Early graft failure after heart transplant: risk factors and implications for improved donor–recipient matching†

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Abstract

Early graft failure (EGF) is a dreaded complication after heart transplantation (HT). Despite several improvements, no effective therapy has been developed and the prognosis is poor. We evaluated the risk factors and clinical impact of EGF. In a consecutive series of 317 HTs performed at a single institution between January 1999 and December 2008, variables associated significantly with EGF were sought in bivariate and multivariable discriminant analyses. The deriving propensity score was used to stratify the study sample into three groups (low, intermediate and high risk for EGF). Comparisons were performed between the higher-risk group and the remaining population in terms of preoperative features and outcomes. EGF occurred in 10.1% of the overall population (2.9, 3.8 and 23.6%, respectively, in the three groups). Overall, EGF-related mortality was 56.3% (100, 75 and 48%, respectively, in the three groups). Determinants of EGF in the highest-risk group were: redo procedure, valvular cardiomyopathy, status one at transplant, recipient male sex, donor–recipient (D/R) weight mismatch, high inotropic donor support, ischaemic time and first day troponin I release. In conclusion, several donor and recipient features predicted EGF. Since such characteristics are not readily modifiable but synergistically determine the occurrence of EGF, optimization of D/R matching is crucial to prevent it.

Keywords: Heart transplantation • Early graft failure • Propensity score

INTRODUCTION

Early graft failure (EGF) is one of the most dreadful complications following heart transplantation (HT). Little progress has been made in the prevention of this rare but dangerous condition, indeed, despite the expanded criteria for suitability of potential donors and the increasing complexity of recipient features, techniques of heart protection, algorithms for donor–recipient (D/R) matching along with treatment strategies for EGF have not consistently evolved [1–3]. As a consequence, this event is still the prime cause of 30-day mortality after HT [4]. Larger studies on risk factors interaction [5] have shown the synergistic effect of donor and recipient risk factors. The purpose of this study was to identify, in a single-centre experience, the risk factors associated with EGF and their interaction and describe the course, treatment and prognosis of EGF.

MATERIALS AND METHODS

Study population and data

Between January 2000 and December 2008, 317 patients underwent HT. Study protocol was approved by the local Ethical Committee which waived the need for consent. Preoperative recipient data, donor-related variables, data about the D/R matching, the procedures, treatments and all clinical perioperative and postoperative outcome data were prospectively entered in a dedicated database.

Surgical methods and graft protection

Donor and recipients were matched for AB0 blood type compatibility and body size. Whenever possible undersized donors (the D/R weight ratio < 0.8) were not used in recipients affected by secondary pulmonary hypertension in whom oversizing (the D/R weight ratio > 1) was attempted.

Prospective human leukocyte antigen (HLA) matching was not used with the exception of recipients with a high level of
panel reactive anti-HLA antibodies who underwent prospective cross-match following the indications of the Department of Transplant Immunology. A coronary angiogram was obtained when indicated by guidelines and logistically feasible; in the other cases, visual evaluation and manual palpation of epicardial coronary arteries prior to harvesting the graft were employed.

High donor inotropic support (dobutamine or dopamine ≥10 µg/kg/min and/or norepinefrine) did not prevent graft harvesting unless the massive dosage (>20 µg/kg/min) was associated with left ventricular ejection fraction <45% in optimal loading conditions.

Donor heart procurement was performed using the standard techniques, and the grafts were protected with the infusion of 2 l of cold (4-8°C) Celsior solution in the aortic root and topical cold saline slush. All recipients underwent the standard orthotopic HT using the btrial technique described by Lower and Shumway. Long ischaemic time was defined as graft ischaemia >180 min, since it had proved an independent risk factor for graft dysfunction in our previous analyses.

Cardiopulmonary bypass weaning and perioperative care

In the early postoperative phase, the transplanted heart allograft was reperfused and circulation supported in a way that maintained haemodynamic stability. Inotropic and vasodilator support were tailored under continuous right heart haemodynamic monitoring. As to pulmonary hypertension treatment, until 2005 prostaglandin-E2 (PGE2) was always used while weaning the patient off cardiopulmonary bypass but, since May 2005, 5–40 ppm inhaled nitric oxide (NO) was used in high-risk patients as starting therapy in a protocol involving the use of oral sildenafil whenever extubation was feasible [6] or in patients with overt right ventricular failure (RVF). Principles of postoperative care have been fully elucidated elsewhere [7, 8]. Briefly, the standard immunosuppressive drug regimen was based on induction therapy with polyclonal antibodies (ATG Fresenius, thymoglobuline). ATG Fresenius was preferentially employed in weaker patients and/or complicated postoperative courses in an attempt to reduce the risk of over-immunosuppression. Calcineurin inhibitors and steroids were introduced after the recovery of renal function. Antiproliferative agents are added only after extubation and achievement of stable clinical conditions.

Event definition

EGF was defined as a mono- or biventricular low output syndrome with a cardiac index <2 l/min/m², higher filling pressures (right atrial pressure or pulmonary capillary pressure >20 mmHg) in the first 24 h with the need of high inotropic support (dobutamine dose >10 µg/kg/min and/or isoprenaline >0.05 µg/kg/min or need for adrenaline or levosimendan), systemic (nitroprusside, nitroglycerin) and/or pulmonary vasodilators (PGE2, NO and sildenafil), intra-aortic balloon pump (IABP), prolonged intubation with high inhaled oxygen concentrations [9]. Patients experiencing low CO syndrome for technical reasons (two cases of pulmonary artery stenosis and one case of narrow left atrial cuff) were excluded from the analysis. Acute kidney injury was defined according to the RIFLE criteria as reported elsewhere [8].

Baseline data of the population

Table 1 shows the preoperative characteristics of the 317 recipients, characteristics of the 317 donors utilized and data regarding the procedures and D/R matching.

Statistical analysis

Variables related to preoperative recipient, donor, matching and procedure characteristics were compared (using the χ² statistic for categorical variables and the Student’s t-test or Wilcoxon signed-rank sum test for continuous variables) between patients developing EGF and the others and then included in a single-step multivariable discriminant analysis in order to create a propensity score for the likelihood to develop EGF. The C-statistic for the propensity model was >0.80. Then, the patient population was divided into three groups corresponding to tertiles of propensity scores. The first two groups (low and intermediate risk) were pooled and the high-risk group was compared with the other patients by bivariate analysis in terms of both preoperative features and outcomes. Data are expressed as the mean ± SD for continuous variables and as percentages for categorical variables. Odds ratio values for outcomes were reported with 95% CI. All statistical analyses were performed with SPSS 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Events

Thirty-two patients (10.1%) experienced low CO syndrome for EGF; 10 cases (3.1%) consisting of an RVF and the other 22 (6.9%) of biventricular failure (BEGF). EGF was the direct or indirect cause of death in 52.9% cases (18 patients; overall deaths were 34, 10.7%). Only one patient (21-years old) was re-transplanted after <24 h of ECMO and died of EGF. The relative mortality of the EGF was 56.5%; 59% for BEGF and 50% for RVF. The incidence of counterpulsation was 25% (27% in BEGF and 20% in RVF). Levosimendan was used in one case (10%) of RVF and three cases (13.3%) of BEGF. Three of the eight (37.5%) patients treated with IABP died (50% with RVF and 33% with BEGF) and similarly two of the four patients (50%) treated with levosimendan (100% in RVF, 33% in BEGF). The incidence of multiple organ failure (MOF) was, respectively, 50% in RVF and 31% in BEGF.

Univariate analysis for EGF

The incidence of the more common risk factors was compared between patients who experienced EGF and those who did not (Table 1). A statistically significant difference emerged in terms of recipient sex, redo surgery and current hospitalization at the moment of HT. Interestingly, EGF rarely occurred in female recipients (1.6%). Preoperative haemoglobin difference was statistically significant even though not clinically relevant (12.4 vs. 13 g/dl). Risk factors related to the donor were: high inotropic support at the time of harvest and total ischaemic time. Modifiable factors related to the procedure were: D/R weight mismatch, higher postoperative troponin peak and units of red blood cells transfused.
Bivariate analysis between propensity score groups

EGF occurred in 2.9, 3.8 and 23.6%, respectively, in the three tertiles of risk according to the propensity score. Overall, glomerular filtration rate-related mortality was 56.3% (100, 75 and 48%, respectively, in the three groups). Univariate analysis between the high-risk group and the remaining population disclosed that in high-risk patients the incidence of EGF, acute kidney injury (a perioperative change in modification of diet in renal disease (MDRD) GFR >50%), MOF, hospital mortality and 1-year mortality were statistically higher (Table 2). Interestingly, no differences emerged in terms of the rate of infections during the first postoperative year, and there was a higher 1-year conditioned to 30-day survival in the low-intermediate risk group. In Fig. 1 relative risks are reported for the mentioned outcomes.

The analysis comparing the two propensity score derived clinical profiles showed that the group at higher risk for EGF had higher prevalence of male sex, non-idiopathic cardiomiopathy, redo operations (52.8 vs. 4.7%) and hospitalized patients (42.5%; Table 3). In Fig. 1, the relative risks of every risk factor evidenced in the high-risk group are shown. In these weaker patients, we had to accept implantation of organs with higher donor age, more frequent weight D/R mismatch, longer total ischaemic time, higher incidence of high donor’s inotropic support and resulting in higher troponin peak. The larger use of red blood cell transfusions in these patients could be related to the higher prevalence of redo procedures.

DISCUSSION

In our experience, EGF occurred in 10.1% of the overall population (16.3% of in-hospital patients).

These data are similar to those issued by the International Registries [4]. Any statistical analysis attempting to identify risk
factors in a small series of patients is challenging and strongly biased by the selection criteria adopted to warrant the best outcome to the individual patient. For example, the higher incidence of EGF observed in patients in higher surgical priority may be due to the declining clinical conditions that indeed prevented an optimal donor/recipient size match.

Overall, EGF-related mortality was 56.3%. These data could be considered good in comparison with those forwarded by Russo et al. [10] or Ibrahim et al. [11], but this could be due to the stricter definition of EGF in our experience compared with others.

The pathophysiology that underlies EGF is generally multifactorial. The present analysis underscores this complexity, mainly related to the interdependence of some of the identified risk factors, which variably interact with each other in determining the individual patient’s risk [12, 13]. Thus, a main message is that EGF risk cannot be quantified in the single recipient unless donor and procedure factors are known and taken into account.

Therefore, the modifiable components of the pathogenesis could change from case to case, in order to avoid the untoward synergism between recipient conditions and donor features that have been proved to interact in EGF development.

Interestingly, haemodynamically significant RV dysfunction rarely occurred in our series in patients with higher pulmonary vascular resistance. This indicates that in this case the D/R match was carefully made to avoid any problem [14]. This is also due to the fact that patients were carefully screened and monitored for the development of pulmonary vascular hypertension while waiting for a suitable donor organ.

The synergistic effect, in terms of higher incidence of EGF, of redo operations and higher blood products consumption observed in our series suggests that surgical haemostasis during reopening or during implantation should be as meticulous as possible even in the constraint of higher ischaemic time. Nevertheless, every effort should be spent to reduce ischaemic time due to the movement of the harvesting team [15].

**Table 2: Outcomes and OR stratified for propensity groups**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Overall (n = 317)</th>
<th>Lower risk* (n = 211)</th>
<th>High risk, (n = 106)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF</td>
<td>32 (10.1%)</td>
<td>7 (3.3%)</td>
<td>25 (23.6%)</td>
<td>9</td>
<td>3.7–21.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>34 (10.7%)</td>
<td>12 (5.7%)</td>
<td>22 (20.8%)</td>
<td>4.3</td>
<td>2.0–9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Actual 1-year mortality</td>
<td>42 (13.2%)</td>
<td>20 (9.5%)</td>
<td>22 (20.8%)</td>
<td>2.5</td>
<td>1.3–4.8</td>
<td>0.005</td>
</tr>
<tr>
<td>AKI (ΔGFR&gt; 50%)</td>
<td>44 (13.9%)</td>
<td>23 (10.9%)</td>
<td>21 (19.8%)</td>
<td>2</td>
<td>1.06–3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>MOF</td>
<td>35 (11%)</td>
<td>12 (5.7%)</td>
<td>23 (21.7%)</td>
<td>4.6</td>
<td>2.2–9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-year infection</td>
<td>47 (18.6%)</td>
<td>33 (18%)</td>
<td>14 (19.8%)</td>
<td>1.1</td>
<td>0.6–2.2</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data presented as numbers (percentages).

*Lower-risk group comprised first and second tertiles of propensity score distribution; Values reported in bold are those statistically significant.

**Figure 1:** Incidence and relative risk of outcomes in the study population stratified for the EGF propensity score.
The correlation between ATG Fresenius usage and EGF could be explained with the strong selection bias operated at our institution. On the basis of our previous experience [7], ATG Fresenius was generally preferred to thymoglobuline when the patient was considered too weak. However, a less efficient protection from the ischaemia/reperfusion damage of the ATG in comparison with thymoglobuline could be also responsible for the association with EGF. This issue remains to be addressed.

All in all, the lesser number of patients dying of EGF could be due to the activity of a large volume centre for HT giving a good chance of optimal D/R matching. In some cases (i.e. rare groups, high surgical priority, immunized or obese recipients), the policy of allocation probably should be modified in order to obtain the best nationwide match.

**Limitations of the study**

This study comes from a single-centre experience and this accounts for the lower number of patients in some subgroups (i.e. ventricular assist device explanation) that could hide the effect of some risk factor well recognized in the Registries and in the cardiac transplant research database. Data were also strongly affected by local clinical practice that could mask the power of some undetected risk factors. Nevertheless, this could be considered as the real world experience of a well-trained group in HT.

**Conclusions**

Several donor and recipient features proved determinants of EGF. Since such characteristics are not readily modifiable but synergistically determine the occurrence of EGF, optimization of D/R matching is crucial to reduce the risk of EGF. Different groups of patients showed a significantly different risk of EGF; a score risk for EGF could help in calculate the individual risk of EGF before surgery and elucidate it to the patient at the time of informed consent. Changes in allocation rules in urgent recipients and in recipients with rare groups, immunized or obese, should be considered looking at the general interest of nationwide listed patients. Changes in strategies of myocardial protection for marginal donors with a long ischaemic time should be evaluated to better protect allograft function, achieve a good haemostasis and warrant good outcomes.

**Conflict of interest:** none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr M. Siepe (Freiburg, Germany): My first question concerns the statistical methods. You split the patients into three different groups with different risk factors, and you came up with the high-risk group (e.g. with a high-risk profile of mismatch), and then afterwards you conclude that mismatch is a significant risk factor. Isn’t that contradictory and repeating itself? The second question concerns your technique. You still use the bialtrial technique, and I wondered whether you have considered changing your technique to bivacal? My third question comes from the manuscript. I saw that whenever early graft failure occurs and you looked at the mortality in the three different risk groups, it was striking that the mortality in the high-risk group, whenever graft failure occurred, was lower. Why?

Dr Amarelli: Regarding the last question, I think it is only a numeric problem. In fact, if you look at the third group, there are many more cases than in the first two groups, so I think that explains the observed difference in terms of mortality of EGF in the three different groups. Regarding the technique, we always used the bialtrial technique. Probably bivacal could be a good alternative, but as our data demonstrated, we had good results also in patients with high pulmonary resistance. So, in our opinion, there is not a clear need to change to bivacal also in a patient with high pulmonary resistance. Moreover, probably the bivacal technique could increase the ischaemic time and the risk of bleeding. With the bialtrial technique, the bleeding risk is reduced due to the better quality of tissue and the lower number of sutures. Coming back to the first question, the study was designed to disclose differences between the three groups. But when we analysed the preoperative features of the first two groups, there were no difference. There was only difference in the incidence of early graft failure, but the relative risk of early graft failure in the first two groups was similar to the general population. Only the third group aggregated patients with a 25% risk of early graft failure. For this reason, only the third group was considered a high-risk group.

Dr Siepe: Well, let me be specific. You stratified your 300 patients into three risk groups according to preoperative data such as mismatch, and then you end up with a high-risk group, and you state afterwards that mismatch was more frequent in the high-risk group, which repeats itself in my mind.

Dr Amarelli: Yes, yes.

Dr Siepe: So it is only a result of your selection of the high-risk group.

Dr Amarelli: The propensity score analysis confirmed and underlined the impact of some factors, while other factors like donor age gained attention. And so the propensity score was made with this intention to better disclose the difference that could be hidden in the data.

Dr Siepe: One more question. What do you think will remain when we start to use the TransMedics product, the Organ Care System? What kind of risk factors will remain?

Dr Amarelli: I think the TransMedics could be useful when we suspect more than three hours of ischaemic time and possibly in patients with marginal donors when you have a long redo to perform. For example, our VAD explantations sometimes are really time-consuming. And so you can open your redo under less pressure and without too many stressors.

Dr M. Berman (Papworth, UK): I have three questions. My personal belief is that most of the outcome of heart transplantation will be decided probably on the donor side; maybe this was addressed in the paper, but it was not shown here in the presentation. You mentioned inotropic support. Did you have a strategy to reduce the alpha-adrenergic agonist to try to switch it to vasopressin or T3 or anything like that? The second question concerns your assessment of organ function, was it visualization, echo, PA catheterization, before and managing the donor? And the third point is, did you find any relevance concerning the interval between the time of the retrieval and the time that brain stem death was declared?

Dr Amarelli: When we evaluate a potential heart donor, we always try to reduce inotropic support. But sometimes the donor is really inotropic-dependent, and it is difficult when we see good ventricular function to discard a well functioning heart only due to the high inotropic support. Probably our data suggests that such donors should be used for patients in a better clinical status without added risk factors, or probably with this organ we should change the strategy. To be clear, if you use the TransMedics, you can put the donor heart on TransMedics and wait to see what happens in terms of lactate production and then decide if you use the donor or not.

The second question was about?

Dr Berman: If you found anything about the assessment of use of TransMedics and any relevance between the time that brain stem was declared and the time of retrieval?

Dr Amarelli: In our district the allocation policy is to reduce to the minimum the time to harvest, so we cannot manage the donor before the harvest and have no data about it. We always go by plane to reduce the ischaemic time as much as possible. Often we do long trips, and probably in that situation it could be useful to change the strategy of myocardial protection.