Pulmonary position cryopreserved homograft in non-Ross patients: how to improve the results?†

David M. Kalfa*, Anderson Loundou†, Yveline Nouaille de Gorce‡, Alain Fraisse§, Dominique R. Metrasa,
Loïc Macé and Bernard Kreitmann†

* Department of Cardiac and Thoracic Surgery, La Timone Children’s Hospital, Marseille, France
† Department of Public Health, Medicine University, Marseille, France
‡ Tissue Bank, Etablissement Français du Sang, Marseille, France
§ Department of Paediatric Cardiology, La Timone Children’s Hospital, Marseille, France

† Corresponding author. Department of Pediatric Cardiac Surgery, Marie Lannelongue Hospital, 133 Av. De la Résistance, 92350 Le Plessis Robinson, France.
Tel: +33-6-17091488; fax: +33-1-40948562; e-mail: davidkalfa@gmail.com (D.M. Kalfa).

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Abstract

OBJECTIVES: The outcomes of homografts (HGs) in the reconstruction of the right ventricular outflow tract (RVOT) in non-Ross patients are often considered disappointing, compared with Ross patients; and the risk factors for HG degeneration are still controversial. The objective of this study was to determine the durability and prognostic factors related to the HGs implanted in non-Ross patients and to propose potential ways to improve the results.

METHODS: A retrospective study (1993–2010) included 115 consecutive non-Ross patients who received a HG for RVOT reconstruction. The median age at implantation was 2.8 years (4 days–58 years). The main heart defects were pulmonary atresia with ventricular septal defect (n = 40; 34%), truncus arteriosus (n = 28; 24%) and tetralogy of Fallot (n = 23; 20%). Thirty-eight percent had preoperative pulmonary hypertension. A low-dose corticosteroid therapy was used during the postoperative period in patients displaying a HG-related inflammatory response (no septic context) (n = 11). The median diameter of the implanted HG was 22 mm (range 9–30 mm). The median age of the HG donor was 14 years (range 0.5–65 years). ABO compatibility rules were not systematically respected for the HG implantation: 43% of the implanted HGs were ABO compatible with the recipient. The endpoints were HG stenosis (peak gradient ≥20 mmHg), regurgitation (moderate or severe), dysfunction (peak gradient ≥50 mmHg or regurgitation moderate or severe) and failure (explantation or balloon dilation).

RESULTS: Freedom from HG explantation and failure were 89 and 80% at 5 years, and 76 and 69% at 10 years, respectively. HG donor age <30 years [hazard ratio (HR): 2; P = 0.012], preoperative pulmonary hypertension (HR: 3; P = 0.02) and HG mismatch (HR: 5; P = 0.04) were multivariate risk factors for HG stenosis, regurgitation and failure, respectively. HG diameter <22 mm was a multivariate risk factor for HG regurgitation (HR: 8; P < 0.001), dysfunction (HR: 9; P = 0.02) and failure (HR: 5; P = 0.03). ABO incompatibility increased the risk of HG stenosis (HR: 4; P = 0.009) and dysfunction (HR: 2; P = 0.04). The use of corticosteroids significantly protected against the risk of HG regurgitation (HR: 0.08; P = 0.04) in the multivariate analysis.

CONCLUSIONS: The cryopreserved HG implanted to reconstruct the RVOT in non-Ross patients remains one of the most acceptable options in this specific non-Ross population. The outcomes of HGs in non-Ross patients might be improved by implanting an ABO-compatible HG with an adapted diameter, coming from a donor >30 years and by optimizing the perioperative afterload of the HG.

Keywords: Allograft/homograft • Congenital heart disease/valve • Paediatric • Statistics/regression analysis • Statistics/risk analysis

INTRODUCTION

‘Non-Ross’ patients undergoing the implantation of a cryopreserved homograft (HG) in the cases of complex right ventricular outflow tract (RVOT) obstruction display a shorter HG survival compared with Ross patients, independent of age. The heterotopic position of the implanted HG, associated with the risk of sternal compression and the use of smaller HGs in younger patients is the main factor that decreases HG durability in non-Ross patients [1–5]. Some non-Ross patient-centred series have described a poor performance of HGs in this specific population, identified too few independent risk factors for HG degeneration and have sometimes recommended not using an HG in this specific population [1]. A retrospective evaluation of our experience with the use of HGs in non-Ross patients for RVOT reconstruction was conducted to determine the durability of this
conduit in this specific heterogeneous population and to highlight as many risk factors for HG degeneration as possible in order to propose potential ways to improve the results of HG in this population.

**PATIENTS AND METHODS**

**Patient population**

A retrospective study (1993–2009) included 115 consecutive ‘non-Ross’ patients who underwent an HG implantation for RVOT reconstruction of the RVOT. Patients who were implanted outside our institution were excluded. The median age at implantation was 2.8 years (range 4 days–58 years). Thirty-six (31%) and 76 (66%) patients were younger than 1- and 10-years old, respectively. Fifty-two (45%) patients were male. The main heart defects were pulmonary atresia with ventricular septal defect (VSD) (n = 40; 34%), truncus arteriosus (n = 28; 24%), tetralogy of Fallot (n = 23; 20%), corrected transposition of great arteries (n = 8; 7%) and double-outlet right ventricles (RVs) (n = 6; 5%). The main types of surgery were repair of pulmonary atresia with VSD (n = 38; 33%), repair of truncus arteriosus (n = 21; 18%), replacement of a RVOT conduit (n = 14; 12%), pulmonary valve replacement after the repair of tetralogy of Fallot (n = 13; 11%) and the Rastelli procedure (n = 8; 7%). Sixty-seven percent of patients had a previous surgery before implantation of the HG. Thirty-eight percent had preoperative pulmonary hypertension (maximal PA pressure >30 mmHg). The study was approved by the institutional review board of the French Society of Thoracic and Cardio-Vascular Surgery.

**Homograft conservation**

After harvesting, the HGs were transported to the same local tissue bank at 2–10°C in the conservation medium [Roswell Park Memorial Institute nr. 1640, before June 2007, n = 108 patients (94%); Solution de Conservation d’Organes et de Tissus (SCOT) solution (MacoPharma®) as from July 2007, n = 7 patients (6%)]. They were then kept in antibiotic solution at 4°C for 4 h (before 1999), 14–18 h (as from 1999): the mean decontamination time was 10.6 ± 5.4 h. The delay between harvest and decontamination was 14–18 h (before 1999), 48–72 h (as from 1999). HGs were finally cryopreserved by gradual freezing up to −150°C and then kept in nitrogen vapour. The changes to this HG conservation protocol were included in the univariate and multivariate statistical analyses.

**Homograft characteristics**

The HG’s origin was pulmonary in 73 (64%) and aortic in 41 (36%) patients. The median diameter of the implanted HG was 22 mm (range 9–30 mm). ABO compatibility rules were not systematically respected for the HG implantation: 43% of the implanted HGs were ABO compatible with the recipient. The median age of the HG donor was 14 years (range 0.5–65 years). Seventy HGs (61%) derived from a donor younger than 30 years of age. All HGs came from beating donors: 35% from transplantation donors, 65% from brain-dead donors. Cold ischaemic time was defined as the interval between harvesting and cryopreservation (mean: 52 ± 24 h). Storage time was defined as the interval between cryopreservation and implantation (median: 14 months, range 1–132).

**Operative technique**

The HG was implanted with monofilament hemisutures for both distal and proximal anastomoses. A hood was added to complete the proximal anastomosis in 66% of cases (n = 76), and was most frequently made of an autologous pericardium treated with glutaraldehyde (n = 37; 49%), polytetrafluoroethylene (ePTFE) (n = 21; 28%) or equine pericardium (n = 11; 14%). HG oversizing was preferred in young patients. No HG was bicuspidized. There were no operative deaths during the primary procedure.

**Postoperative follow-up**

A low-dose corticosteroid therapy was used for 6 days during the postoperative period when the patients displayed a fever with a biological inflammatory reaction without any septic aetiology, which could be related to a HG-related immunological response.

Serial transthoracic echographic measurements (Hewlett-Packard Sonos 2500 System; Hewlett-Packard Co., Andover, MA, USA) were performed at discharge, and then yearly thereafter, by the same in-house cardiologist whenever possible. The maximum velocities across the pulmonary valve were calculated by a continuous-wave Doppler imaging transducer. To determine the pressure gradient, the Bernoulli equation was used. A semi-quantitative assessment (mild, moderate and severe) of HG regurgitation was based on the length and width of the regurgitant jet. The mean follow-up was 5.3 ± 0.5 years (median: 3.3 years; range 6 days–17.9 years) and was complete in 114 (99%) patients.

**Definitions**

The endpoints were HG stenosis (defined as an echographic peak gradient ≥20 mmHg, to detect early mild stenosis), HG regurgitation (moderate or severe), HG dysfunction (an echographic peak gradient ≥50 mmHg or regurgitation moderate or severe) and HG failure (requirement for HG explantation, percutaneous balloon dilation, percutaneous implantation of a pulmonary Melody© valve or HG-related death). A reintervention or percutaneous procedure was required when the right ventricular/left ventricular pressure ratio was >2/3, or when HG dysfunction occurred or when a moderate-to-severe HG regurgitation was associated with at least one of the following criteria: right ventricular end-diastolic volume (magnetic resonance) >150 ml/m², clinical symptoms, decreased exercise tolerance, ventricular arrhythmias and a moderate-to-severe tricuspid regurgitation.

**Statistical analysis**

Data analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). The data are expressed as mean and range. The cut-off of variables was defined using their distribution in the population: the cut-off of HG diameter (22 mm) was
the median of HG diameters. The comparison of percentages, means and medians was achieved with the χ² test or Fisher exact test for dichotomous variables, and the Student’s t-test or non-parametric Mann–Whitney U-test for continuous variables. The univariate analysis of time-related events was achieved with the log-rank test and the univariate Cox model, which allowed selecting the variables (P < 0.05) that were included in the multivariate analysis. The multivariate Cox regression analysis was performed as conditional backward stepwise proportional hazards regression (P-values were based on the log-rank test). The Kaplan–Meier product-limit and multivariate Cox regression methods were used for actuarial survival analysis and the analysis of freedom from the endpoints. The main adjustment factors for the multivariate analysis included the HG origin (pulmonary/aortic), the age and sex of the patient, HG diameter, period of surgery, sternal HG compression, surgeon, HG decontamination and storage times, protocol of HG conservation, distal pulmonary artery (PA) branch stenosis and preoperative pulmonary hypertension. For all tests, a P-value of <0.05 was considered significant.

RESULTS

Overall outcomes and actuarial dynamics of the implanted homograft

Overall patient survival is 82% at a maximal follow-up of 18 years. Twenty-one patients (pulmonary atresia with VSD, n = 11; truncus arteriosus, n = 5 and absent pulmonary valve syndrome, n = 5) died between 6 days and 7 years after the HG implantation, from HG-unrelated causes (haemodynamic failure, n = 10; respiratory failure, n = 5; vascular cerebral disease, n = 4 and chronic pulmonary hypertension, n = 2). Eleven (10%) patients were administered a low-dose of corticosteroids after the HG implantation, without any of the side effects of such a therapy.

An echographic peak gradient ≥20 mmHg occurred in 61% of patients (n = 70), with a mean time of 6.3 ± 0.4 years after the implantation. Regurgitation moderate or severe occurred less frequently (37%, n = 43) but earlier (mean time of appearance: 3.3 ± 4.1 years). Only two patients displayed a severe regurgitation. HG dysfunction occurred in 50% of cases (n = 57). HG dysfunction occurred in 63% of patients younger than 10-year old (n = 48/76) and 23% of older patients (n = 9/39) (P < 0.001).

HG failure occurred in 24 (21%) patients. Among them, 17 (15%) patients required a reoperation, 4.6 ± 4.3 years (mean) after implantation (without any previous percutaneous procedure in 13 cases; after a percutaneous procedure in four cases). These HG explantations were required because of an isolated HG stenosis in 12 cases, combined HG stenosis and regurgitation in four cases and endocarditis in one case. This patient with endocarditis benefited by the replacement of this HG by another HG, 10 months after implantation and is currently alive without any comorbidity. Among the 24 patients with HG failure, seven patients benefited by one or two percutaneous procedures without reoperation. The percutaneous procedures included balloon dilations without stenting (n = 5), balloon dilations with stenting of the HG (n = 6) and implantations of a percutaneous pulmonary Melody® valve (n = 2). All of the patients who suffered from a failure of the HG were younger than 17-years old at the time of implantation (P = 0.013).

Actuarial freedoms from HG stenosis, regurgitation, dysfunction, explantation and failure at 5 and 10 years after the implantation are summarized in Table 1, along with the median event-free survivals. Freedom from HG explantation and HG failure were 89 and 80% at 5 years, 76 and 69% at 10 years, respectively.

Ten years after implantation, the actuarial patient survival is 79% (Fig. 1A). Ten years after implantation, freedom from the explantation of an HG whose donor was younger than 30 years was only 38%, whereas more than 3/4 of the HGs derived from an older donor were still explantation-free after the same time interval (P < 0.001) (Fig. 1B).

The development of HG regurgitation is increased in the small conduits (<22 mm, P < 0.001, Fig. 2A). More than 80% of the HGs implanted in patients with the preoperative pulmonary hypertension were regurgitant at 10 years, versus <50% for patients without the preoperative pulmonary hypertension (P = 0.01, Fig. 2B). A mild HG regurgitation at discharge significantly increased the risk for HG regurgitation (P = 0.007, Fig. 2C).

The small conduits (<22 mm) developed an earlier dysfunction, compared with larger ones (P < 0.001, Fig. 3A). HG failure was significantly increased in the case of truncus arteriosus (P = 0.01, Fig. 3B). Freedom from HG failure at 5 years was 42% after implantation of a HG with a diameter mismatch (defined as a diameter <2 or >+2 standard deviation of the theoretical pulmonary annulus diameter) versus 83% for HG without a diameter mismatch (P = 0.004, Fig. 3C).

Risk factors for homograft stenosis, regurgitation, dysfunction and failure

The significant results of the univariate statistic analysis for HG stenosis, regurgitation, dysfunction and failure are presented in Table 2. The univariate risk factors were related to the characteristics of the HG, the patient, the cardiac defect and the surgical procedure.

The significant results of the multivariate statistic analysis are presented in Table 3. Multivariate risk factors for HG dysfunction were HG diameter <22 mm (HR = 9; P = 0.02), the recent 2001–09 period of implantation (HR = 3; P = 0.04), ABO
incompatibility (HR = 2; \( P = 0.04 \)) and HG regurgitation at 8 months (HR = 3; \( P = 0.03 \)). Multivariate risk factors for HG failure were HG diameter <22 mm (HR = 5; \( P = 0.03 \)), HG mismatch (HR = 5; \( P = 0.04 \)) and truncus arteriosus (HR = 4; \( P = 0.02 \)). A preoperative pulmonary hypertension was a risk factor for HG explantation in the multivariate analysis (HR = 8; \( P = 0.03 \)). HG donor age <30 years was a risk factor for HG stenosis in the multivariate analysis (HR = 2.3; \( P = 0.012 \)). The use of corticosteroids was significantly associated with a lower risk of HG regurgitation (HR = 0.08; \( P = 0.04 \)) in the multivariate analysis.

DISCUSSION

Despite high rates of stenosis, regurgitation and dysfunction, the cryopreserved HGs implanted to reconstruct the RVOT in non-Ross patients does not require a reintervention in more than 3/4 of cases at 10 years and thus remains one of the most acceptable options in this specific non-Ross population. Multivariate risk factors for HG degeneration in non-Ross patients include the young donor age, HG diameter mismatch, perioperative pulmonary hypertension, ABO incompatibility and the absence of a postoperative low-dose corticosteroid therapy. In the absence of an ideal RV-PA conduit, the use of HGs in non-Ross patients should not be discarded for the benefit of other conduits and their outcomes might further be improved by implanting an ABO-compatible HG with an adapted diameter, coming from a donor >30 years and by optimizing the perioperative HG afterload.

Some series in the literature often insist on the disappointing outcomes of the HG as a tool to reconstruct the RVOT in non-Ross patients, compared with Ross patients, especially in the youngest ones [1, 6–13]. Some authors sometimes recommend using an alternate conduit in this specific population [1] or techniques of repair that avoid the use of conduits [10]. But (i) actuarial freedoms from HG explantation and HG failure in our non-Ross patient-centered experience are actually excellent (89 and 80% at 5 years, 76 and 69% at 10 years, respectively) and compare favourably to other series of HG in this specific

Figure 1: (A) Survival after HG implantation in non-Ross patients. (B) Freedom from HG explantation.

Figure 2: (A) Freedom from homograft regurgitation (at least grade moderate). (B) Freedom from homograft regurgitation (at least grade moderate) with donor age >30 years. (C) Freedom from homograft regurgitation (at least grade moderate) with no preoperative pulmonary hypertension.

Figure 2: Freedom from HG regurgitation.
non-Ross population [1, 6, 7, 10, 11, 13]; (ii) in this specific indication, the cryopreserved HG compared well with the other conduits such as Hancock porcine-valved Dacron conduits [14, 15] and allow the implantation of a percutaneous pulmonary Melody© valve in a good way; (iii) the anatomical possibility of using the surgical techniques that avoid the use of conduits in non-Ross patients is unfortunately relatively rare. That’s why the use of HGs in non-Ross patients should not be discarded for the benefit of the other conduits and surgeons should further try to improve the outcomes of such a tool for RVOT reconstruction.

The multivariate Cox regression analysis of our experience highlighted potentially modifiable risk factors for HG degeneration in non-Ross patients, contrary to some other papers in the literature [6–8, 12]. These factors can be related to the HG by itself (donor age <30 years, diameter <22 mm, HG mismatch), to the patient (truncus arteriosus, preoperative pulmonary hypertension, small preoperative PA branches), to the HG–patient interaction (ABO incompatibility, the absence of use of corticosteroids) and to the surgery (the 2001–09 period of implantation).

In view of these significant prognostic factors, the outcomes of the HGs implanted to reconstruct the RVOT in non-Ross patients might be improved by the following means:

(i) Choosing an HG derived from a donor older than 30 years. The numerous studies identified an increasing HG donor age (>50, 55 or 65 years depending on the series) as a risk factor. However, more recent studies reported a significant association with young donor age (<30 or <5 years) [3, 16]. This significant association of a donor age <30 years with an increased risk of HG stenosis was demonstrated in the present non-Ross-centered series, as it was in a previously published paper studying the overall population including Ross and non-Ross patients in the same institution [17]. The cryopreserved HGs from younger donors might be more antigenic owing to the persistence of histocompatibility antigen expression or cell viability and thus more subject to immunological damage [18]. Nevertheless, there are currently no biological or immunological data allowing us to state that a younger donor-derived HG when treated identically to an adult donor-derived one displays more antigens on its surface.

(ii) Optimizing the HG afterload and the anatomy of PA branches during the perioperative period. Indeed, numerous univariate and multivariate risk factors for HG degeneration are related to an increased perioperative afterload for HGs or obstructive PA branches: preoperative pulmonary hypertension (maximal PA pressure >30 mmHg, \( P = 0.02 \)), preoperative RV pressure >40 mmHg (\( P = 0.003 \)), small PA branches (\( P = 0.02 \)), mechanical ventilation time >48 h (\( P = 0.01 \)), maximal PA pressure at discharge >39 mmHg (\( P = 0.02 \)), pulmonary hypertension 8 months after implantation (\( P = 0.01 \)). Moreover, the younger age at implantation, with a higher risk of pulmonary hypertension crisis, was previously reported in the literature as an independent risk factor for HG failure [15]. Thus, optimizing the HG afterload through an early surgical extensive plasty of the PA branches (even in the case of moderate stenosis) or peri-operative implantation of stents, before or during the implantation of a HG, might improve the durability of the HG, especially in the youngest patients.

(iii) Limiting the HG-related inflammatory and immunological responses by respecting ABO compatibility rules [9, 12]. Indeed, the recipients of the HG valves undergo donorspecific humoral and cell-mediated immune responses, which may play a role in the degeneration of HG [19, 20]. Legare \textit{et al.} [21] showed that in a rat model of allograft valve transplantation, the immune destruction is T-cell mediated. In this animal model, immune-modulatory therapies (cyclosporin and anti-integrin monoclonal antibodies) did prevent the allograft valve structural failure [22].

(iv) Using an HG with a diameter between a \(-2\) and \(+2\) \(z\)-score of theoretical pulmonary annulus diameter. This confirms

Figure 3: (A) Freedom from HG dysfunction. (B and C) Freedom from HG failure.
Direction of risk: each significant factor reported in this table increases the risk of the endpoint (when P < 0.05).

HG: homograft; LV: left ventricle; NS: non-significant; PA: pulmonary artery; RV: right ventricle.

| Table 2: Univariate analysis of risk factors for HG stenosis, regurgitation, dysfunction and failure |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Univariate analysis for                                      | HG stenosis (P-value)                                         | HG regurgitation (P-value)                                     | HG dysfunction (P-value)                                       | HG failure (P-value)                                           |
| Age at implantation <1 year                                   | <0.001                                                       | 0.001                                                       | 0.004                                                       | 0.03                                                         |
| Age at implantation <10 years                                 | <0.001                                                       | 0.001                                                       | 0.004                                                       | 0.03                                                         |
| Truncus arteriosus                                            | NS                                                           | NS                                                          | NS                                                          | 0.02                                                         |
| Preoperative RV pressure >40 mmHg                            | 0.005                                                        | 0.02                                                        | 0.003                                                       | NS                                                           |
| Preoperative pulmonary hypertension                           | NS                                                           | 0.01                                                        | 0.008                                                       | 0.006                                                        |
| Preoperative RV hypertrophy                                   | 0.04                                                         | 0.01                                                        | 0.01                                                        | NS                                                           |
| Small preoperative PA branches (diameter <7 mm)              | NS                                                           | 0.02                                                        | NS                                                          | NS                                                           |
| Use of a hood at the proximal anastomosis                    | 0.01                                                         | 0.01                                                        | <0.001                                                     | 0.006                                                        |
| Postoperative pulmonary complications                         | NS                                                           | 0.01                                                        | NS                                                          | NS                                                           |
| Absence of the postoperative use of corticosteroids           | NS                                                           | 0.02                                                        | NS                                                          | NS                                                           |
| Maximal PA pressure at discharge >39 mmHg                    | 0.02                                                         | NS                                                          | NS                                                          | NS                                                           |
| HG donor age <30 years                                        | 0.001                                                        | <0.001                                                     | 0.009                                                       | NS                                                           |
| HG diameter <22 mm                                            | 0.002                                                        | 0.002                                                       | 0.009                                                       | NS                                                           |
| Decontamination time <12 h                                   | 0.03                                                         | NS                                                          | NS                                                          | 0.04                                                         |
| Time between harvesting and decontamination <24 h            | 0.006                                                        | NS                                                          | NS                                                          | 0.01                                                         |
| Cold ischaemic time <2 days                                  | 0.003                                                        | NS                                                          | NS                                                          | NS                                                           |
| Storage time <14 months                                      | NS                                                           | 0.03                                                        | NS                                                          | NS                                                           |
| Aortic origin of the HG                                       | NS (0.17)                                                    | NS (0.7)                                                    | NS (0.6)                                                    | NS (0.8)                                                    |

HG: homograft; LV: left ventricle; NS: non-significant; PA: pulmonary artery; RV: right ventricle.

The immediate postoperative use of corticosteroids was significantly associated with a lower long-term risk of HG regurgitation (HR = 0.08; P = 0.04) in the multivariate analysis. Nevertheless, only 11 patients benefited from this therapy after HG implantation, and only during a short period (6 days). We would not recommend the clinical systematic use of corticoid after HG implantation, on the sole basis of this (yet multivariate) statistical analysis. The large prospective studies are needed to evaluate the real clinical impact of such a measure.

This study displays some limitations, related to its retrospective historical cohort nature and the small numbers of patients at risk after 10 years. Surprisingly, the multivariate analysis demonstrates that later year of implantation significantly increases the risk for HG regurgitation and dysfunction, as previously shown by Niwaya et al. [3] and Stark et al. [10]. This could be explained by the increased incidence of early degeneration of the HG implanted during the last years, related to the implantation of HG in younger and younger patients with more and more complex cardiac defects.

It is also surprising and interesting to note that the aortic origin of the HG does not fall out as a risk factor for HG failure in this specific non-Ross population, although it does in a previously published paper [17] studying the overall population including Ross and non-Ross patients in the same institution. In the same way, in the literature, the aortic origin of the HG was reported as a risk factor for HG degeneration in non-Ross population in only two papers [23, 24], and was not in 10 non-Ross patient-centred series [1, 6–13, 25], while it is a very
frequently reported prognostic factor in Ross patient-centred series.

Thus, the cryopreserved HG implanted to reconstruct the RVOT in non-Ross patients remains one of the most acceptable options in this specific population. Multivariate risk factors for degeneration of the HG in non-Ross patients are related to the HG, the patient, the HG–patient interaction, the surgery and the postoperative use of low-dose corticosteroids. The outcomes of HGs in non-Ross patients might be improved by choosing an ABO-compatible HG with an adapted diameter, coming from a donor >30 years and by controlling the increased pressure after-load of the HG during the perioperative period. Large prospective studies are needed to evaluate the real impact of such measures, including the use of a short 6-day low-dose corticosteroid therapy during the early postoperative period, on the outcomes of the cryopreserved HGs implanted in this specific non-Ross population.

**Conflict of interest:** none declared.

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