Primary graft failure after cardiac transplantation: prevalence, prognosis and risk factors

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Abstract

OBJECTIVES: Primary graft failure (PGF) is a common and devastating complication, despite the advances in perioperative treatment. We aim to evaluate the prevalence of PGF and its impact on survival and to explore associated risk factors.

METHODS: From November 2003 through December 2015, 290 patients submitted to cardiac transplantation were classified into non-PGF (243; 84%) and PGF (47; 16%) groups. The characteristics of the recipients were similar regarding age (54.6 ± 10.6 vs 54.0 ± 9.4 years; P = 0.74), male gender (78.2% vs 72.3%; P = 0.38) and transpulmonary gradient (9.4 ± 4.2 vs 10.5 ± 5.6 mmHg; P = 0.15); donors to the PGF group had similar age (35.5 ± 11.4 vs 37.5 ± 10.7 years; P = 0.27) but were predominantly female (21% vs 42.6%; P = 0.002).

RESULTS: Mean ischaemic (89.0 ± 36.8 vs 103.3 ± 44.7 min; P = 0.019) and cardiopulmonary bypass (92.8 ± 14.5 vs 126.3 ± 62.4 min; P < 0.001) times were longer in the PGF group. Length of hospital stay was 13.5 ± 7.5 vs 28.9 ± 35.2 days (P = 0.005). Hospital mortality was 4.1% [1.6% for non-PGF and 17% for PGF (P < 0.001)]. Survival at 1, 5 and 10 years was 95.5 ± 1.3% vs 55.3 ± 7.3%, 84.1 ± 2.5% vs 47.4 ± 7.6% and 67.1 ± 3.8% vs 14.4 ± 12%, respectively (P < 0.001). Risk factors for PGF were female donor [odds ratio (OR): 2.56; 95% confidence interval (CI): 1.29–5.09; P = 0.007], total ischaemic time (OR: 1.01; 95% CI: 1.00–1.02; P = 0.032) and preoperative mechanical extracorporeal circulatory support (OR: 11.90; 95% CI: 2.62–54.12; P = 0.001).

CONCLUSIONS: Our results demonstrate that PGF is associated with poor outcomes that extend beyond the 1st month and the 1st year after heart transplantation. We found female donor, total ischaemic time and preoperative mechanical extracorporeal circulatory support to be risk factors for PGF.

Keywords: Cardiac transplantation • Primary graft failure • Risk factors

INTRODUCTION

Early graft failure (EGF) occurs frequently in the immediate postoperative period following cardiac transplantation and is associated with significant morbidity and mortality.

The definition and limits of primary graft failure (PGF) have not been clearly defined, which reflects the wide discrepancies of reported incidences between 2.3% and 28.2%. PGF is most likely a result of multifactorial mechanisms with contributing elements from the donor, recipient and transplantation process [1]. Recent data from the International Society of Heart and Lung Transplantation (ISHLT) show an 8% mortality during the 1st month of post-transplantation, of which 39% is attributed to early graft dysfunction [2]. Furthermore, the high morbidity associated with graft dysfunction and its treatment significantly contributes to the increased mortality over the following months, generally attributed to infection or rejection. In fact, it is estimated that graft dysfunction is, directly or indirectly, associated with 40% of causes of death during the 1st year of post-transplantation [2].
filing pressures (pulmonary capillary wedge pressure, direct left atrial pressure >18 mmHg or central venous pressure >15 mmHg), requiring high-dose inotropic support (>15 μg/kg/min of dobutamine, >0.1 μg/kg/min of epinephrine or any association of inotropes), prolonged inotropic support beyond 48 h after transplantation or the need for mechanical circulatory support post-transplant. In the absence of an alloimmune response (hyperacute rejection), pulmonary hypertension and technical complications affecting the graft or sepsis, EGF was considered primary [3]. After the application of these definitions, 6 additional patients with EGF were excluded: 3 patients with right heart failure secondary to pulmonary hypertension, 2 with accelerated acute rejection and 1 with arrhythmogenic cardiomyopathy of the transplanted heart—all confirmed by necropsy study.

Patients were classified into a non-PGF group—243 (84%) patients—and a PGF group—047 (16%). Following the recent consensus of the definition of ISHLT and the exclusion criteria for PGF [1], these patients were classified into 3 grades based on hemodynamic parameters and left ventricular function. Mild or moderate PGF was considered when the need for inotropic support was restricted to the use of 1 or more inotropes such as dobutamine, epinephrine or others in high doses or the need for an intra-aortic balloon pump. Those requiring ECMO were classified as severe.

Origin and collection of data

The data for this study were obtained from our dedicated national transplantation society database, especially designed for the prospective registration of the data of the recipient, donor, surgery and follow-up of patients undergoing cardiac transplantation.

All surviving patients were followed by regular consultation at the Surgical Centre by a dedicated medical/surgical team, from a minimum of 1 year to a maximum of 14 years, and none was lost to follow-up. The mean follow-up period was 6.1 ± 3.9 years (total of 1750 patient-years).

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and comparison was made using the χ² test or the Fisher’s exact test, when appropriate. Continuous variables are presented as mean ± standard deviation and compared using the Student’s t-test for normally distributed variables and the Mann–Whitney U-test for variables with non-normal distribution. The normality of variables was evaluated by the Kolmogorov–Smirnov and Shapiro–Wilk tests.

Overall survival and group survival were calculated by the Kaplan–Meier method, and statistical significance was analysed using the log-rank test. Values of P < 0.05 (2-tailed) were considered statistically significant. Multivariable analysis to identify the risk factors for PGF was performed using logistic regression models. Criteria for entry and retention into multivariable models were set at the 0.2 and 0.05 confidence level, respectively. The data were analysed using the statistical package program IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

Donor procurement and surgical technique

All hearts were harvested from beating-heart, brain-dead donors. Clinical and laboratorial evaluation and transthoracic echocardiography of the donor were available in all cases. Coronary angiography was generally obtained for donors with significant risk factors for cardiovascular disease.

During harvesting, all allografts were protected by 1000 cc of cold (4°C) cardioplegic solution (Celsior®), in antegrade perfusion of the aortic root, and immersed in a cold physiological saline solution during transportation. No further cardioplegia is usually given after donor hearts are removed from cold storage. The mean distance of procurement was 98 ± 101 km (127 ± 120 and 92 ± 98 km) resulting in a mean cold ischaemic time of 64.7 ± 43.7 and 52.1 ± 36.4 min, respectively, for PGF and non-PGF groups (P = 0.037).

All transplantations were performed using the bicaval method. The need for further inotropic support or post-transplantation mechanical assistance was determined after a period of adequate reperfusion, and this decision was based on intraoperative direct visualization of the heart, hemodynamic signs and transoesophageal echocardiography.

Immunosuppression therapy and rejection monitoring

Routine induction therapy consisted of mycophenolate mofetil (1 g oral), methylprednisolone (500 mg i.v.) and basiliximab (20 mg i.v.) administered prior to and during transplantation. After the procedure, patients entered a protocol consisting of a calcineurin inhibitor (mostly cyclosporine), dose adjusted to blood levels assessed by monoclonal fluorescence polarization immunoassay, mycophenolate mofetil (500–1000 mg twice daily) and steroids (prednisone, 0.8 mg/kg/day during the 1st week and then tapered off in the subsequent 4 weeks to 0.2 mg/kg per day).

Right ventricular endomyocardial biopsies were performed following a routine protocol or when it was clinically considered necessary. Rejection was treated if graded >2 R of the ISHLT classification [4].

RESULTS

Recipients and donors

The baseline characteristics of the 290 patients are presented in Table 1. Demographic data were similar between groups as were the prevalence of cardiovascular risk factors or the pretransplant haemodynamic parameters. Incidences of idiopathic dilated cardiomyopathy and ischaemic aetiology were also identical. No statistically significant differences were observed in most laboratory values, but serum bilirubin (1.3 ± 0.9 vs 1.7 ± 1.0; P = 0.003) and blood urea nitrogen (33.5 ± 17.9 vs 40.1 ± 21.4; P = 0.027) were lower in the non-PGF group. Likewise, there were fewer patients in high urgency for transplantation in the non-PGF than in the PGF group (28.4% and 48.9%, respectively, P = 0.006).

The characteristics of the donors, as well as the results of the comparative analysis, are detailed in Table 2. No significant differences were observed between the 2 groups but female donors were more common in the PGF group (21% vs 42.6%; P = 0.002),
as was gender mismatch (donor female/recipient male, 14% vs 31.9%; \( P = 0.003 \)). A difference with regard to blood group AB0 mismatch (27.7% vs 15.6%; \( P = 0.048 \)) was also observed. Finally, no significant difference was observed in the inotropic use of the donor (longer than 1 week or high doses; 23.5% vs 23.4%; \( P = 0.99 \)).

**Surgery**

The surgical data, as well as the results of the comparative analysis of the 2 groups, are presented in Table 3. Statistically significant differences were observed in ischaemic time (89 ± 36.8 vs 103 ± 44.7 min; \( P = 0.019 \)). On the basis of the large experience of the centre with this procedure, concomitant mitral valvuloplasty was performed in 14 (4.8%) donor hearts previously known to have moderate mitral valve regurgitation (rheumatic or degenerative) as a method to expand the numbers of donors: 12 in the non-PGF group (4.9%) and 2 in the PGF group (4.2%).

The mean length of hospital stay for the non-PGF group was 13.5 ± 7.5 days vs 28.9 ± 35.2 days for the PGF group (\( P = 0.005 \)). The mean follow-up was 6.7 ± 3.7 years vs 2.8 ± 3.1 years, respectively, for the non-PGF and the PGF groups. Survival at 1, 5 and

<table>
<thead>
<tr>
<th>Table 1: Characterization of the recipient population and univariable comparative analysis of preoperative data of non-PGF and PGF groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient group</strong></td>
</tr>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
</tr>
<tr>
<td>Essential hypertension, n (%)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
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<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Prior cardiac surgery, n (%)</td>
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<tr>
<td>Ischaemic aetiology, n (%)</td>
</tr>
<tr>
<td>Dilated aetiology, n (%)</td>
</tr>
<tr>
<td>Valvular aetiology, n (%)</td>
</tr>
<tr>
<td>Other aetiology, n (%)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (WU), mean ± SD</td>
</tr>
<tr>
<td>Transpulmonary gradient (mmHg), mean ± SD</td>
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<tr>
<td>sPAP (mmHg), mean ± SD</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²), mean ± SD</td>
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<td>Bilirubin (mg/dl), mean ± SD</td>
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<tr>
<td>Glomerular filtration rate (ml/min), mean ± SD</td>
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<tr>
<td>Creatinine level (mg/dl), mean ± SD</td>
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<tr>
<td>Blood urea nitrogen (mg/dl), mean ± SD</td>
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<tr>
<td>High urgency classification*, n (%)</td>
</tr>
<tr>
<td>Extracorporeal MCSb, n (%)</td>
</tr>
<tr>
<td>Follow-up (years), mean ± SD</td>
</tr>
</tbody>
</table>

**P-values statistically significant appear in bold.**

*Inotropic support pretransplantation.

**MCS: mechanical circulatory support.**

**PGF: primary graft failure; SD: standard deviation; sPAP: systolic pulmonary artery pressure.**

<table>
<thead>
<tr>
<th>Table 2: Characterization of the donor population and univariable analysis of comparative data of non-PGF and PGF groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient group</strong></td>
</tr>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Mean donor age (years), mean ± SD</td>
</tr>
<tr>
<td>Donor age ≥50 years, n (%)</td>
</tr>
<tr>
<td>Gender (female), n (%)</td>
</tr>
<tr>
<td>Donor female/recipient male, n (%)</td>
</tr>
<tr>
<td>sPAP (mmHg), mean ± SD</td>
</tr>
<tr>
<td>Donor female/recipient male, n (%)</td>
</tr>
<tr>
<td>Ventilation support &gt;1 week, n (%)</td>
</tr>
<tr>
<td>Cause of death, n (%)</td>
</tr>
<tr>
<td>Haemorrhagic cerebral accident</td>
</tr>
</tbody>
</table>

**P-values statistically significant appear in bold.**

*Blood group 0 donor for recipient of other groups.

**PGF: primary graft failure; SD: standard deviation.**
10 years was 95.5 ± 1.3%, 84.1 ± 2.5% and 67.1 ± 3.8%, respectively, for the non-PGF group, and 55.3 ± 7.3%, 47.4 ± 7.6% and 14.4 ± 12% for the PGF group (P < 0.001; Fig. 1).

Ventricular dysfunction

Following the grading system of the ISHLT, 15 of the 47 PGF cases were classified as mild, 17 were moderate, and 15 (5.2%) were severe. In this experience, and following clinical and haemodynamic parameters, 23% of these cases had isolated left ventricular dysfunction and in 29% there was predominantly right ventricular dysfunction. The remaining patients (48%) had biventricular dysfunction.

Postoperative renal failure

Before transplantation, patients in the PGF group had higher blood urea nitrogen levels than those in the non-PGF group (40.1 ± 21.4 vs 33.5 ± 17.9; P = 0.027), although similar creatinine level (1.5 ± 0.8 vs 1.5 ± 1.7 mg/dl; P = 0.88) and glomerular filtration rates were observed (62 ± 30 vs 62 ± 23 ml/min; P = 0.88) (Table 1).

By the 1st month of post-transplantation, the creatinine level was higher in the PGF group (1.7 ± 1.2 vs 1.3 ± 0.6 mg/dl; P = 0.11), the blood urea nitrogen had risen (44.4 ± 23.3 vs 35.5 ± 16.1 mg/dl; P = 0.026) and the glomerular filtration rate suffered some deterioration (47 ± 34 vs 63 ± 28 ml/min; P = 0.001). A comparable renal function was observed in the surviving patients of both groups at the 3rd month of post-transplantation, and this trend persisted at 12 months after transplantation (glomerular filtration rate: 58 ± 23 vs 51 ± 15 ml/min; P = 0.019; Table 3).

Acute cellular rejection

The data on acute cellular rejection during the 1st year of post-transplantation in the non-PGF and PGF groups is shown in Fig. 2A. Survival free from acute cellular rejection grade ≥2 R was not different between the 2 groups (81.0 ± 2.6% vs 74.7 ± 7.4%; P = 0.31).

Severe infections

The incidence of serious infections requiring hospitalization and intravenous antibiotics post-transplantation was higher in the PGF Group as survival free from serious infections was significantly better in the non-PGF group (89.6 ± 2.0% vs 41.1 ± 7.7%; P < 0.001; Fig. 2B).

Mortality

Overall 30-day mortality was 4.1% for the entire cohort and 1.6% and 17% for the non-PGF and PGF groups, respectively (P < 0.001). The most frequent causes of death in the 1st month in PGF patients were cardiac failure and stroke. At 1 year, the most frequent causes of death in both groups were infections (2.1% vs 21%; P < 0.001), stroke (0.4% vs 2.1%; P = 0.30) and cardiac failure (0% vs 7.7%; P = 0.004) (Table 4). The median survival time was 12.7 years. As indicated earlier, a significant difference was observed in the survival between the 2 groups, but the differences are not as pronounced when comparing patients who survived the 1st year after transplantation (Fig. 3).

### Table 3: Peri- and post-operative data and univariable analysis of comparative data of non-PGF and PGF groups

<table>
<thead>
<tr>
<th>Recipient group</th>
<th>Overall</th>
<th>Non-PGF</th>
<th>PGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>290</td>
<td>243</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Cold ischaemic time, mean ± SD</td>
<td>54.1 ± 37.9</td>
<td>52.1 ± 36.4</td>
<td>64.7 ± 43.7</td>
<td>0.037</td>
</tr>
<tr>
<td>Total ischaemic time (min), mean ± SD</td>
<td>91.4 ± 38.5</td>
<td>89.0 ± 36.8</td>
<td>103 ± 44.7</td>
<td>0.019</td>
</tr>
<tr>
<td>CPB time (min), mean ± SD</td>
<td>98.3 ± 30.9</td>
<td>92.8 ± 14.5</td>
<td>126 ± 62.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Mechanical ventilation (h), mean ± SD</td>
<td>25.1 ± 60.2</td>
<td>14.7 ± 8.4</td>
<td>77.4 ± 137.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Mitral valvuloplasty, n (%)</td>
<td>14 (4.8)</td>
<td>12 (5.0)</td>
<td>2 (6.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Length of hospital stay (days), mean ± SD</td>
<td>17.1 ± 9.1</td>
<td>13.5 ± 7.3</td>
<td>35.9 ± 37.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Renal function, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR 1st month (ml/min)</td>
<td>60 ± 31</td>
<td>63 ± 28</td>
<td>47 ± 34</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine 1st month</td>
<td>1.4 ± 0.8</td>
<td>1.3 ± 0.6</td>
<td>1.7 ± 1.2</td>
<td>0.11</td>
</tr>
<tr>
<td>BUN 1st month (mg/dl)</td>
<td>36.9 ± 17.3</td>
<td>35.5 ± 16.1</td>
<td>44.4 ± 23.3</td>
<td>0.026</td>
</tr>
</tbody>
</table>

*P*-values statistically significant appear in bold.

BUN: blood urea nitrogen; CPB: cardiopulmonary bypass; GFR: glomerular filtration rate; PGF: primary graft failure; SD: standard deviation.
In our experience, patients in whom any kind of MCS was required had higher mortality, both in the short and medium terms (Fig. 4).

Risk factors for primary graft failure

By multivariable analysis, risk factors for PGF were donor female sex [odds ratio (OR): 2.56; 95% confidence interval (CI): 1.29–5.09; \( P = 0.007 \)], total ischaemic time (OR: 1.01; 95% CI: 1.00–1.02; \( P = 0.032 \)) and preoperative MCS (OR: 11.90; 95% CI: 2.62–54.12; \( P = 0.001 \)).

DISCUSSION

From the ISHLT data of the period 2005–2013, it is estimated that the cumulative incidence of graft failure was 3.8% during the 1st month, and EGF caused 50.6% of the early deaths, the vast majority being PGF [5].

However, the deleterious effect of PGF goes beyond its direct and immediate effect. In fact, the high morbidity associated with PGF and its treatment is closely linked with a high percentage of later-occurring deaths that are generally attributed to other causes, especially infections and rejections [6].

Although a definition of PGF was established at the 33rd Annual International ISHLT Meeting in 2013, it requires an accurate diagnosis [1]. Currently, the primary diagnostic tools used in daily practice are based on clinical, imaging and haemodynamic data. Consequently, there is a great variability in the reported incidence of this complication and the ability to differentiate primary from secondary graft failure is not always within reach. Here is where endomyocardial biopsy may be of help in obtaining a pathological correlation. In most cases of EGF, there may be signs of rejection, ischaemia reperfusion injury or previously unknown heart disease [1].
In any case, the pathological information does not always fully explain the occurrence of this phenomenon. PGF is still unpredictable, its mechanisms are poorly understood and risk factors have not yet been fully characterized [7]. The occurrence of PGF may be explained by the cumulative effect of a series of injuries associated with myocardial ischaemia during organ retrieval, transportation and implantation, but other factors such as reperfusion or the natural immune response of the recipient may play an important role.

Factors related to the donor

In the past decade, the availability of donors has decreased significantly, which has resulted in greater flexibility in the selection criteria, thus increasing the number of marginal donors used. As could be expected, this was found to be related to the increased incidence of PGF [8]. However, in the experience reported here, a higher percentage of donors with inotropic support did not prove to have a significant influence in the development of PGF. Furthermore, concomitant mitral valvuloplasty was performed in a number of donor hearts, and we did not find a negative impact in the immediate or medium-term outcome [9].

The mean donor age in our series (35.9 ± 11.3 years) was higher than that reported in the ISHLT database (34.0 years) [5] and has rapidly increased in the past decade (now 47 years). Sixteen percent of our donors were >50 years of age. However, we were unable to recognize donor age as a predictive factor of PGF [7]. Blanche et al. [10] also did not find a higher early rate of death in recipients of donor hearts above 50 years of age. In contrast, Gupta et al. [11] suggested that the older donor hearts may have inherent properties that make them less likely to survive in the early period after transplantation.

On the other hand, some authors found that donors above 60 years of age are a strong predictor for PGF and calculated the risk of developing PGF as 2.7% for each additional year of donor age, which may be explained by the observation that aged myocytes have a reduced ability to withstand ischaemia/reperfusion injury [10, 11].

The donor cause of death did not seem to have a significant impact in the development of PGF in our series. However, we have registered a significant increase in donors whose death was caused by a primary neurovascular injury, which is frequently associated with cardiovascular risk factors with implications in the transplantation outcomes that are still not clear.

Finally, we analysed the importance of the donor sex. Confirming data that we had previously published, female donors were more common in the PGF group, and we have found a strong negative influence of female donor/male recipient mismatch [12]. In a study by Young et al. [13], the female donor has been shown to be an independent predictor for the development of EGF, especially when the small donor female hearts are transplanted in males. More recently, Khush et al. [14] analysed the ISHLT Registry and concluded that sex mismatch reduces survival on both male and female recipients.

The worst perioperative myocardial performance of the female donor is explained by Weiss et al. [15], concluding that ‘the increase in cardiac output depends primarily on the increase in stroke volume at the expense of increased filling pressures. Small hearts have lower reserves and greater difficulty to adapt to the new situation. If we add to these conditions an increase in right ventricular afterload, cardiac output may be compromised’.

In this regard, Reed et al. [16] suggested that the current system of matching according to the donor-recipient weight, which assumes a direct correlation between weight and cardiac size, functions poorly to inform decisions for optimal organ allocation. In this study, they applied models to predict total heart mass for recipient and donor pairs and to evaluate the effects of cardiac size matching in orthotopic heart transplantation.

Factors related to the recipient

Other factors related to the recipients may also have a significant influence on the development of EGF. The analysis of our experience unveiled situations where development of this complication could have been highly influenced by the recipient [8].
For example, we found a higher incidence of pretransplant renal and hepatic dysfunction in recipients who were to develop PGF which, naturally, may simply be related to a preoperative higher severity of cardiac failure. In fact, there was a higher percentage of patients (48.9%) in the urgency list for transplantation (inotropic support/dependence) in the PGF group, and this circumstance was also highlighted in the predictive model IMPACT [8].

Factors related to the technical aspects

The ischaemic time was one of the most significant predictors of PGF. The effect of prolonged cold ischaemia on PGF may be related to inadequate preservation, causing myocardial damage or stunning and reperfusion injury. Contrary to the results reported by Morgan et al. [17], and even considering our relatively short ischaemic times by comparison with other series, we found this impact for the whole range of ischaemic times. In this respect, our results are closer to the experiences reported by D’Alessandro et al. [7, 18]. As discussed earlier, this may also result from the confluence of ischaemic time and increasing donor age, likely related to the decreased ability of the aged heart to tolerate ischaemic insults as well as to the increased incidence of intrinsic cardiac pathology with age [19]. This aspect has been reinforced in the RADIAL score and especially in the IMPACT scale which points to doubling 1-year mortality in patients receiving hearts from older donors with increased ischaemic times [8, 20].

Hence, it is important to make all efforts to reduce ischaemic time, related to both the logistics of transportation and the surgical technique. With regard to the latter, we have, for a long time, now modified it to release the aortic cross-clamp immediately after construction of the left atrial and aortic anastomoses, leaving the other anastomoses (pulmonary artery and venae cavae) to be performed during reperfusion, which can usually be done with no technical difficulty. This modification saves ~30 min of warm ischaemia and avoids a new dose of cardioplegia, except when cold ischaemic time exceeds 90 min.

Treatment of primary graft failure

Therapeutic options for cardiac graft failure are limited to the pharmacological intervention or mechanical support. Inotropes constitute the first line of treatment. From our experience, dopamine and epinephrine may have a paradoxical effect, especially in patients with pulmonary hypertension. High-dose (up to 40 µg/kg/min) dobutamine appeared to be far more efficacious.

Intra-aortic balloon pump is of some value, especially in borderline situations but ECMO support may be necessary, which has the potential advantage of avoiding too long periods with high-dose inotropic support, multiorganic hypoperfusion and graft overload, allowing both ventricles to rest and eventually recover. Several authors consider ECMO the standard treatment for PGF, also captivated by its easier management and lower cost [7, 21, 22]. However, ECMO has its own drawbacks, as it adversely affects coagulation parameters and causes thrombocytopenia, sometimes resulting in relentless bleeding complications. Less likely, but not unusual, are other complications such as cerebrovascular accident (CVA) and septic shock, which may occur later, even after weaning the assistance, and may also be related to patient fragility.

In our experience, patients in whom any kind of MCS was required had higher mortality both in the short and medium terms (Fig. 4), but our cohort may be of insufficient size to derive definitive conclusions. However, our patients with no MCS did not have substantially increased survival. We can hypothesize that the early introduction of MCS may avoid multiorgan dysfunction. In fact, some authors have shown that patients surviving after ECMO have the same 1-year conditional survival rates as patients who had not suffered a PGF [23]. Other forms of MCS, such as left ventricular assist devices, may be required for longer duration assist, but their role is more important as a bridge in the pretransplantation period.

Finally, retransplantation may be the ultimate solution in a minority of cases, but it may raise other questions of ethical nature, due to the limited supply of donors and the known poor results of retransplantation [2]. Yet, it was used in 3 of our patients with 2 survivals.

Limitations

The present work reflects a single-centre experience, with an average of 25 heart transplantations per year, with a limited number of patients, which may not reflect a general practice.

CONCLUSIONS

Our results demonstrate that PGF is associated with poor outcomes that extend beyond the 1st month and the first year after heart transplantation. We found donor female gender, total ischaemic time and preoperative MCS to be risk factors for PGF. Identification of risk factors, both recipient and donor related, for accurate prediction of short-term mortality in heart transplantation is of paramount importance, especially aiding in organ selection, influencing policy regarding allocation, predicting recipient prognosis and facilitating future research.

Conflict of interest: none declared.

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