Predictive risk factors for primary graft failure requiring temporary extra-corporeal membrane oxygenation support after cardiac transplantation in adults

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Abstract

Objective: Primary graft failure (PGF) is a major risk factor for death after heart transplantation. We investigated the predictive risk factors for severe PGF that require extra-corporeal membrane oxygenation (ECMO) circulatory support after cardiac transplantation. Methods: Between January 2003 and December 2008, 402 adult patients underwent isolated cardiac transplantation at our institution. PGF was defined as the need for ECMO support in the immediate postoperative period. Thirty-three recipient and 37 donor variables were analyzed for the risk of PGF occurrence. Results: PGF occurred in 91 (23%) patients. Predictive risk factors for PGF occurrence were, in the recipient, being aged >60 years (odds ratio (OR) 2.11, \( p = 0.01 \)) and preoperative mechanical circulatory support (MCS) (OR 2.65, \( p = 0.01 \)); in the donor, they were mean norepinephrine dose (OR 2.02, \( p < 0.01 \)), trauma as the cause of death (OR 2.45, \( p < 0.01 \)), left-ventricle ejection fraction (LVEF) <55% (OR 2.72, \( p = 0.02 \)), and the ischemic time (OR 1.01, \( p < 0.01 \)). Weaning and discharge rates after ECMO support for PGF were, respectively, 60% (55/91 patients) and 46% (42/91 patients). The absence of PGF was correlated with improved long-term survival: 78% at 1 year and 71% at 5 years without PGF versus 39% at 1 year and 34% at 5 years with PGF ( \( p < 0.01 \)). Surviving patients treated with ECMO for PGF have similar conditional 1-year survival rates as non-PGF patients: 93% at 3 years and 91% at 5 years without PGF versus 93% at 3 years and 84% at 5 years with PGF ( \( p = 0.46 \), NS).

Conclusions: Occurrence of PGF is a multifactorial event that depends on both donor and recipient profiles. ECMO support is a reliable treatment for severe PGF; furthermore, surviving patients treated with ECMO have the same 1-year conditional survival rates as patients not having suffered a PGF.

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Keywords: Primary graft failure; Heart transplantation; Extra-corporeal membrane oxygenation

1. Introduction

Primary graft failure (PGF) represents the most common cause of in-hospital mortality after cardiac transplantation [1], with a negative impact on early and long-term survival [2]. Its incidence ranges between 4% and 24% [2—5]; this wide variability may be caused by the definition of PGF, according to whether it is strictly based on the need for mechanical support, or if it also includes patients needing high-dose inotropic support. Despite its high mortality rate, the mechanisms underlying PGF are still poorly understood, and the risk factors that predict complications have not yet been characterized. In this study, we sought to identify the predictive risk factors for PGF after cardiac transplantation by strictly defining it as the need for ECMO support in the immediate postoperative period. Furthermore, we evaluated the 5-year survival rates after PGF in cardiac transplantation.

2. Materials and methods

2.1. Patients

Our study was a retrospective analysis that involved 402 consecutive patients, who underwent isolated cardiac transplantation at our institution between January 2003
and December 2008. Patient care conformed to the standard transplant procedures currently used at our institute, and no further written informed consent was asked for after inscription on the waiting list. Because of the retrospective profile of the analysis, this study was not submitted to our ethical committee board (Comité de Protection des Personnes se Prêchant à la Recherche Biomédicale, CCPPRB Pitié-Salpêtrière, Paris, France).

Until July 2004, the recipients’ data were obtained from patients’ charts. After July 2004, a digital database system was introduced at our institution (DxCare, Medasys Corporation), and was then used as the source of data for all patients. Donor data as well recipient allocation were obtained from ‘Cristal’, the database of the French regulatory agency for transplantation, the ‘Agence of Biomedecine’. To prioritize organs for critically ill patients, a national, high-emergency waiting list was opened in July 2004.

The preoperative recipient and donor variables are listed in Tables 1 and 2.

Pulmonary vascular resistance (PVR) values were only available for 253 (63%) patients: 149 (37%) patients had not undergone right-heart catheterization before transplantation or mechanical circulatory support (MCS) in an urgency setting. Although we supported such unstable patients with a Swan–Ganz catheter, the PVR values were not collected.

### Table 1. Univariate analyses on the occurrence of PGF: recipient factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 402)</th>
<th>No PGF (n = 311)</th>
<th>PGF (n = 91)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>89 (22%)</td>
<td>71 (23%)</td>
<td>18 (20%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>48 ± 14</td>
<td>48 ± 14</td>
<td>47 ± 17</td>
<td>0.55</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>232 (58%)</td>
<td>175 (56%)</td>
<td>57 (63%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Age ≥55 years</td>
<td>165 (41%)</td>
<td>123 (40%)</td>
<td>42 (46%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>87 (22%)</td>
<td>61 (20%)</td>
<td>26 (29%)</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>4 ± 5</td>
<td>24 ± 6</td>
<td>24 ± 5</td>
<td>0.70</td>
</tr>
<tr>
<td>BSA (m², mean ± SD)</td>
<td>1.83 ± 0.22</td>
<td>1.83 ± 0.21</td>
<td>1.84 ± 0.23</td>
<td>0.54</td>
</tr>
<tr>
<td>Weight (kg, mean ± SD)</td>
<td>71 ± 15</td>
<td>71 ± 15</td>
<td>72 ± 16</td>
<td>0.49</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>136 (34%)</td>
<td>104 (33%)</td>
<td>32 (35%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>166 (41%)</td>
<td>130 (42%)</td>
<td>36 (40%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Congenital</td>
<td>12 (3%)</td>
<td>8 (3%)</td>
<td>4 (4%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other</td>
<td>88 (22%)</td>
<td>69 (22%)</td>
<td>19 (21%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Time on waiting list (days, mean ± SD)</td>
<td>144 ± 279</td>
<td>137 ± 276</td>
<td>167 ± 287</td>
<td>0.39</td>
</tr>
<tr>
<td>Diabetes</td>
<td>58 (14%)</td>
<td>44 (14%)</td>
<td>14 (15%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l, mean ± SD)</td>
<td>117 ± 59</td>
<td>114 ± 56</td>
<td>127 ± 67</td>
<td>0.14</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min, mean ± SD)</td>
<td>81 ± 42</td>
<td>82 ± 41</td>
<td>79 ± 44</td>
<td>0.56</td>
</tr>
<tr>
<td>Prior sternotomy</td>
<td>155 (39%)</td>
<td>106 (34%)</td>
<td>49 (54%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>More than one prior sternotomy</td>
<td>31 (8%)</td>
<td>18 (6%)</td>
<td>13 (14%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>63 (16%)</td>
<td>46 (15%)</td>
<td>17 (19%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>102 (25%)</td>
<td>84 (27%)</td>
<td>18 (20%)</td>
<td>0.16</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td>15 (4%)</td>
<td>10 (3%)</td>
<td>5 (5%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>55 (14%)</td>
<td>40 (13%)</td>
<td>15 (16%)</td>
<td>0.38</td>
</tr>
<tr>
<td>History of cancer</td>
<td>18 (4%)</td>
<td>13 (4%)</td>
<td>5 (5%)</td>
<td>0.59</td>
</tr>
<tr>
<td>PVR (Woods units, mean ± SD)*</td>
<td>3.2 ± 2.1</td>
<td>2.9 ± 2.1</td>
<td>3.7 ± 2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>PVR &gt;4.5 Wood units*</td>
<td>47 (19%)</td>
<td>31 (16%)</td>
<td>16 (30%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Inotrope dependent</td>
<td>110 (27%)</td>
<td>88 (28%)</td>
<td>22 (24%)</td>
<td>0.44</td>
</tr>
<tr>
<td>MCS dependent</td>
<td>90 (22%)</td>
<td>58 (19%)</td>
<td>32 (35%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VAD</td>
<td>41 (10%)</td>
<td>27 (9%)</td>
<td>14 (15%)</td>
<td>0.06</td>
</tr>
<tr>
<td>ECMO</td>
<td>49 (12%)</td>
<td>31 (10%)</td>
<td>18 (20%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Days on MCS (mean ± SD)</td>
<td>15 ± 60</td>
<td>13 ± 57</td>
<td>22 ± 68</td>
<td>0.79</td>
</tr>
<tr>
<td>Infected VAD</td>
<td>20 (5%)</td>
<td>13 (4%)</td>
<td>7 (8%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ventilator dependent</td>
<td>34 (8%)</td>
<td>20 (6%)</td>
<td>14 (15%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High-emergency waiting list</td>
<td>107 (27%)</td>
<td>82 (26%)</td>
<td>25 (27%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

BMI, body mass index; BSA, body-surface area; PTCA, percutaneous transluminal coronary angioplasty; PVR, pulmonary vascular resistances; MCS, mechanical circulatory support; VAD, ventricular assist device; ECMO, extra-corporeal membrane oxygenation.

* PVR data are analyzed only for the 253 patients with a known PVR value.

2.2. Definitions and outcomes

Primary outcomes were the occurrence of PGF, 1-year mortality rates, and 5-year survival rates. PGF was defined as the need for support with an ECMO in the immediate postoperative 48-h period, and was divided into the following two groups:

- impossibility to wean from a cardiopulmonary bypass (CPB); and
- refractory cardiogenic shock after a high-dose inotropic infusion that occurred after protamine administration or after admission to the intensive care unit (ICU).

Any need for ECMO support beyond the 48th postoperative hour was defined as secondary ECMO.

2.3. Organ preservation and immunosuppressive regimens

The preservation solution consisted of Celsior solution. After retrieval, hearts were transported immersed in hypothermic Ringer Lactate solution. At the time of implantation, white-cell unfiltered cold-blood cardioplegia was infused into the aortic root to aid myocardial protection.
and to remove air. Postoperative immunosuppression consisted of an induction therapy of anti-thymocyte globulin (ATG) followed by a triple maintenance therapy based on cyclosporine or tacrolimus, in combination with mycophenolate mofetil and steroids. Other recent immunosuppressive drugs, such as everolimus, were only used in selected patients. All patients were followed up in our transplant outpatient department.

2.4. ECMO characteristics and techniques

Techniques of surgical ECMO implantation and weaning protocols have been described in detail elsewhere [6]. In brief, the extra-corporal system consists of polyvinyl chloride tubing, a membrane oxygenator, a centrifugal pump, and either an arterial and venous femoral or central right-atrial and aortic cannulae. An oxygen/air blender was used to ventilate the membrane oxygenator. When femoral ECMO was used, an additional 5-Fr cannula was inserted distally into the femoral artery to prevent possible leg ischemia. If a central cannulation was chosen, left-ventricular venting through the pulmonary artery was implemented when there was total absence of cardiac contractility. Patients were anticoagulated with heparin to achieve an activated partial thromboplastin time (aPTT) that was twice the control.

2.5. Statistical analyses

Univariate analysis was performed using chi-square tests for categorical variables; an unpaired t-test was used for normally distributed data, after assessment of equality of variances. Otherwise, the Mann—Whitney test was used. A stepwise logistic regression was performed to determine predictors for the occurrence of PGF, with a cut-off of \( p = 0.10 \). To measure model discrimination, c-statistics (area under the receiver operating characteristic curve) were used, and the Hosmer—Lemeshow test was used for goodness-of-fit assessment. PVR was excluded from the models, since values were missing for 149 patients; however, a sensitivity analysis was carried out for patients with a known PVR value. Data are expressed as means ± standard deviations for continuous variables, and percentages for qualitative variables. All p values were two-tailed. The Kaplan—Meyer method was used for survival analysis and survival curves were compared using a log-rank test.

All statistical analyses were performed with the SAS V8 statistical package.
3. Results

3.1. Occurrence of PGF

A severe PGF that needed ECMO support occurred in 91 (23%) patients. Peripheral cannulation was used in 33 patients, while 58 patients underwent central cannulation. Left-ventricular venting was also used in 19 patients. Weaning and discharge rates after ECMO support for PGF were, respectively, 25% (4/16 patients) and 6% (1/16 patients). After ECMO support for secondary graft failure were, acute rejection in two cases. Weaning and discharge rates after ECMO support for PGF were, respectively, 25% (4/16 patients) and 6% (1/16 patients).

3.2. Risk factors for PGF

The predictive factors for the occurrence of PGF as assessed by univariate analysis are shown in Tables 1 and 2. Independent predictors for the occurrence of PGF, as assessed by multivariate analysis, were, in the recipient, being 60 years old or older (odds ratio (OR) 2.11) and having preoperative MCS (OR 2.65); for the donor, they were receiving mean norepinephrine dose (OR 2.02), trauma as the cause of death (OR 2.45), a left-ventricle ejection fraction (LVEF) <55% (OR 2.72), and the ischemic time (OR 1.01) (c-statistics = 0.766, Table 3). According to the sensitivity analysis, only the following donor variables were independent risk factor for the occurrence of PGF: mean norepinephrine dose (OR 2.87), trauma as the cause of death (OR 3.21), and the ischemic time (OR 1.01) (c-statistics = 0.762, Table 3).

3.3. One-year mortality

Overall 1-year mortality was 30% (120 patients). One-year mortality for patients, who did not experience PGF, was 21% (64/311 patients). Causes of death were infection (n = 44), cerebrovascular accident (CVA) (n = 7), respiratory failure (n = 2), graft rejection (n = 4), thoracic bleeding (n = 1), unknown (n = 1), arrhythmia (n = 1), gastrointestinal bleeding (n = 2), trauma (n = 1), and cancer (n = 1).

One-year mortality for patients supported with ECMO after PGF was 62% (56/91 patients). Thirty-three patients died while on ECMO support: causes of death were low-output cardiac syndrome (n = 2), CVA (n = 7), septic shock (n = 10), postoperative surgical bleeding (n = 7), refractory vasoplegia (n = 6), and gastrointestinal bleeding (n = 1). Both patients bridged to TAH died: causes of death were CVA (n = 1) and septic shock (n = 1). Twenty-one patients died after weaning: causes of death were low-output cardiac syndrome (n = 1), CVA (n = 2), septic shock (n = 11), hypoxic arrest during weaning after a tracheotomy (n = 2), acute rejection (n = 1), gastrointestinal bleeding (n = 1), and an iatrogenic hemothorax (n = 1). Two patients had refractory graft failure after removal of the ECMO. Both patients died after ECMO reimplantation: causes of death were surgical bleeding (n = 1) and septic shock (n = 1).

Univariate analysis of details of ECMO support for PGF, such as site of cannulation or delay of implantation after transplantation, showed no predictors of 1-year mortality (Table 4).

3.4. Late results

Overall survival was 69% at 1 year and 63% at 5 years. Absence of PGF was correlated with improved long-term survival: 78% at 1 year and 71% at 5 years without PGF versus 39% at 1 year and 34% at 5 years with PGF (Fig. 1, p < 0.01). Surviving patients treated with ECMO for PGF have a similar conditional 1-year survival rate as non-PGF patients: 93% at 3 years and 91% at 5 years without PGF versus 93% at 3 years and 84% at 5 years with PGF (Fig. 2, p = 0.46, NS).

4. Discussion

Despite being the principle cause of death after cardiac transplantation, PGF is still an unpredictable and poorly understood complication. Although previous studies have warned of the risks of choosing non-standard donors for less healthy patients [7], recent articles have focused on cardiac-donor quality, cautioning on donors who require high-dose inotropes [8], or trying to identify a donor-serum marker that could be associated with postoperative graft dysfunction [9].

Our results confirm that not only the donor, but also the recipient profiles, are important in determining PGF: thus, we can clearly suggest that there are not only ‘marginal donors’ but also ‘marginal recipients’.

From multivariate analysis, recipient risk factors for PGF were preoperative MCS and an age ≥ 60 years. A recipient of >60 years was a strong predictor for PGF. It is well known that recipient age adversely affects 1- and 5-year survival rates [1]; our data suggest that this increased mortality could be linked to the higher PGF risk in these patients. Similar to Lima et al. [2], we have also found that preoperative MCS was an independent risk for PGF: mediastinal adherences due to a prior sternotomy may...
increase the difficulty of surgical dissection and prolong the explantation period, which requires a longer CPB time. This may translate to a greater inflammatory response, which could subsequently have an impact on the occurrence of PGF.

From multivariate analysis, the donor-risk factors for PGF were LVEF < 55%, the mean norepinephrine dose, trauma as the cause of death, and the ischemic time.

Our results confirm that, as reported by Santise et al. [8], a donor requirement for inotrope plays a key role in PGF because of the detrimental effect of catecholamines on right-ventricular function [10]. Despite the fact that data from the International Society for Heart and Lung Transplantation (ISHLT) showed no association between the donor's cause of death and the recipient's outcome [1], Santise et al. noticed that donors, who had died from head trauma, were at lower risk for PGF [8]. Indeed, traumatic death should be less associated with PGF because of the younger age of donors. As reported by Ganesh et al. [11] in a large multicenter study, post-trauma donors were more likely to be younger, male, and have a lower body mass index (BMI). This work apparently confirmed the relationship between post-trauma donors and improved post-transplant survival, although this relationship was not maintained after adjustment for confounding variables. By contrast, we surprisingly found that trauma as the cause of death was a powerful risk factor for PGF. A possible reason may be that, in our series, donor age and gender were not significant related to the occurrence of PGF, even in univariate analysis; on the other hand, the potential advantages of trauma donors were overcome by more frequent unfavorable weight mismatches of ≥0.15, and higher doses of inotropes (data not shown).

Despite the results reported by Morgan et al. [12], we are sincerely convinced that time does matter: Ischemic time is the best recognized risk factor for PGF [2–5]. Marascco et al. reported a 43% increased risk of graft failure for every hour of ischemic time after the fourth hour [5]. The utmost importance of ischemic time in affecting early mortality [1], eventually exacerbated by an older donor age [13,14], could be explained by its fundamental role in the genesis of PGF.

Interestingly, despite its well-established role in the genesis of PGF [3,5], our results failed to recognize donor age as a predictive factor for PGF. This could be because of the generally older donors available in France: mean donor age in our series was almost 10 years older than from the ISHLT data, and from other reports [2,3,5,15,16]: 47% of our donors were ≥50 years (Table 2), which is greater by far than the 8% currently reported [15,16].

The last consideration regarding donors is concerned with organs retrieved concomitantly with the heart graft. We collected information on this after reading the interesting findings of Russo et al. [17]: they reported that concomitant lung retrieval was associated with worse results because of the conflicting management of lung donors, who need fluid restriction and increased administration of inotropes. Not only did our analysis not confirm this scenario, but, astonishingly, it revealed a protective effect for concomitant liver retrieval as assessed by univariate analysis. However, because we did not have access to the reasons for liver acceptance, we could only speculate on the positive effect played by a better donor profile, which would otherwise have led to liver graft discarding.

The incidence of PGF in our series is quite high, taking into account that its definition is strictly based on the need for ECMO support. As other authors have reported [18,19], we also noticed, in previous work [6], that the incidence of PGF has increased over the years: this trend could be explained by the interaction between evolving recipient and donor profiles. A comparison between the two eras shows that recipients in the more recent era are more often diabetic,
respectively, 60% and 46% (Table 4), which are comparable to and Chou et al. (weaning 84%, survival 53%) [4]. The those published by Taghavi et al. (weaning 77%, survival 54%) [18] have previously reported superior results with ECMO rather than a dedicated right-ventricular assist device (RVAD) for patients with right-ventricular failure, which has also been our experience [6]. Indeed, ECMO provides full circulatory support with minimal surgical trauma, avoiding end-organ damage and allows both ventricles to rest and recover. In our opinion, ECMO is the standard treatment for PGF, also taking into account its easier management and the lower cost of the ECMO system [19].

Because PGF can manifest as a univentricular failure, MCS using short-term VADs could be a therapeutic option, considering the reliability and low anticoagulation requirement that is now available for VADs. However, Taghavi et al. [18] have previously reported superior results with ECMO rather than PGF related: in our experience [6], ECMO was clearly not a mortality associated with PGF is limited to the perioperative period (Fig. 2). On the other hand, ECMO was clearly not a multifactorial event that depends on both the donor’s and recipient’s profiles. ECMO support is a reliable treatment for PGF, who have experienced PGF, is similar to that of other transplant patients; the burden of the higher mortality associated with PGF is limited to the perioperative period (Fig. 2). On the other hand, ECMO was clearly not a reliable therapeutic option regarding secondary failure caused by septic shock or rejection.

4.1. Limits

As stated in Section 2, this study carries all the limits that a retrospective design implies. Although PGF was strictly defined as the immediate postoperative need for ECMO support, the decision for ECMO implantation, apart from the impossibility of coming off CPB, was taken according to hemodynamic, echographic, and biochemical parameters, which were not collected and hence were not available for further analysis. Furthermore, PVRs were not available for 37% of patients, for the reasons stated in Section 2.

5. Conclusions

Despite the limits of its retrospective design, this study represents the largest single-center report on ECMO circulatory support for PGF: it confirms that PGF is definitely a multifactorial event that depends on both the donor’s and recipient’s profiles. ECMO support is a reliable treatment for severe PGF; furthermore, surviving patients treated with ECMO have the same 1-year conditional survival rates as patients who have not suffered a PGF.

Fig. 2. Kaplan–Meier 1-year conditional survival rates. Surviving patients treated with ECMO for PGF have a similar 1-year conditional survival rate as patients who have not suffered a PGF: 93% at 3 years and 91% at 5 years without PGF versus 93% at 3 years and 84% at 5 years with PGF ($p = 0.46$, NS).
A larger, multicenter study is needed to establish and evaluate preoperative PGF scoring, to avoid matching marginal donors and recipients, and to eventually determine a proper threshold for ECMO support.

Acknowledgments

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References


Appendix A. Conference discussion

Dr R. Bonser: The literature on primary graft failure is quite different as there is no agreed core definition, and that’s a problem. At one extreme, primary graft failure should designate allograft loss, so either the patient dies or historically was salvaged by re-retransplantation. Allograft dysfunction that does not lead to graft loss, such as in the group that you described in part, is commonly termed ‘primary graft dysfunction.’ This is again poorly defined, but certainly includes those patients in your cohort. In the UK at the present time, primary graft dysfunction, defined as a low cardiac output state due to either univentricular or biventricular dysfunction and requiring either prolonged high-dose inotropic or mechanical support, has an incidence of 30%, and approximately a third of these patients die as a consequence, so very similar data to what you’re reporting. I’ve got some questions for you. I would like to hear a more explicit definition of primary graft dysfunction and your threshold for using ECMO. I would like to know more about the troponin assay that you used and how you determined this cut-off level of 3 ng/ml and whether you performed area under the curve analysis to see if this was more discriminate.

Your report also details that trauma as a cause of death was a risk factor, and that’s quite controversial, as other European studies have not identified this, and I would like to offer some explanation for this discrepancy. Fourthly, did you find any relationship between the incidence of graft failure and the time period from coming or brain stem death? Lastly, you report a relationship between norepinephrine and graft failure, with a higher dose of norepinephrine having a higher incidence of graft failure, but when is that dose recorded? Is it the maximum dose or the dose at the time of retrieval, and how do you incorporate that into your clinical decision-making as to when or when not to take a donor?

Dr D’Alessandro: We were very surprised to find that trauma as cause of death was associated with an increased risk of graft dysfunction, despite the younger age of trauma donors. In our series, these younger donors were matched with larger recipients, with a consequent unfavorable weight mismatch, and they needed higher dose inotropic support. I think that these factors could explain the higher risk of graft dysfunction. However, this phenomenon could be related to the specific donor population in France. Regarding the inotropic support of donors, the norepinephrine dose is collected by the French Agency of Donor Regulation. It is the maximum level of inotrope just before harvesting, and in my opinion, the ratio between the mean arterial pressure and the dose of norepinephrine is crucial in the decision-making about whether or not to take a donor. For example, if you have a low mean arterial pressure despite a high dose of inotrope, the graft will not be good. Conversely, even if you have 190, 180 mmHg with some inotropic support, it could be normal. I forgot the first question.

Dr Bonser: The first question was on your threshold, so an explicit definition of graft dysfunction in your series, which you may just want to put in...
your manuscript, and just a little bit more about your troponin assay, and when did you measure the troponin?

**Dr D’Alessandro**: We analyzed the peak level of donor troponin. I don’t know the time of the assay because this variable was also collected by the National French Agency of Donor Regulation.

**Dr Bonser**: So it’s a donor troponin?

**Dr D’Alessandro**: It’s a donor factor. It’s not a recipient factor.

Concerning the threshold for ECMO implantation, it was the result of an ongoing process. At the beginning of our experience, we were very reluctant to implant an ECMO because we were not aware of the late results. Nowadays we do not accept an inotropic support with epinephrine over 2 mg/h because of the high risk of a late refractory shock.

**Dr A. Almeida (Melbourne, Australia)**: How has this study impacted your practice at your hospital?

**Dr D’Alessandro**: Honestly, we have not modified our practice very much yet. As with many other centers, we have a big problem with donor shortage and we discard very few donors. However, on the recipient side now we know that if we put an old patient with pulmonary hypertension on the waiting list, we cannot expect a good outcome.

**Dr Almeida**: If I can answer that question from my point of view, I think the value of this paper is matching donors and recipients. You brought up several issues, and I think that should be a discussion point in your paper. Having an understanding of the factors then allows you to try and match donors and recipients to get a good outcome for the organs, which are limited.

**Dr D’Alessandro**: Yes. Unfortunately, sometimes we are obliged to match sicker patients and marginal donors. In such a case, and that reflects a real change in our policy, we do not try to assist the patient or spend hours in order to wean off the pump, we just put the patient on ECMO.

**Dr Johanna J.M. Takkenberg (Rotterdam, The Netherlands)**: Yesterday there was another paper about ECMO after heart transplantation from the Cleveland Clinic, and I noticed that it only happens in 3.5% of their patients and it’s 23% in your patients. That’s a big difference. You may want to compare those two series, actually, to find clues on why it doesn’t happen that often in their clinic.

**Dr D’Alessandro**: Yes, it’s quite a big difference. We started using ECMO for graft dysfunction in 2003. Before that, the only therapeutic solution we had for graft failure was mechanical circulatory support with VADs, but it was associated with very poor outcomes, therefore we were very cautious with donor acceptance. After 2003, with the introduction of ECMO, we extended our criteria for donor acceptance, doing exactly what we suggest not to do: under the pressure of a terribly high mortality on the waiting list, we matched the marginal donors and recipients, and our incidence of graft failure peaked at 30%. Now we are more cautious with donor acceptance. Our actual incidence of graft failure is around 15%.

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### Editorial comment

**Primary graft failure — the stepchild of cardiac transplantation**

Keywords: Cardiac transplantation; Primary graft dysfunction; ECMO

1. Introduction

Cardiac transplantation is an established therapy for end-stage heart failure. Since the first human heart transplantation in 1967, results have improved dramatically. One-year survival has increased to 85–90%. Within the first year, the early phase after transplantation is associated with the highest risk of death. In their article, D’Allesandro and colleagues have analyzed incidence, risk factors, and outcomes of primary graft failure after cardiac transplantation [1]. The authors have to be congratulated for writing an honest and very detailed analysis about their data. Based on the International Society for Heart and Lung Transplantation (ISHLT) registry, the rate of death from graft failure early after transplantation is 3–4% [2]. In his article, D’Allesandro reports a rate of early death of 8%.

For many years, nobody discussed primary graft failure and only a few reports have been published [3,4]. Until recently, one could get the impression that this complication has become so rare and nobody seems to care about it anymore. Still patients die from it directly or due to associated complications. The real problems lurking below the surface were discussed among colleagues only behind closed curtains and after one or two bottles of wine maybe.

If results from D’Alessandro’s analysis are compared with reports from non-European centers, one might get the impression that D’Allesandro’s results are inferior. However, more and more data are available that shows significant differences of the cardiac donor population and its management in the USA and Europe [2]. In Europe, donors are significantly older and are treated with a different inotropic regimen than in the USA. According to the ISHLT registry, the rate of donors who are >50 years of age has been constant at 10% over the last years. This is in sharp contrast to the donor population in this cohort, which comprises 50% of donor hearts aged 50 and above. Norepinephrine support in doses >0.3 μg kg⁻¹ min⁻¹ was used in >80% of donors. According to the definitions of marginal donors, this center has been using marginal donors in many cases. Over the last 10 years, using so-called ‘marginal donors’ has become the routine in Europe’s cardiac transplantation programs. If centers would only use standard donor hearts, they would have a significant reduction in transplant numbers.

Another very important aspect of the manuscript by D’Allesandro is the definition of primary graft failure. There is no clear defined endpoint for primary graft dysfunction/failure in cardiac transplantation. Literature shows a broad spectrum of different definitions. It includes longer periods of reperfusion, high inotropic support, problems in weaning patients off bypass, and the need for mechanical support after transplantation [3,4]. Moreover, there is no standard of care as to how to treat primary graft dysfunction/failure. Extracorporal Membrane Oxygenator (ECMO) support seems to be an acceptable tool for bridging patients to potential graft recovery.

D’Allesandro and colleagues have contributed important insights on risk factors and outcome of primary graft failure after cardiac transplantation. However, there is a