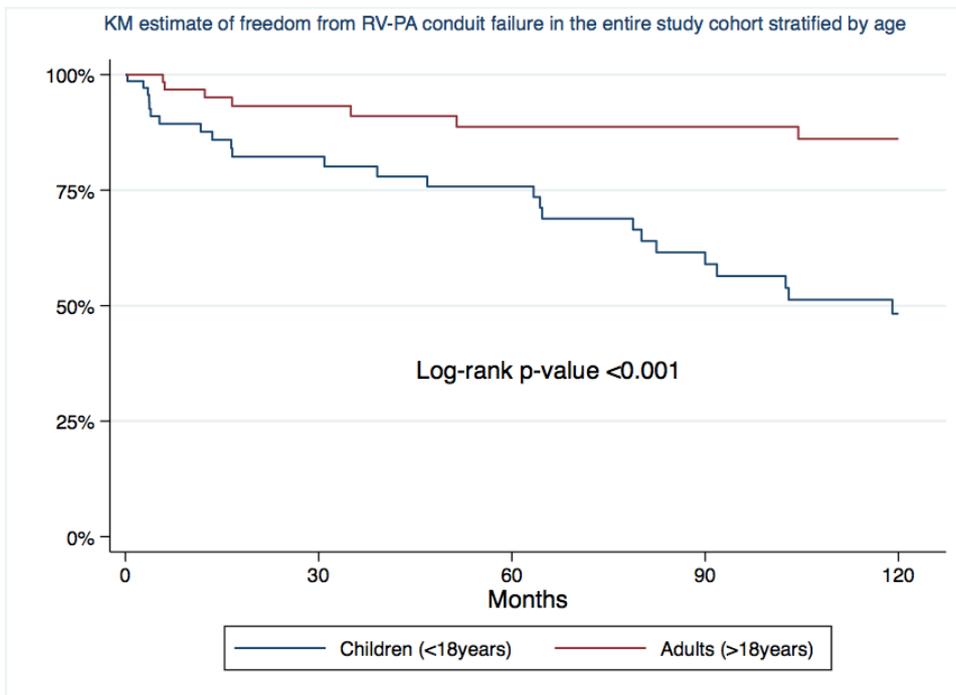
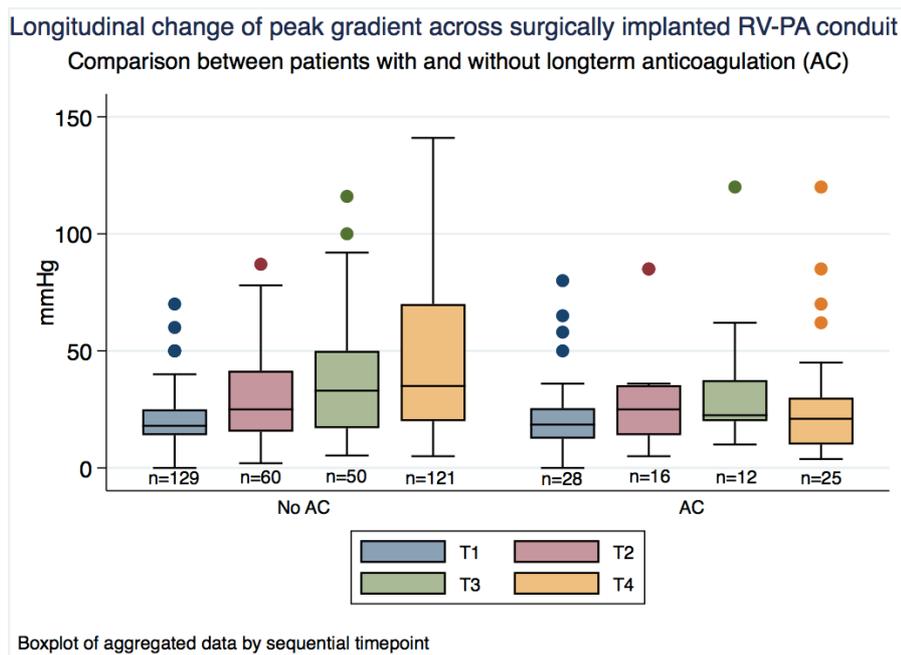
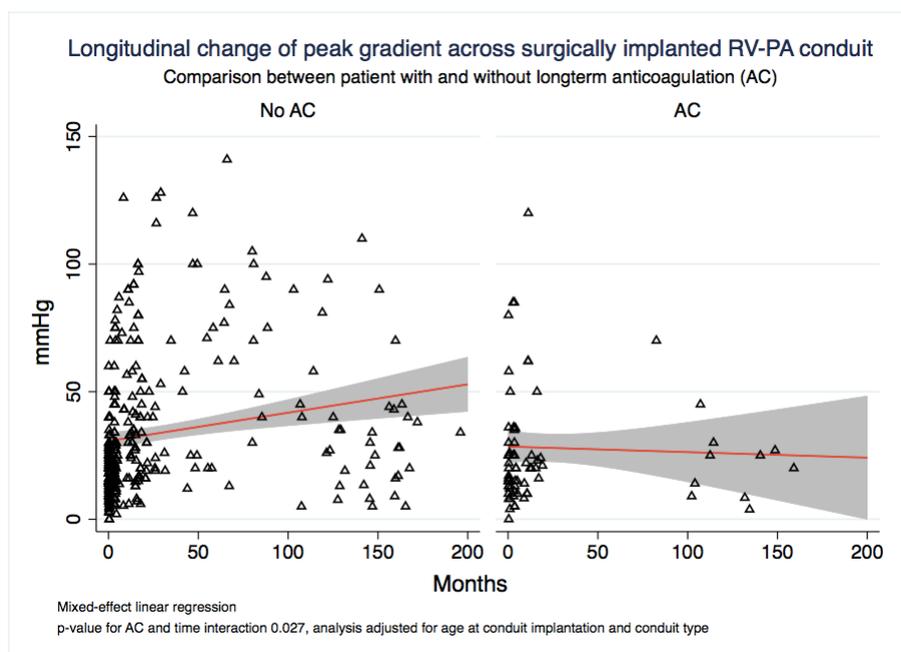


Figure 5. Results of longitudinal analysis of peak echocardiographi RVOT gradient over time in the study population in patients with and without longterm anticoagulation. Figure 5A reports box-plot of aggregated data by sequential time-points. Figure 5B compares scatter plot of data-point over time with fitted linear regression overlay along with 95% CI confidence limit in the two groups. Results from mixed-effect linear regression model are reported.

5A.



5B.



TABLES

Table 1. Clinical demographics, CHD details and procedural variable in the entire study cohort and by age group at RV-PA conduit implantation.

| Variable | Overall cohort (n=252) | Children (<18 years) (n=127) | Adults (≥ 18 years) (n=125) | p-value |
|---|---------------------------|------------------------------------|-----------------------------------|---------|
| Age at intervention, years | 16 (6-31) | 8 (1-14) | 33 (23-47) | <0.001 |
| Weight, Kg | 55 (29-70) | 29 (15-55) | 65 (55-75) | <0.001 |
| Height, cm | 160 (135-170) | 135 (97-162) | 166 (166-174) | <0.001 |
| BSA, m ² | 1.01 (0-1.68) | 0.58 (0-1.33) | 1.56 (1.35-1.83) | <0.001 |
| Primary CHD, n (%) | | | | <0.001 |
| Tetralogy of Fallot | 88 (35%) | 31 (25%) | 57 (46%) | |
| Tetralogy of Fallot with PA | 45 (18%) | 32 (25%) | 13 (10%) | |
| Truncus arteriosus | 29 (12%) | 28 (22%) | 1 (1%) | |
| Pulmonary stenosis | 25 (10%) | 6 (5%) | 19 (15%) | |
| TGA-related spectrum | 15 (6%) | 11 (8%) | 4 (3%) | |
| PA-IVS | 9 (3%) | 6 (5%) | 3 (2%) | |
| DORV | 4 (1%) | 3 (2%) | 1 (1%) | |
| Other | 37 (15%) | 10 (8%) | 27 (22%) | |
| Number of previous surgical procedures, n (%) | | | | 0.41 |
| 0 | 107 (43%) | 60 (47%) | 47 (37%) | |
| 1 | 71 (28%) | 34 (27%) | 37 (30%) | |
| 2 | 56 (22%) | 26 (20%) | 30 (24%) | |
| 3 | 18 (7%) | 7 (6%) | 11 (9%) | |
| Previous RV-PA conduit, n (%) | 71 (28%) | 54 (43%) | 17 (14%) | <0.001 |
| Current indication for conduit implantation, n (%) | | | | <0.001 |
| Regurgitation | 81 (32%) | 22 (17%) | 59 (47%) | |
| RVOTO | 24 (10%) | 18 (14%) | 6 (5%) | |
| Mixed RVOTO and regurgitation | 22 (9%) | 16 (13%) | 6 (5%) | |
| Endocarditis | 3 (1%) | 2 (2%) | 1 (1%) | |
| Other (including primary surgical repair) | 122 (48%) | 69 (54%) | 53 (42%) | |
| Additional surgical procedures, n (%) | | | | <0.001 |
| Rastelli/Truncus surgery | 18 (7%) | 18 (14%) | 0 (0%) | |
| Branch pulmonary plasty | 10 (4%) | 8 (6%) | 2 (2%) | |
| TV repair | 7 (3%) | 0 (0%) | 7 (6%) | |
| AV replacement | 3 (1%) | 1 (1%) | 2 (2%) | |
| AV repair | 2 (1%) | 1 (1%) | 1 (1%) | |
| MV replacement | 2 (1%) | 0 (0%) | 2 (2%) | |
| TV replacement | 2 (1%) | 0 (0%) | 2 (2%) | |
| Ross procedure | 2 (1%) | 2 (2%) | 0 (0%) | |
| MV repair | 1 (1%) | 1 (1%) | 0 (0%) | |
| Other | 34 (12%) | 26 (20%) | 8 (6%) | |
| Current implanted conduit type, n (%) | | | | <0.001 |
| Homograft | 98 (39%) | 39 (31%) | 59 (47%) | |

| | | | | |
|--|--------------|--------------|--------------|--------|
| Biopulmonic | 42 (17%) | 19 (15%) | 23 (18%) | |
| Contegra | 30 (12%) | 29 (23%) | 1 (1%) | |
| Matrix | 20 (8%) | 20 (16%) | 0 (0%) | |
| Carpentier | 16 (6%) | 5 (4%) | 11 (9%) | |
| Labcor | 6 (2%) | 6 (5%) | 0 (0%) | |
| Hancock | 2 (1%) | 0 (0%) | 2 (2%) | |
| Vascutek | 1 (1%) | 1 (1%) | 0 (0%) | |
| Other | 37 (15%) | 8 (6%) | 29 (23%) | |
| Conduit nominal diameter, mm | 22 (18-25) | 19 (16-22) | 24 (23-25) | <0.001 |
| Cardiopulmonary bypass time, minutes | 111 (83-148) | 124 (84-157) | 102 (80-140) | 0.02 |
| Cross-clamp time, minutes | 66 (50-96) | 80 (54-110) | 61 (41-78) | 0.001 |
| Fever within 7-days from surgery, n (%) | 52 (21%) | 36 (28%) | 16 (13%) | 0.002 |
| Large conduit (>22mm), n (%) | 155 (62%) | 42 (33%) | 113 (90%) | <0.001 |
| Longterm anticoagulation, n (%) | 33 (13%) | 8 (6%) | 25 (20%) | 0.001 |

AV, Aortic Valve; CHD, Congenital Heart Disease; DORV, Doublet Outlet Right Ventricle; MV, Mitral Valve; PA, Pulmonary Artery; PA-IVS, Pulmonary Atresia with Intact Ventricular Septum; PV, Pulmonary Valve; RVOTO, Right Ventricular Outflow Tract Obstruction; RV-PA, Right Ventricle to Pulmonary Artery; TGA, Transposition of the Great Arteries

Table 2. Comparison of clinical demographics, CHD details and procedural data between patients excluded and included in the follow-up analysis.

| Variable | Overall cohort (n=252) | Patients excluded from follow-up analysis (n=101) | Patients included in follow-up analysis (n=151) | p-value |
|--|-------------------------------|--|--|----------------|
| Age at intervention, years | 16 (6-31) | 11 (1-19) | 19 (10-33) | <0.001 |
| Weight, Kg | 55 (29-70) | 56 (22-74) | 55 (37-70) | 0.83 |
| Height, cm | 160 (135-170) | 158 (118-168) | 160 (138-170) | 0.85 |
| Primary CHD, n (%) | | | | <0.001 |
| Tetralogy of Fallot | 88 (35%) | 23 (23%) | 65 (43%) | |
| Tetralogy of Fallot with PA | 45 (18%) | 16 (16%) | 29 (19%) | |
| Truncus arteriosus | 29 (12%) | 16 (16%) | 13 (9%) | |
| Pulmonary stenosis | 25 (10%) | 5 (5%) | 20 (13%) | |
| TGA-related spectrum | 15 (6%) | 6 (6%) | 9 (6%) | |
| PA-IVS | 9 (3%) | 6 (6%) | 3 (2%) | |
| DORV | 4 (1%) | 2 (2%) | 2 (1%) | |
| Other | 37 (15%) | 27 (26%) | 10 (7%) | |
| Number of previous surgical procedures, n (%) | | | | <0.001 |
| 0 | 107 (43%) | 86 (85%) | 21 (14%) | |
| 1 | 71 (28%) | 8 (8%) | 63 (42%) | |
| 2 | 56 (22%) | 4 (4%) | 52 (34%) | |
| 3 | 18 (7%) | 3 (3%) | 15 (10%) | |
| Previous RV-PA conduit, n (%) | 71 (28%) | 79 (78%) | 102 (68%) | 0.06 |

| | | | | |
|---|--------------|--------------|--------------|------------------|
| Current indication for conduit implantation, n (%) | | | | <0.001 |
| Regurgitation | 81 (32%) | 6 (6%) | 75 (49%) | |
| RVOTO | 24 (10%) | 2 (2%) | 22 (15%) | |
| Mixed RVOTO and regurgitation | 22 (9%) | 0 (0%) | 22 (15%) | |
| Endocarditis | 3 (1%) | 0 (0%) | 3 (2%) | |
| Other (including primary surgical repair) | 122 (48%) | 93 (92%) | 29 (19%) | |
| Additional surgical procedures, n (%) | | | | 0.02 |
| Rastelli/Truncus surgery | 18 (7%) | 11 (11%) | 7 (5%) | |
| Branch pulmonary plasty | 10 (4%) | 0 (0%) | 10 (7%) | |
| TV repair | 7 (3%) | 2 (2%) | 5 (3%) | |
| AV replacement | 3 (1%) | 0 (0%) | 3 (2%) | |
| AV repair | 2 (1%) | 0 (0%) | 2 (1%) | |
| MV replacement | 2 (1%) | 0 (0%) | 2 (1%) | |
| TV replacement | 2 (1%) | 2 (2%) | 2 (1%) | |
| Ross procedure | 2 (1%) | 0 (0%) | 2 (1%) | |
| MV repair | 1 (1%) | 1 (1%) | 0 (0%) | |
| Other | 34 (12%) | 16 (16%) | 18 (12%) | |
| Current implanted conduit type, n (%) | | | | <0.001 |
| Homograft | 98 (39%) | 35 (35%) | 63 (42%) | |
| Biopulmonic [®] | 42 (17%) | 1 (1%) | 41 (27%) | |
| Contegra [®] | 30 (12%) | 14 (14%) | 16 (10%) | |
| Matrix [®] | 20 (8%) | 11 (11%) | 9 (6%) | |
| Carpentier [®] | 16 (6%) | 6 (6%) | 10 (7%) | |
| Labcor [®] | 6 (2%) | 0 (0%) | 6 (4%) | |
| Hancock [®] | 2 (1%) | 2 (2%) | 0 (0%) | |
| Vascutek [®] | 1 (1%) | 1 (1%) | 0 (0%) | |
| Other | 37 (15%) | 31 (30%) | 6 (4%) | |
| Conduit nominal diameter, mm | 22 (18-25) | 20 (15-23) | 23 (20-25) | 0.002 |
| Cardiopulmonary bypass time, minutes | 111 (83-148) | 135 (89-156) | 109 (81-145) | 0.06 |
| Cross-clamp time, minutes | 66 (50-96) | 82 (54-107) | 64 (50-86) | 0.14 |
| Fever within 7-days from surgery, n (%) | 52 (21%) | 10 (10%) | 42 (28%) | 0.001 |
| Large conduit (>22mm), n (%) | 155 (62%) | 61 (60%) | 94 (62%) | 0.76 |
| Longterm anticoagulation, n (%) | 33 (13%) | 6 (6%) | 27 (18%) | 0.006 |

AV, Aortic Valve; CHD, Congenital Heart Disease; DORV, Doublet Outlet Right Ventricle; MV, Mitral Valve; PA, Pulmonary Artery; PA-IVS, Pulmonary Atresia with Intact Ventricular Septum; PV, Pulmonary Valve; RVOTO, Right Ventricular Outflow Tract Obstruction; RV-PA, Right Ventricle to Pulmonary Artery; TGA, Transposition of the Great Arteries

Table 3. Univariable and multivariable Cox regression model for the primary endpoint of conduit failure.

| Variable | Univariable analysis | | | Multivariable analysis | | |
|--------------------------------------|----------------------|-----------|---------|------------------------|-----------|---------|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Male | 0.64 | 0.34-1.20 | 0.17 | | | |
| Age at intervention | 0.96 | 0.93-0.98 | 0.001 | 1.03 | 0.99-1.09 | 0.13 |
| Adult | 0.19 | 0.09-0.42 | <0.001 | 0.11 | 0.02-0.47 | 0.003 |
| Previous conduit | 1.25 | 0.67-2.35 | 0.48 | | | |
| Homograft | 0.25 | 0.12-0.50 | <0.001 | 0.34 | 0.16-0.74 | 0.006 |
| Baseline gradient across RVOT | 1.01 | 0.99-1.02 | 0.06 | | | |
| Pulmonary regurgitation | 0.57 | 0.30-1.09 | 0.08 | 1.04 | 0.50-2.18 | 0.92 |
| Conduit diameter >22mm | 0.44 | 0.24-0.84 | 0.01 | 0.87 | 0.35-2.19 | 0.77 |

HR, Hazard Ratio; RVOT, Right Ventricular Outflow Tract

Table 4. Univariable and multivariable logistic regression model for early occurrence of the primary end-point of conduit failure.

| Variable | Univariable analysis | | | Multivariable analysis | | |
|---------------------------------------|----------------------|------------|---------|------------------------|------------|---------|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Male | 0.43 | 0.13-1.39 | 0.16 | | | |
| Age at intervention | 0.99 | 0.96-1.02 | 0.54 | | | |
| Adult | 0.35 | 0.11-1.12 | 0.07 | 0.57 | 0.16-1.96 | 0.37 |
| Previous conduit | 1.76 | 0.60-5.15 | 0.30 | | | |
| Homograft | 0.23 | 0.05-1.02 | 0.054 | 0.26 | 0.05-1.21 | 0.09 |
| Baseline gradient across RVOT | 1.01 | 0.99-1.02 | 0.4 | | | |
| Pulmonary regurgitation | 1.93 | 0.67-5.51 | 0.2 | | | |
| Conduit diameter >22mm | 0.93 | 0.32-2.71 | 0.9 | | | |
| Fever within 7 days of surgery | 5.01 | 1.72-14.56 | 0.003 | 4.29 | 1.41-13.01 | 0.01 |

OR, Odds Ratio; RVOT Right Ventricular Outflow Tract

REFERENCES

1. Rastelli Gc, Ongley Pa, Davis Gd, Kirklin Jw. Surgical Repair For Pulmonary Valve Atresia With Coronary-Pulmonary Artery Fistula: Report Of Case. *Mayo Clin Proc.* 1965 Jul;40:521-7. PMID: 14346186.
2. Dearani JA, Danielson GK, Puga FJ, et al. Late follow-up of 1095 patients undergoing operation for complex congenital heart disease utilizing pulmonary ventricle to pulmonary artery conduits. *The Annals of Thoracic Surgery.* 2003;75(2):399-411. doi:10.1016/S0003-4975(02)04547-2
3. Mery CM, Guzmán-Pruneda FA, De León LE, et al. Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. *The Journal of Thoracic and Cardiovascular Surgery.* 2016;151(2):432-441.e2. doi:10.1016/j.jtcvs.2015.10.069
4. Dalziel K, Huang L, Saxena A, Winlaw DS. Utilization of hospital inpatient resources by children requiring a right ventricle–to–pulmonary artery conduit in the first 10 years of life. *The Journal of Thoracic and Cardiovascular Surgery.* 2020;159(1):e73-e75. doi:10.1016/j.jtcvs.2019.06.074
5. Morray BH, McElhinney DB, Boudjemline Y, et al. Multicenter Experience Evaluating Transcatheter Pulmonary Valve Replacement in Bovine Jugular Vein (Contegra) Right Ventricle to Pulmonary Artery Conduits. *Circ Cardiovasc Interv.* 2017;10(6). doi:10.1161/CIRCINTERVENTIONS.116.004914
6. Alkashkari W, Alsubei A, Hijazi ZM. Transcatheter Pulmonary Valve Replacement: Current State of Art. *Curr Cardiol Rep.* 2018;20(4):27. doi:10.1007/s11886-018-0966-y
7. Boethig D, Thies W, Hecker H, Breymann T. Mid term course after pediatric right ventricular outflow tract reconstruction: a comparison of homografts, porcine xenografts and Contegras. *European Journal of Cardio-Thoracic Surgery.* 2005;27(1):58-66. doi:10.1016/j.ejcts.2004.09.009
8. Poynter JA, Eghtesady P, McCrindle BW, et al. Association of Pulmonary Conduit Type and Size With Durability in Infants and Young Children. *The Annals of Thoracic Surgery.* 2013;96(5):1695-1702. doi:10.1016/j.athoracsur.2013.05.074
9. Belli E, Salihoğlu E, Leobon B, et al. The Performance of Hancock Porcine-Valved Dacron Conduit for Right Ventricular Outflow Tract Reconstruction. *The Annals of Thoracic Surgery.* 2010;89(1):152-158. doi:10.1016/j.athoracsur.2009.09.046
10. Manavitehrani I, Ebrahimi P, Yang I, et al. Current Challenges and Emergent Technologies for Manufacturing Artificial Right Ventricle to Pulmonary Artery (RV-PA) Cardiac Conduits. *Cardiovasc Eng Tech.* 2019;10(2):205-215. doi:10.1007/s13239-019-00406-5
11. Wells WJ, Arroyo H, Bremner RM, Wood J, Starnes VA. Homograft conduit failure in infants is not due to somatic outgrowth. *The Journal of Thoracic and Cardiovascular Surgery.* 2002;124(1):88-96. doi:10.1067/mtc.2002.121158
12. Mokhles MM, van de Woestijne PC, de Jong PL, et al. Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit☆☆☆.

European Journal of Cardio-Thoracic Surgery. Published online December 4, 2010;S1010794010008869. doi:10.1016/j.ejcts.2010.10.023

13. Karamlou T, Blackstone EH, Hawkins JA, et al. Can pulmonary conduit dysfunction and failure be reduced in infants and children less than age 2 years at initial implantation? *The Journal of Thoracic and Cardiovascular Surgery*. 2006;132(4):829-838.e5. doi:10.1016/j.jtcvs.2006.06.034
14. Lewis MJ, Malm T, Hallbergson A, et al. Long-Term Follow-Up of Right Ventricle to Pulmonary Artery Biologic Valved Conduits Used in Pediatric Congenital Heart Surgery. *Pediatr Cardiol*. 2023;44(1):102-115. doi:10.1007/s00246-022-02956-3
15. Thuraisingam A, Skillington P, Ludhani P, et al. Long-term outcomes of right ventricle-to-pulmonary artery conduit insertion in adults with congenital heart disease: survival analysis by National Death Index. *European Journal of Cardio-Thoracic Surgery*. 2021;60(4):939-946. doi:10.1093/ejcts/ezab148
16. Buber J, Assenza GE, Huang A, et al. Durability of large diameter right ventricular outflow tract conduits in adults with congenital heart disease. *International Journal of Cardiology*. 2014;175(3):455-463. doi:10.1016/j.ijcard.2014.06.023
17. Shinkawa T, Chipman C, Bozzay T, Tang X, Gossett JM, Imamura M. Outcome of Right Ventricle to Pulmonary Artery Conduit for Biventricular Repair. *The Annals of Thoracic Surgery*. 2015;99(4):1357-1366. doi:10.1016/j.athoracsur.2014.07.095
18. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the Evaluation of Valvular Regurgitation After Percutaneous Valve Repair or Replacement. *Journal of the American Society of Echocardiography*. 2019;32(4):431-475. doi:10.1016/j.echo.2019.01.003
19. Egidy Assenza G, Krieger EV, Baumgartner H, et al. AHA/ACC vs ESC Guidelines for Management of Adults With Congenital Heart Disease. *Journal of the American College of Cardiology*. 2021;78(19):1904-1918. doi:10.1016/j.jacc.2021.09.010
20. Feltes TF, Bacha E, Beekman RH, et al. Indications for Cardiac Catheterization and Intervention in Pediatric Cardiac Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2011;123(22):2607-2652. doi:10.1161/CIR.0b013e31821b1f10
21. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease. *Journal of the American College of Cardiology*. 2019;73(12):e81-e192. doi:10.1016/j.jacc.2018.08.1029
22. Backer JD, Babu-Narayan SV, Budts W, et al. The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC).
23. Ansari MM, Cardoso R, Garcia D, et al. Percutaneous Pulmonary Valve Implantation. *Journal of the American College of Cardiology*. 2015;66(20):2246-2255. doi:10.1016/j.jacc.2015.09.055
24. Mastropietro CW, Amula V, Sassalos P, et al. Characteristics and operative outcomes for children undergoing repair of truncus arteriosus: A contemporary multicenter analysis. *The Journal of Thoracic and Cardiovascular Surgery*. 2019;157(6):2386-2398.e4. doi:10.1016/j.jtcvs.2018.12.115

25. Rebollal-Leal F, Felipe-Abella R, Gutierrez-García F, A. Mestres C, Bautista-Hernandez V. Prosthetic pulmonary valve and conduit endocarditis in congenital heart disease. *Asian Cardiovasc Thorac Ann.* 2019;27(4):265-270. doi:10.1177/0218492319832769
26. Beckerman Z, De León LE, Zea-Vera R, Mery CM, Fraser CD. High incidence of late infective endocarditis in bovine jugular vein valved conduits. *The Journal of Thoracic and Cardiovascular Surgery.* 2018;156(2):728-734.e2. doi:10.1016/j.jtcvs.2018.03.156
27. Herrmann JL, Larson EE, Mastropietro CW, et al. Right Ventricular Outflow Tract Reconstruction in Infant Truncus Arteriosus: A 37-year Experience. *The Annals of Thoracic Surgery.* 2020;110(2):630-637. doi:10.1016/j.athoracsur.2019.11.023
28. Hoekstra F, Knoop C, Vaessen L, et al. Donor-specific cellular immune response against human cardiac valve allografts. *The Journal of Thoracic and Cardiovascular Surgery.* 1996;112(2):281-286. doi:10.1016/S0022-5223(96)70250-7
29. Hawkins JA, Breinholt JP, Lambert LM, et al. Class I and class II anti-hla antibodies after implantation of cryopreserved allograft material in pediatric patients. *The Journal of Thoracic and Cardiovascular Surgery.* 2000;119(2):324-330. doi:10.1016/S0022-5223(00)70188-7
30. El-Hamamsy I, Zaki M, Stevens LM, et al. Rate of Progression and Functional Significance of Aortic Root Calcification After Homograft Versus Freestyle Aortic Root Replacement. *Circulation.* 2009;120(11_suppl_1). doi:10.1161/CIRCULATIONAHA.108.843748
31. Selcuk A, Kilic Y, Korun O et al. High incidence of fever in patients after biointegral pulmonic valved conduit implantation. *J Card Surg* 2021;36:3147-3152.
32. Tiete AR, Sachweh JS, Roemer U, Kozlik-Feldmann R, Reichart B, Daebritz SH. Right ventricular outflow tract reconstruction with the Contegra bovine jugular vein conduit: a word of caution. *The Annals of Thoracic Surgery.* 2004;77(6):2151-2156. doi:10.1016/j.athoracsur.2003.12.068