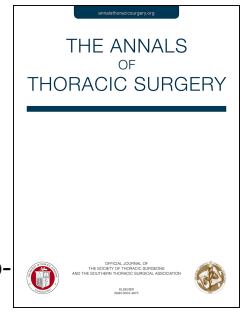

Predictive Factors for Pulmonary Homograft Dysfunction After Ross Surgery: A 20-year Follow-up

Azahara Fernández-Carbonell, MD, Enrique Rodríguez-Guerrero, MD, Carlos Merino-Cejas, MD, PhD, M Teresa Conejero-Jurado, MD, Rafael Villalba-Montoro, MD, PhD, M Carmen Romero-Morales, Pedro Alados-Arboledas, MD, PhD, Jaime Casares-Mediavilla, MD, Marta Fernández-Carbonell, Pedro López-Cillero, MD, PhD, José Rafael Caro-Barrera, PhD

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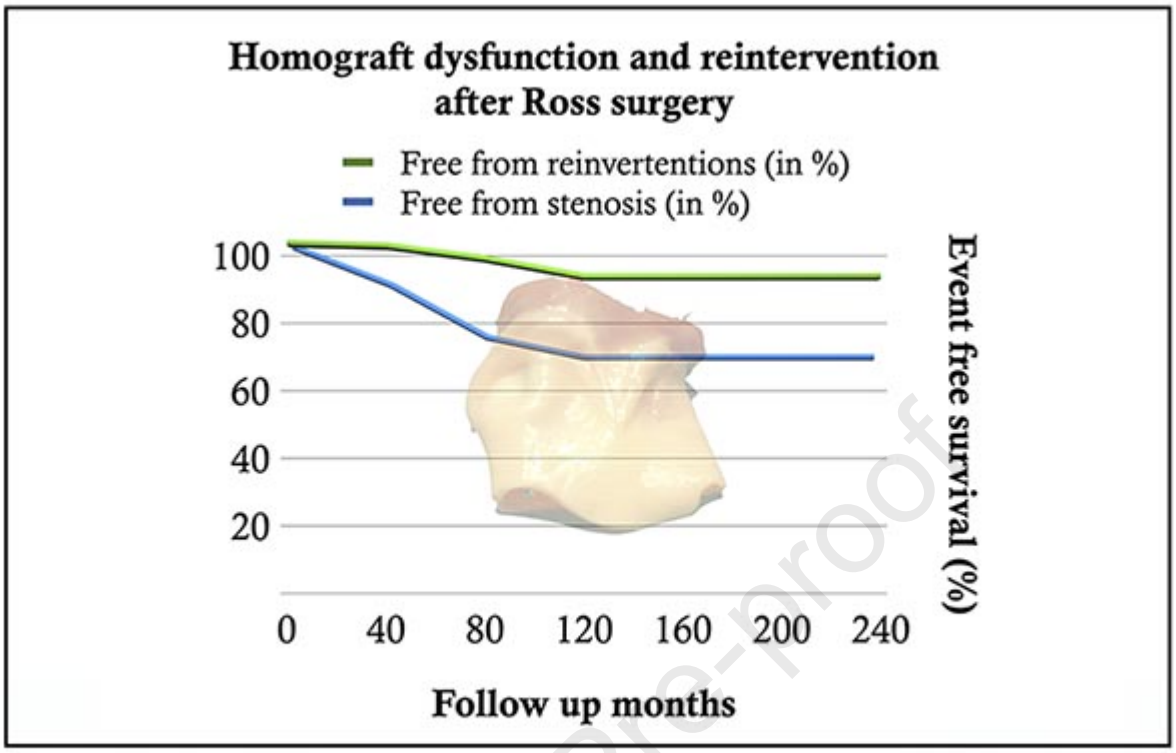

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Predictive Factors for Pulmonary Homograft Dysfunction After Ross Surgery: A 20-year Follow-up

Running head: Findings from a Single Institution

Azahara Fernández-Carbonell, MD[a*]; Enrique Rodríguez-Guerrero, MD[b]; Carlos Merino-Cejas, MD, PhD[a]; Mª Teresa Conejero-Jurado, MD[a]; Rafael Villalba-Montoro, MD, PhD[c]; Mª Carmen Romero-Morales[a]; Pedro Alados-Arboledas, MD, PhD[a]; Jaime Casares-Mediavilla, MD[a]; Marta Fernández-Carbonell[d]; Pedro López-Cillero, MD, PhD[e]; José Rafael Caro-Barrera, PhD[f].

[a] *Department of Cardiovascular Surgery, Reina Sofía University Hospital, Córdoba, Spain.*

[b] *Family and Community Medical Service, Clinic of Lucena, Córdoba, Spain.*

[c] *Regional Blood Transfusion Center and Tissue Bank. Reina Sofía University Hospital, Córdoba, Spain.*

[d] *Salud Responde (Public Health Emergencies Company, Counseling of Health and Families), Jaén, Spain.*

[e] *Hepatobiliary Surgery and Liver Transplant Service, Reina Sofía University Hospital, Córdoba, Spain.*

[f] *Department of Statistics, Econometrics and Operational Research, University of Córdoba, Spain.*

* Corresponding Author: Azahara Fernández-Carbonell, Avda. Andalucía nº 30 1º A, 18014, Granada, Spain. e-mail: *azasa89@hotmail.com*

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Abstract

Background: We studied the determinants of hemodynamics and analyzed the incidence, risk factors, and clinical impact of pulmonary homograft dysfunction following Ross surgery, after a 20-year follow-up at our referral center.

Methods: From 1997 to 2017, a total of 142 patients underwent surgery using the Ross procedure. The development of moderate-severe stenosis (peak transhomograft pressure gradient ≥ 36 mmHg), and surgical and/or percutaneous Ross homograft reinterventions, were evaluated by echocardiography in the immediate postoperative period and at annual intervals.

Results: After 20 years of follow-up, 31% of patients had developed moderate-severe homograft stenosis, and 9.1% had had to undergo one or two reinterventions, of which, six were valve replacements, and seven were percutaneous interventions. At 1, 5, and 20 years, 89.4%, 74.6%, and 69% of these patients, respectively, were free from moderate-severe stenosis, and 99.3%, 95.7%, and 90.9%, respectively, had freedom from homograft reintervention. The pediatric group had a higher risk factor for homograft stenosis (hazard ratio [HR]:3.70; 95% confidence interval [CI]:1.56-7.20, *p*= 0.002), while donor age behaved as a protective factor (HR:0.98; 95%CI: 0.95-0.99, *p*= 0.044). Pulmonary homograft stenosis tended to appear in the first year (10.6%) or at 5 years (25.4%).

Conclusions: Pulmonary homografts implanted in the Ross procedure offer satisfactory long-term results, but the level of homograft dysfunction is not negligible. Young recipient and donor age were associated with a higher rate of homograft stenosis during follow-up. Moreover, homograft dysfunction usually occurred during the first few years of follow-up, which may have been related to immune responses.

Despite continuous technological advances, the ideal prosthesis for human heart valve replacements has not yet been developed. However, since 1967, the Ross procedure[1] has proven to be a valuable alternative to aortic valve replacement in children and young adults. Autografts such as the Ross procedure have excellent hemodynamic characteristics, growth capacity, a low incidence of thromboembolic events, do not require anticoagulant treatments, and are very resistant to the appearance of endocarditis. Therefore, the use of pulmonary autografts in leading centers of expertise has become a more common alternative in the management of aortic valve disease, especially in children, women of childbearing age, and young patients, albeit with an implicit learning curve.[2–3]

However, in recent years, increasing attention has focused on the dysfunction and hemodynamic complications associated with these interventions in both the immediate and late postoperative periods. One of the most common complications in this setting is pulmonary homograft stenosis (PHS), which can appear during follow-ups in patients who underwent the Ross procedure. To date, very few echocardiographic studies examining the occurrence of pulmonary homograft dysfunction have been published. However, substantial research showing excellent long-term survival, the absence of reinterventions, and a high patient quality of life has been published.[4–5]

Here, we analyzed the incidence and clinical impact of pulmonary homograft dysfunction in patients who had undergone the Ross procedure at our center during their follow-ups over 20 years. We considered three main elements in this study: the appearance of PHS, the need for reintervention(s), and possible predictive factors associated with these complications.

Patients and Methods

This study was approved by the Regional Biomedical Research Ethics Committee in Andalusia, Spain. Patient consent was not required for this study because of its retrospective design.

Study Design

It was an observational, descriptive, longitudinal, and retrospective study of 142 patients who underwent the Ross procedure at our center from 1997 to November 2017, inclusive. We excluded patients who underwent the Ross-Konno procedure in order to avoid the potential effects of right ventricular outflow (RVOT) distortion on the homograft function outcomes measured. We recorded adverse events related to pulmonary homografts, such as pulmonary homograft regurgitation (PR), PHS, and/or the need for reintervention(s) during the follow-up interval.

Because of the low rate and degree of PR that appeared in this series, we decided to focus our analysis only on PHS. According to the 2006 American College of Cardiology and American Heart Association guidelines[6], stenosis homograft dysfunction with a transhomograft pressure gradient ($TPG_{peak} \geq 36$ mmHg) is considered equivalent to a moderate-severe stenosis.

We considered homograft replacements, as well as percutaneous interventions (valvuloplasty, stent placements, or percutaneous implantation of Melody pulmonary valves) as reinterventions. The indications for reintervention included significant homograft functional impairment with symptomatic worsening (functional class > II) and/or an objective worsening of right ventricular function versus progressive dilation of the right ventricle. Another possible indication was infective endocarditis refractory to medical treatment.

In the reintervention, we used the percutaneous valve implant as the first-choice procedure, except in cases of inadequate homograft size or when there was insufficient distance between the homograft and the left coronary artery.

Surgical Ross Technique

The procedure was carried out according to the technique described by Donald Ross and published at the end of the 1980s by Stelzer et al.[7], using the autograft as a free root.

The RVOT was reconstructed in every case by using a pulmonary homograft cryopreserved in liquid nitrogen at −196°C that had been treated at the Sectorial Tissue Bank Institution following the standards established by the Spanish Association of Tissue Banks.[8] Human leukocyte antigen (HLA) typing and ABO compatibility were not performed for logistical reasons.

The diameter of the homograft was selected based on a theoretical range determined using the patient body surface area (established in the tables commonly used in cardiovascular surgery), with an oversized Z-score < 3, except in the pediatric group, where we usually implanted homografts with a higher size Z-score to try to compensate for the natural growth of these patients. All our patients were postoperatively treated with low-dose aspirin.

Echocardiographic Measurements

After surgery, all the patients were clinically followed-up, and echocardiography was performed in our center in the immediate postoperative period and at annual intervals by cardiologists and the cardiovascular surgeon responsible for each case. An identical echocardiography protocol was used to study the structure and function of the pulmonary homograft in all the cases using an Acuson Sequoia 256® cardiac ultrasound machine (Siemens, Mountain View, CA, USA) and an iE33® ultrasound system (Philips, Amsterdam, The Netherlands). Among other data collected, the valvular structure and function were evaluated with two-dimensional and Doppler echocardiography. The peak and average pressure gradients, size of the pulmonary annulus, and the size and function of the right ventricle were measured using the transvalvular flow rate by applying the modified Bernoulli formula.[9]

Statistical Analysis

The data were analyzed using SPSS® software (version 25; IBM Corp., Armonk, NY), and all the measurements were expressed as the mean ± standard deviation. We used χ^2 tests, Fisher exact tests, and Student's *t*-tests for the univariate analyses, and demographic and preoperative or postoperative data were compared between the groups using unpaired *t*-tests. *P*-statistic values < 0.05

were considered significant, with 95% confidence intervals and with a statistical power of 80%. Possible determinants of PHS were assessed using a multiple logistical regression model. Finally, we used Kaplan-Meier analysis to represent the probability of freedom from stenosis or homograft reinterventions at several time points during the 20-year follow-up.

Results

Preoperative Patient Characteristics

As shown in **Table 1**, from 1997 to November 2017, a total of 142 patients underwent the Ross procedure at our center: 98 male (69%) and 44 female (31%). Of the overall sample, 32 (22.5%) were children aged under 16 years (according to standardized criteria used in the pediatric area at our center).

Follow-up

After 20 years of follow-up (median 15 y; range: 11–17 y), a total of three deaths had been recorded in our series. One was an intraoperative death in a pediatric patient with a complex congenital heart disease (severe aortic stenosis and coarctation of the aorta), another died after reintervention of the autograft for a pseudoaneurysm, and the third patient died due to extrinsic compression of the left coronary artery during stent implantation over the homograft. A total of 31% of patients had developed moderate-severe PHS by the end of the follow-up. The appearance of pulmonary stenosis generally occurred in the first few postoperative years: 10.6% in year 1, and 25.4% in year 5 **(Figure 1)**. Regarding the homograft reinterventions, 13 patients (9.1%) had had to undergo one (n = 8) or two reinterventions (n = 5), of which 6 (46.1%) were valve replacements and 7 (53.8%) were percutaneous interventions. One of these patients required homograft replacement due to endocarditis, which had been refractory to medical treatment.

The rate of freedom from the occurrence of moderate-severe PHS was 89.4% at the first follow-up in year 1, 74.6% at 5 years, and 69% by the 20-year follow-up **(Figure 2A)**. When

separated by age groups, 75.4% of adults versus 47% in the pediatric group were free from moderate-severe PHS at the last follow-up **(Figure 2B)**. In years 1, 5, and 20, 99%, 95.7%, and 90.9% of the patients, respectively, had freedom from homograft reintervention **(Figure 2C)**. When separated by age groups, 92.7% of adults compared to 84.4% of the pediatric group had remained reintervention free by the last follow-up at 20 years **(Figure 2D)**. Only 7% of patients had developed PR > grade 2, but they had freedom from any reinterventions for this reason. All the surviving patients were classified as functional class I, and 14.5% of cases, with severe pulmonary stenosis, remain under close clinical surveillance.

Univariate Analysis

In the univariate risk analysis in **Table 2**, the pediatric age of the homograft recipient behaved as a risk factor both when expressed either as continuous or dichotomous values. Moreover, the pediatric group had a higher risk of homograft stenosis (hazard ratio [HR]: 3.70; 95% confidence interval [CI]: 1.56-7.20, $p = 0.002$), while the donor age was a protective factor (HR: 0.98; 95%CI: 0.95-0.99, $p = 0.044$). A history of previous surgeries and modified homograft techniques also tended to be associated with the development of moderate-severe PHS, but these factors did not reach statistical significance. Other variables such as recipient sex, donor sex, freezing time, and the use of blood products were not significantly associated with the development of moderate-severe PHS during the patient follow-up.

Probabilistic Analysis

The risk of developing moderate-severe PHS or requiring reintervention over time was higher during the first 5 years post-surgery but significantly decreased after 10 years of follow-up **(Figures 3A** and **3B)**. When we analyzed our data by age group, the probability of freedom from moderate-severe PHS at 1 year, 5 years, and 15 years, was 99%, 95%, and 74% in adults and 95%, 80%, and 44% in children, respectively, $p = 0.0045$ **(Figure 3C)**. The probability of freedom from reintervention during the 20-year follow-up was higher in the adult group than in the pediatric group but was not statistically significant ($p = 0.25$) **(Figure 3D)**.

Discussion

The most frequent pulmonary homograft complication after the Ross procedure was stenosis. In our series, 31% of our patients developed moderate-severe PHS, and 9.1% had to undergo one or more surgical or percutaneous reinterventions over a 20-year follow-up period. In terms of remaining stenosis free during the 20-year follow-up, our results were similar to those already reported in the literature[4,10]. Nonetheless, some studies such as that by Mokles et al.[11], which included 1,624 patients, report higher rates of remaining PHS-free, perhaps because of differences such as the inclusion of patients aged over 16 years and the use of an average follow-up period of 5.5 years. In another study by David et al.[12], of the 212 patients included, 25 had developed a pulmonary homograft dysfunction over a 20-year follow-up, but only 8 had been re-operated. Other series have shown 10-20-year reintervention-free rates ranging from 92% to 95% [4-5,13-14].

There seems to be a non-linear propensity for the development of PHS over time; patients appear to have a higher probability of developing moderate-severe stenosis during the first few post-surgery months or years, which could indicate the involvement of host reactions against the homograft in the immediate postoperative period.[10] In our sample, most homograft dysfunction occurred within the first 5 years (10.6% in year 1 and 25.4% in year 5), compared to 31% by the end of the follow-up. As shown in our previous work[15], immune mechanisms predominate during this period, which points to possible involvement in the development of the PHS. Interestingly, Travelli et al.[16] reported evidence for the increased durability of pulmonary homografts when ibuprofen prophylaxis was administered. Similarly, Andrew et al.[17], showed excellent results by treating pulmonary homograft patients with ibuprofen postoperatively and then transitioning them to lifetime aspirin. Therefore, it appears that the anti-inflammatory effect of aspirin use in these patients contributes to homograft durability. These studies indicate that after an initial phase of homograft dysfunction, cases of PHS and reintervention stabilize, with no apparent homograft deterioration caused by long-term degenerative effects when prophylactic aspirin is used.

Very few studies have found a relationship between immune discordance and homograft stenosis, so the need for typing remains controversial. Indeed, for logistical reasons, we did not perform HLA typing and ABO compatibility tests in our series. However, any viable cells capable of expressing surface antigens remaining in the grafts would have triggered a systemic immune response against the receptor HLA antigens in the recipients[18-19], and so, when available, we tried to use ABO-compatible homografts.

Another predictive factor, recipient age, was significantly associated with the development of homograft stenosis during the follow-ups. The risk of stenosis was more than three times higher in the pediatric group than in the adult group. However, the pediatric group did not have a significantly higher risk of requiring reintervention. In our series, the reduction in homograft diameter was higher in the pediatric group (about 23.1%) during the first post-intervention year compared to the 12.3% reduction observed in adult homograft patients ($p < 0.005$).

Young donor age also behaved as a risk factor for reintervention and early dysfunction, while homografts from older donors showed a lower TPG_{peak} during follow-up. Similar results were reported in studies such as those by Kalfa et al.[20] and Hörer et al.[21]. It may be because the tissues from younger donors are more viable, which could cause a more robust recipient immune response. Thus, the use of homografts from older donors should be considered in the future for the Ross procedure.

We used a modified technique (adventitia resection and reduction of the muscle skirt) to prepare the homografts we used in the patients from the last few years included in this study. However, the differences in the results we obtained for these patients were not statistically significant ($p = 0.067$), and we observed a tendency towards a decreased incidence of homograft dysfunction in more recently operated patients. Nonetheless, Nordmeyer et al.[22] reported that the use of this surgical technique determined pulmonary homograft complications in their study.

In our center, we systematically implanted oversized homografts concerning the recipient. Only four patients received a homograft with a diameter of less than 22 mm. We did not observe any association between the size of the homograft and the evolution to PHS, although there was some linear association in terms of size. A recent study by Oeser et al.[23] which included 274 patients followed-up for 25 years, showed similar rates of freedom from stenosis and reintervention, as well as dysfunction predictors, as those in the sample we describe here, with the use of oversized grafts being a protective factor for the appearance of stenosis. The study by Razzouk et al.[24] concluded that homograft sizes exceeding 24 mm had higher rates of freedom from reintervention, while the study by Karamlou et al.[25] concluded that the implantation of an oversized homograft had no benefit. Of note, Kalfa et al[26]. showed that small graft sizes (less than 22 mm) were a possible risk factor for pulmonary homograft dysfunction. Likewise, in a study of 75 patients by Lenzi et al.[27], a homograft size of less than 21 mm and a pulmonary homograft Z-score of < 0 mm or > 3 mm, were considered risk factors. Thus, given the disparity of the results currently available in the literature, future research should be designed to study this aspect in more detail.

A recent publication by Pardo et al.[28], which followed up 107 patients for 15 years, concluded that the use of blood products was not significantly associated with homograft dysfunction. It contrasts with our previous work carried out in a group of 76 patients for a mean of 27 months, which indicated that the use of blood products in the perioperative period was higher in the group with pulmonary stenosis[15]. However, the results we obtained in this current study, which had both a more extended follow-up period and a larger sample size, differ from our previous findings because here, we did not find any association between the use of blood products and homograft stenosis. Thus, more work will be required to clarify this situation.

Finally, in our center, we continue to use cryopreserved homografts. No previous studies have shown the superiority of new substitutes such as bovine jugular vein grafts over cryopreserved homografts. Indeed, in a study including 379 patients carried out over 12 years, Ugaki et al. concluded that the use of bovine jugular vein conduit for RVOT reconstruction was associated with a

significantly higher incidence of bacterial endocarditis and conduit deterioration as a late complication.[29]

Study Limitations

There are limits to the ways this data can be interpreted because it was a single-center observational study and so the sample size was smaller than other series, and, as a result, its statistical power was more limited. Also, the low incidence of events, especially reinterventions, prevented us from drawing definitive conclusions about our analyses of possible stenosis or reintervention predictors. Similarly, the results from our Kaplan-Meier estimations for survival and freedom from pulmonary homograft reintervention over a 20-year follow-up should be interpreted with caution because relatively few patients were at risk, especially in the pediatric group.

Comment

Although this sample was relatively small, here we provide our long-term follow-up experiences from a pioneering Spanish center of excellence. We believe that the advantages of using pulmonary autografts to treat aortic valve disease, in appropriately selected patients and at an experienced center, outweigh the disadvantages derived from the procedure itself.

Pulmonary homografts carried out using the Ross procedure continue to offer satisfactory long-term results, but homograft dysfunction is not negligible, with moderate-severe stenosis and reintervention rates at 20 years of 31% and 9.1%, respectively. Young recipient or donor age was associated with a higher rate of homograft stenosis during follow-up. Moreover, homograft dysfunction occurred significantly more often during the first few years of follow-up, which may be related to immune responses. Future work should focus on the separate analysis of larger cohorts of pediatric and adult patients in order to improve the robustness of the univariate analyses.

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Table 1. Baseline characteristics of patients undergoing the Ross procedure

	Total *(n = 142)*	**Adults** *(n = 110)*	**Pediatric (aged <16 years)** *(n = 32)*
Recipient age (years)	28±11.8 [3-51]	32.9±8.6 [17-51]	11.8±3.8 [3-16]
Recipient sex			
Male	98(69)	77(70)	21(65.6)
Female	44(31)	33(30)	11(34.4)
Congenital etiology	91(64)	59(53.6)	32(100)
Previous cardiac surgery	34(24)	19(17.3)	15(46.9)
Donor age(years)	42.8±13.1 [15-69]	44.3±12.1 [16-69]	37.4±15.3 [15-54]
Donor sex n=127			
Male	81(64)	67(67)	14(51.9)
Female	46(36)	33(33)	13(48.1)
Pulmonary annulus(mm)	21.6±3.9	23.1±2.4	16.6±4.1
Freezing time(months)	6.9±8.8 [0.2-56.7]	6.7±9.5 [0.9-54.2]	7.3 ±10.4 [0.2-56.7]
Homograft size(mm)	25.5±2.8 [16-32]	26± 2.6 [22-32]	23.5±3 [16-32]

Data are expressed as frequency (%) or mean ± standard deviation.

Table 2. Cox proportional hazards regression for homograft dysfunction. Univariate predictors for homograft dysfunction (peak transhomograft pressure gradient ≥ 36 mm Hg)

	Rate of outcomes			HR (95%CI)	*P*
	Present[a]	Absent[a]	*P*		
Recipient age (years)				0.96(0.92-0.99)	0.03
Pediatric group (< 16 years)	13/32(40)	29/112(26)	0.0045	3.70(1.56-7.20)	0.002
Donor age(years)				0.98(0.95-0.99)	0.044
Previous cardiac surgery	13/15(86)	19/127(20)	0.091	2.22(0.93-5.05)	0.07
Recipient sex: male	23/71(32)	7/27(26)	0.42	1.45(0.53-3.45)	0.50
Homograft size (mm)				0.92(0.77-1.12)	0.45
Donor sex: male	30/51(58)	46/79(59)	0.38	0.72(0.35-1.55)	0.40
Freezing time (months)				1.16(0.70-1.90)	0.60
Modified homograft technique				2.50(0.06-3.07)	0.067
Use of blood products					
Plasma (units)				1.05(0.98-1.09)	0.22
Platelets (units)				1.01(0.98-1.04)	0.93
Erythrocytes (units)				1.02(0.96-1.08)	0.49
Total blood products (units)				1.00(0.99-1.01)	0.71

CI: confidence interval; HR: hazard ratio; a. Data are expressed as *n*/*n* (%).

Figure Legends

Figure 1. Evolution of the percentage of patients who developed moderate-severe PHS. PHS: pulmonary homograft stenosis.

Figure 2: Kaplan-Meyer analysis of freedom from moderate-severe stenosis ($TPG_{peak} \geq$ 36 mmHg) and freedom from pulmonary homograft reintervention (surgical or percutaneous). **A:** Moderate-severe PHS freedom of the total series. **B:** Freedom from moderate-severe PHS by age groups. **C:** Freedom from reintervention of the total series homograft. **D:** Freedom from reintervention of the homograft by age groups. PHS: Pulmonary homograft stenosis. TPG: Transhomograft pressure gradient.

Figure 3. Risk model for homograft dysfunction and reintervention (surgical or percutaneous) after the Ross procedure. **A:** Probability of moderate-severe PHS freedom. **B:** Probability of homograft reintervention freedom. **C:** Probability of moderate-severe PHS freedom by age groups. **D**: Probability of homograft reintervention freedom by age group. PHS: Pulmonary homograft stenosis.